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Geriatric Psychiatry

A Case-Based Textbook

Springer

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Foreword

The Institute of Medicine (IOM) [1] estimates that the population of adults age 65 years and older will increase from 40.3 million in 2010 to 72.1 million in 2030. The IOM further estimates that about 1 in 6 of these older adults will suffer from a mental health problem including substance use disorder. Yet the training of specialists who might be expected to care for these patients has fallen far short of projected needs. In the USA, geriatric psychiatry was accredited as a subspecialty in 1991, and initially, the number of accredited programs and subspecialists certified grew; however, from 2000 to 2011, the number of physicians graduating from geriatric psychiatry fellowships fell by more than 50%, and the numbers continue to remain low. So as the population of older adults steadily grows, the number of specialists trained to manage their mental health problems is declining. The situation is unlikely much different elsewhere. In Canada, geriatric psychiatry has only been recognized as a subspecialty in 2009, with the first Royal College of Physicians and Surgeons of Canada subspecialty exam in 2013. Although one hope of subspecialty recognition in Canada was to increase recruitment, challenges in accrediting psychiatrists already caring for older adults have been noted, particularly in the form of disinterest in completing the geriatric psychiatry examination [2].

This widening gap for the provision of services is not limited to geriatric psychiatry. The number of physicians trained in geriatric medicine initially grew as new programs developed, but from 2002 to 2011, the number plateaued at about 300 graduating geriatricians per year. Of course other disciplines are involved in the care of older adults, yet similar trends are observed. Again the IOM report indicates only about 4% of licensed psychologists focus on the care of older adults. The IOM report is titled *The Mental Health and Substance Use Workforce for Older Adults: In Whose Hands?* The title asks an important question, who will provide care for these older patients?

The answer is partially addressed by Colenda and colleagues [3] who examined the 2002 National Survey of Psychiatric Practice. In their sample of respondents to the survey, after excluding child, addiction, and forensic psychiatrists, 26% of those surveyed identified themselves as being high geriatric providers. Board-certified geriatric psychiatrists were a minority of this group. These data suggest that with a growing need, general psychiatrists either by choice or recognizing the need have begun to fill this gap. Given the limited number of clinicians with specialized training in geriatrics, it is likely that this phenomenon will be repeated across specialties and disciplines. In other words, the mental health needs of this growing population of older adults will be provided by clinicians who did not consider themselves to be geriatric specialists.

As a consequence of these trends, training in geriatric psychiatry and geriatric medicine will become important for all clinicians. And new trainees will be just a small part of this effort. The more immediate issue is education for those already in practice. National meetings and CME programs can partially address this need. Other educational materials will be important, and that is where this book, *Geriatric Psychiatry: A Case-Based Textbook*, can play a crucial role.

This book includes many chapters that clinicians will find interesting and useful in their practice. Dr. Bourgeois' chapter on psychosomatic medicine or consultation psychiatry is an excellent place to start since as he points out, it bridges the gap between psychiatry and medicine. Because older patients are overrepresented among the hospitalized medically ill, the consultation service, which is primarily hospital based, is an excellent example of a psychiatric subspecialty which becomes a "high geriatric provider." Many clinicians will have received training about dementia at some point in their career; however, the chapter on major neurocognitive disorder due to Alzheimer disease will prove to be a useful review. It is particularly timely because it explains changes in diagnostic nomenclature introduced by DSM-5. It also describes the biomarkers that may help to establish diagnosis. Because the assessment of cognition is central to several of the most common disorders in geriatric psychiatry, clinicians will find the chapter on neuropsychological testing very useful. It is clearly written and describes the major domains of cognition, how they can be impaired, and how they are tested. Each of the chapters is followed by cases that provide examples of the concepts presented. Some clinicians will find this especially useful because it demonstrates how to apply the information discussed. In addition, learning the information in a case-related format may facilitate retention.

In summary, the rapidly growing population of older adults, sometimes referred to as the "silver tsunami," will quickly overwhelm the workforce trained in geriatric specialties. This has already begun to occur. As a consequence, general adult psychiatrists, primary care physicians, psychologists, nurse practitioners, and other clinicians will find themselves caring for the mental health needs of their older patients. Education of these clinicians will become a priority. Health-care providers interested in learning more about geriatric psychiatry will find this book an excellent place to start.

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Preface

The *Geriatric Psychiatry: A Case-Based Textbook* is a comprehensive volume, whereby the editors hope to bring deftness in mastering the skills for learning and integration of concepts, mostly not leaving medical trainees who are learning the concepts for the first time wanting for information, and yet not limited to a particular demographic. Problem-based learning, a widely adopted teaching model during medical training, has already shown to have positive effects on physician competency after graduation, both in cognitive and social domains [1] and which are highly required competencies in the real-world clinical practice of physicians [2]. Since nothing is static in the future of curricular development, medical institutions are starting to experience effects of a curricular change, namely, a shift from problem-based learning to case-based learning. Case-based learning is preferred because it is a structured approach, enhances clinical skills, and keeps the learning relevant. Contemporary trainees must continue to have access to teachers who serve as the inspirational role models that traditional curriculum offers. Case-based learning emerges as a promising teaching method for trainees in all medical fields including geriatric psychiatry.

Trainees in general psychiatry and subspecialty of geriatric psychiatry need exposure to high-yield, real-world cases in order to master core competencies in geriatric psychiatry. This textbook is ideal not only for trainees studying for the basic rotation in psychiatry residency training but also for those studying for subspecialty exit examination in geriatric psychiatry, as well as apposite for those training in other disciplines, not just medical specialties. Undergraduates will find the cases a useful addition to their resources during their placements involving the care of older adult patients.

Beyond the needs of trainees (e.g., residents and fellows in psychiatry and psychiatric subspecialties), the volume is intended to be equally valuable to practicing physicians. We envision two groups of practicing physicians who may benefit from the comprehensive and case-based approach we have taken. Psychiatrists who have the need for periodic recertification will find this book an efficient review of topics in geriatric psychiatry to facilitate validation of clinical currency and to enhance exam preparation. Perhaps more importantly, psychiatrists who wish to further their knowledge and skills in geriatric psychiatric practice and other specialty physicians whose work verges on geriatric psychiatry (geriatricians, internists, neurologists, physical medicine, and rehabilitation, to name a few) will find this volume a needed resource to enhance clinical problem-solving skills and to give these other specialists a pragmatic grounding in the clinical aspects of geriatric psychiatry that relate to their work within the framework of other medical specialties.

Therefore, this textbook format has an innovative, cutting-edge format by melding two concepts together, the traditional textbook and the case-based learning style, for the following reasons:

- Trainees learn from the case-based approach: the argument is that this demographic needs to employ learning skills that will resonate longer and provide more learning support than a mere case-based book would.
- This novel concept sets this textbook apart from others; it is not nearly as abstract as a standard textbook, while editors believe learning by example is the way of the future.
- The trainees can have the pros of a case-studies and academic book without any of the cons: it has the engagement level of a case-studies book, while it has the learning tools that will reinforce the concepts, including the graphics, teaching points, key objectives, and review questions.

The advantages of this case-based textbook format are manifold; it is trainee-focused, allows for active and self-directed learning, and enhances content knowledge while simultaneously fostering the development of communication, critical thinking, problem solving, and collaboration while optimally positioning trainees to function using real-world clinical experiences. This novel breed of case-based textbook aims to be a comprehensive reference (as conventional texts aim to be) and also retain the ability to serve as a quick reference for readers. As such, the chapter authors have emphasized quality reviews and meta-analyses though not intended to be as comprehensive as textbooks of the past, and yet it is hoped it may help to retain the relevance of the textbook in this steadfast era of the Internet and PubMed.

This volume covers main topics within geriatric psychiatry, whereas topics such as substance use disorders and sexuality and sexual dysfunction in later life are becoming even more relevant now

that the baby boomers are beginning to age. This volume is practical and concise, featuring 35 chapters on geriatric psychiatry topics, each comprising a clinical background, followed by a question-and-answer section format accompanying cases designed to carry on teaching while enhancing the reader's diagnostic ability and clinical understanding. Majority of the chapters include two cases of various clinical complexities, highlighting teaching points and reviewing multiple-choice questions. The text is arranged in three sections covering basic principles in assessment and management of geriatric neuropsychiatric syndromes, common psychiatric diagnoses in late life, and a range of specific topics. The covered material matches the existing postgraduate curricula in geriatric psychiatry and, we hope, will help prepare candidates for their specialty and subspecialty certification examinations. The cases map well to the American Association for Geriatric Psychiatry and Canadian Academy of Geriatric Psychiatry and other international postgraduate curricula in geriatric psychiatry.

Written and edited by geriatric psychiatrists, consultation-liaison psychiatrists, general psychiatrists, geriatricians, and other specialists in the care of older adults, this book will provide the editors' and authors' clinical experience with evidence-based information, expert opinions, and contemporary clinical guidelines for geriatric neuropsychiatric syndromes. Key features consist of being an easy-to-reference, heavily illustrated, specialty-specific guidance on how to diagnose and manage problems that arise in clinical practice, and it should be as succinct and clinically relevant as possible. The chapters present the main DSM-5 categories with reference to later life. Moreover, the explanations for the cases will emphasize evidence-based mechanistic principles rather than merely memorized questions and answers. The clinical cases will be written to be representative of more typical patient presentations rather than the portentous presentation.

As the case examples illustrate throughout the textbook, psychiatric complexity and comorbidity are the rule (especially in aging populations). In evaluating such patients, the reader might be tempted to simplify the complexity by applying a more reductionistic and illness-focused nomenclature of the diagnostic classification systems. Although both DSM and ICD classification systems will continue to adapt as scientific advances in psychiatric phenomenology progress over time, they likely will endeavor to capture the complex interactions of psychiatric illness, medical comorbidity, multiple pharmacologic agents, the processes of normal aging, and the patient's unique functional and psychosocial status. Thus, the psychiatric care of older patients must strive to be holistic in its scope. Additionally, a somewhat unusual or "atypical" clinical presentation might be evocative of some cultural or generational factors that modify the "textbook" presentations on which illness classifications are based. Hippocrates is reputed to have said [3], "It is more important to know what sort of person has a disease than to know what sort of disease a person has." We believe that our elaborate cases in the second part of each chapter underscore the challenges of diagnosing and managing psychiatric morbidity in older adults and encourage an integrative approach that acknowledges the dynamic interplay of psychiatric, medical, cultural, pharmacologic, and social factors. We hope that this book fosters an interest in understanding the specific patient's unique narrative and clinical presentation. We also hope that the cases presented in this volume serve to encourage the reader to stretch beyond habitual zones of clinical comfort while advancing pragmatic clinical knowledge and judgment.

A uniform and contemporary nomenclature has been endeavored so as to not confuse the readers. For example, the "typical" antipsychotics, ironically, are now used less than the "atypical," so now the "typicals" are used "atypically," while the "atypicals" are used "typically"; as such, it is timely to make a clear break from this irony and hereafter use the terms "first generation" for those antipsychotics antedating the release of clozapine (e.g., 1990 in the USA) and "second and third generation" for those medications (from clozapine to aripiprazole) of similar mechanisms and released subsequently. Such nomenclature is analogous to the familiar series of "first-, second-, and third-generation antibiotics," a scheme that has been universally accepted. In this volume, we do not use the clearly anachronistic term "neuroleptic" other than in the name of the illness neuroleptic malignant syndrome; individual chapter authors were welcome to use the terms first and second generation in parallel with typical and atypical antipsychotics. The editors hope that when we write a second edition, the "generation" scheme will have become normative.

The authors and editors of this book have also endeavored to use the latest DSM-5 nomenclature to describe psychiatric illnesses, both regarding broad categories and specific illnesses. The DSM-5 was published in 2013, and much of the research and clinical literature based on

data acquired before 2013 was written in DSM-IV (and earlier DSM versions). Therefore, the chapter authors/editors quoted sources by using the terminology in force at the time of the original publications, while, when writing about the current state, they use the DSM-5 nomenclature. When needed for clarity, "transduction" language, e.g., "major neurocognitive disorder (DSM-5), formerly dementia (DSM-IV)," is used to assist the reader to manage this admittedly sometimes semantically awkward period of transition. This is accomplished in the service of clarity of thought, and the authors/editors hope that such terminology assists the reader.

The editors have built their careers on their aptitudes as both professionals and educators, which has led to shaping this curriculum. It is their hope that this book is intended as a hands-on, real-world approach to learning that will keep readers engaged, able to understand the key factors that drive the medical decision-making process, and covers the bioethical aspects, presentation, management, and biopsychosocial treatment of the most common neuropsychiatric illnesses in older adults. We hope this academic textbook remains on bookshelves during fellowships and beyond, even during professional medical practice.

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Basic Principles in the Assessment and Treatment of Late-Life Neuropsychiatric Syndromes

Contents

Physiology and Pathology of Aging

Calvin H. Hirsch and Ana Hategan

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1

1.1 Background

1.1.1 Normal Versus Normative Aging

The conventional paradigm of human aging involves an ineluctable decline in function culminating in death. Ideal survival, whether it is survival free from disability, disease-free survival, or total longevity, would be expected to depend on genetic variation within the population that tends to be expressed later in life. The ideal, or species-specific, survival curve (see Fig. 1.1) shows a rectangular shape, with a narrow downward slope due to attrition from accidents and congenital disease until advanced old age, when genetically programmed longevity theoretically leads to a rapid decline in population survival that accelerates near the species-specific maximum. This ideal survival is referred to as "normal aging." By contrast, "normative aging" is the actual survival of a population due to the interaction of environment (e.g., air pollution, infectious agents), behavioral factors (e.g., smoking, diet), and societal factors (e.g., socioeconomic status, education) at the level of the host's genome (epigenetics) and at the macro level through interactions with individual cells and entire organs. Epidemiological and demographic research has attributed only 15–30% of longevity to heritable factors [1], but these low percentages are biased by the paucity of studies of exceptional survivors, i.e., individuals living to 100 years and beyond. Nonetheless, the gap between normal and normative aging remains large. Chronic disease arising congenitally or from host-environment or host-behavioral interactions pushes the curve to the left, while preventive and disease-specific health care attempts to push it to the right. The gap between survival free of multimorbidity and length of life (see Fig. 1.1) represents a period of comorbidity that can diminish quality of life, result in higher health-care costs, and lead to prolonged disability, i.e., dependence on others for activities involved in independent living. The overarching goal of preventive and disease-specific health care is to compress this period of comorbidity while simultaneously "rectangularizing" the survival curve to resemble normal (ideal) survival. Preventing, recognizing, and correctly treating systemic medical and psychiatric conditions prevalent in old age depend on an understanding of the physiology underpinning both normal and normative aging. Understanding common physiologic pathways during the aging process can provide insight into how seemingly unrelated conditions can co-occur. For example, anxiety and depressive disorders in geriatric patients can be independently associated with the development of urinary incontinence, falls, and functional dependence [2].

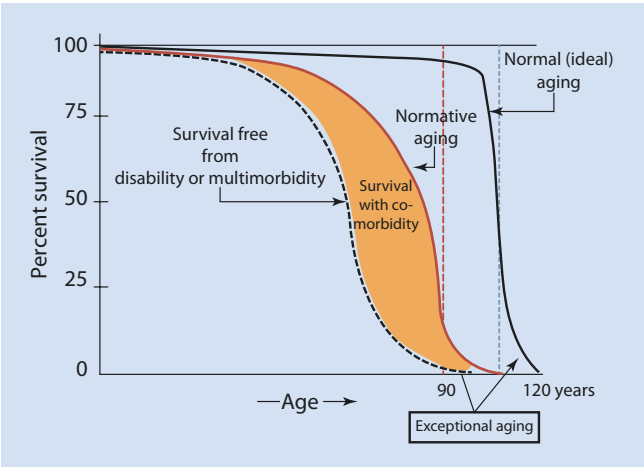

Fig. 1.1 Theoretical survival curves. The solid black curve represents normal or ideal aging, with mortality related largely to accidental death and trauma until the genetically determined maximum life expectancy. Some premature mortality also would be expected due to genetically determined diseases. The red curve reflects normative aging, i.e., the survival of individuals within a society due to the interaction of the host's genome, cells, and organs with environmental and behavioral factors. The dotted line represents survival free of disability or multimorbidity. The orange area represents the interval of life spent with comorbidity

1.1.2 Loss of Resilience

Changes in structure and function occur in all organ systems during normal aging, but accelerated aging can result from behavioral and environmental stressors. For example, excess exposure to UV radiation because of tanning can prematurely age the skin, causing permanent solar damage and predisposing to skin cancer. While organ systems do not age uniformly, they all experience a decline in physiologic reserve, or resilience [3], such that stressors to homeostasis (e.g., acute or chronic illness) can exceed the compensatory capacity. This loss of resilience can lead to decompensation that spreads from the affected organ to the entire organism (see Fig. 1.2). For example, a patient with severe weakness, urinary incontinence, atrial fibrillation, and heart failure

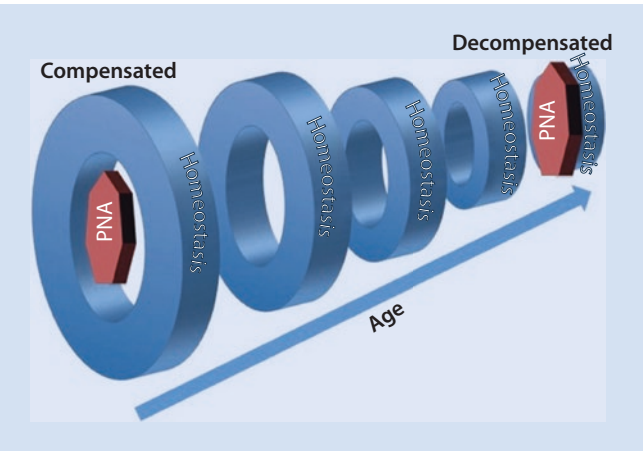

Fig. 1.2 The narrowing homeostatic cylinder of aging. PNA = pneumonia. As physiological resilience declines with age, stressors to normal homeostasis, such as pneumonia, become more likely to exceed the ability of the individual to compensate, resulting in generalized dysfunction that may affect more than one organ system

develops delirium related to acute multi-organ decompensation precipitated by an episode of pneumonia brought on by a virus that merely caused sniffles and a day or two of fever in her grandchild. That patient's comorbidities, and, to some extent, their treatment, contributed to her decompensation.

Teaching Point
Normative aging refers to survival within a society as a result of the interactions of the individual's genome, cells, and organ systems with environmental and behavioral factors.

1.1.3 Construct of Frailty

Although most clinicians think that they recognize frailty when they see it, only in recent years have investigators attempted to develop systematic, valid, and reproducible definitions of frailty that provide meaningful constructs for clinical and epidemiological research. The Fried and Rockwood indices are the two most commonly used. The Fried index, modified for use in the clinical setting, is based on a phenotype consisting of four components [4]:

- Self-reported exhaustion (defined by difficulty walking from one room to another)
- Low physical activity
- Weakness (defined as difficulty carrying 10 pounds (4.5 kg))
- Low body weight (BMI $\leq$ 18.5 kg/m^2)

Individuals meeting 3–4 of the frailty characteristics are considered frail, those with 1–2 characteristics are pre-frail, and those with none of the criteria are considered robust [4]. Notably, the Fried index does not equate frailty either with multiple comorbidities ("multimorbidity") or with disability, although in observational studies, there is considerable overlap among the three (see Fig. 1.3) [5]. The Rockwood Frailty index is based on the age-related accumulation of comorbidities, functional impairment, clinical signs and symptoms (e.g., visual loss), specific laboratory values associated with poor outcomes, and factors such as health-care utilization, number of medications, and self-reported health. The index has been modified over time and for different usages, ranging from 70 items to under 30 [5]. Both frailty models predict mortality, disability, and health-care utilization [4–7], and the accumulated deficits model predicts cardiovascular events [7]. Psychiatrists caring for frail seniors should recognize that frail older adults have as much as a threefold greater likelihood of developing a depressive disorder, compared to non-frail seniors [8, 9], and that frailty predicts neurocognitive decline. For example, in the Honolulu-Asia Aging Study, a 10% increase in frailty based on the deficits frailty index was associated with a 5.0 point decline on the Cognitive Abilities Screening Instrument, and both baseline and within-person changes in frailty predicted cognitive trajectories [10]. Other studies have linked physical frailty with increased risk for major or mild neurocognitive disorder due to Alzheimer disease or vascular disease [11].

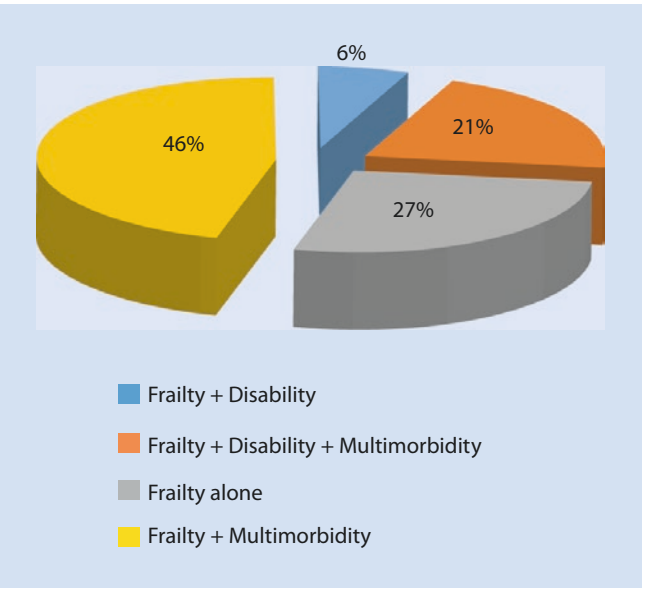

Fig. 1.3 The overlap among frailty, disability, and comorbidity

Teaching Points

- With aging, there is a loss of physiological resilience to perturbations to organ-system and organismal homeostasis, which can result in the dysfunction of organ systems unrelated to the diseased organ. Thus, for example, pneumonia can precipitate falls, urinary incontinence, and delirium.
- Frailty can now be characterized by objective, validated indices, and objective measures of frailty have been linked to neurocognitive disorders and depression.

1.1.4 Multimorbidity

Prevalence of Multimorbidity in the Older Adults

The incidence and prevalence of multiple comorbidities (multimorbidity) rise with age. Conditions included in epidemiological studies of multimorbidity in older adults have varied. Barnett et al. selected 40 common conditions to study based on consensus about their importance from a public-health perspective [12], and collected data on the prevalence of these conditions from 1,751,841 residents drawn from 314 medical practices in Scotland in 2007. Figure 1.4a shows their findings for adults 45 years and older. Both the percentage of individuals with multimorbidity and average number of comorbidities increased with age. The combined prevalence

1

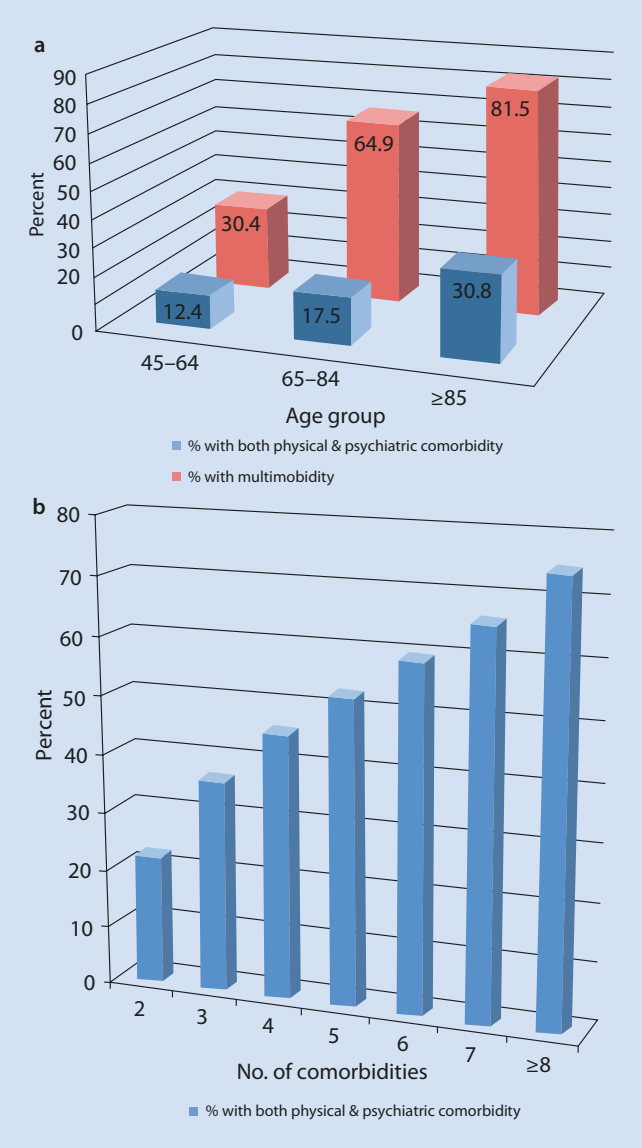

Fig. 1.4 Demographics of multimorbidity in Scottish primary care patients in 2007. Panel **a:** Percent with multimorbidity (*red bars*) and the percent of individuals whose multimorbidity includes both physical and psychiatric comorbidities (*blue bars*). Panel **b:** The percent of individuals with combined physical and psychiatric comorbidity as a function of the total number of comorbidities [12]

of psychiatric disorders with physical morbidity also rose with age, and the co-occurrence of psychiatric comorbidities increased with the total number of disorders (see Fig. 1.4b).[1] The prevalence of subjective memory complaints and neurocognitive impairment in older adults also rise with the number of comorbidities [13–15]. Multimorbidity in older adults has been associated with lower socioeconomic status, even in societies with a national health-care system and low barriers to accessing health care [12, 16].

1 The authors used a standardized definition for psychiatric disorders but did not disclose the conditions included in the definition.

Teaching Point

Multimorbidity and disability precede death, and the goal of prevention and medical therapy is to compress the duration of morbidity by moving the morbidity-free survival curve closer to normative survival and, in so doing, potentially moving normative survival closer to ideal, or normal, survival.

Physiological Mechanisms Underlying Multimorbidity and Functional Decline

Many theories have been put forward to explain the physiological changes that occur within organ systems and the diseases that result. A number of diseases which are prevalent in old age (e.g., chronic obstructive and interstitial lung disease, ischemic heart disease, osteoarthritis, major neurocognitive disorder due to Alzheimer disease) can be considered evidence of accelerated aging [16], caused by environmental/behavioral factors (e.g., smoking) or genetic predisposition that interacts with host mechanisms. Research has provided varying levels of evidence to explain how numerous pathways might lead to organ-system changes and dysfunction. In practice, multiple interacting pathways likely contribute to cellular aging within organ systems, and investigators have begun to show how different theories of aging are linked. Oxidative stress appears to be a common pathway to cellular damage and accelerated aging and is itself a by-product of reactive oxygen species produced by dysfunctional mitochondria [17] as well as by activated inflammatory cells. Baptista et al. evaluated oxidative stress in 280 men and women (mean age, 79.9 years) divided into usual gait speed of < 0.8 m/second (slow gait) or ≥ 0.8 m/second (normal gait speed). Using production of superoxide anion as an expression of oxidative stress, they found that superoxide production was significantly higher among the slow walkers ($p = 0.004$) [18].

The Aging Effects of Chronic Inflammation

Chronic Inflammation and Physical Performance

The prevalence of chronic inflammation increases with aging, as it is found at low levels in chronic conditions like atherosclerosis [19]. In older men and women from the longitudinal Cardiovascular Health Study, markers of low-level inflammation were associated with the phenotypic model of frailty, with the three highest quartiles of C-reactive protein (CRP) and fibrinogen each independently showing an increased adjusted odds ratio of frailty, relative to not frail, even when patients with a history of cardiovascular disease or diabetes mellitus (both of which are inflammatory conditions) were excluded. A cross-sectional CRP > 5.77 mg/L corresponded to a 2.8-fold relative risk of frailty compared to participants with a normal CRP [20]. The association of biomarkers of inflammation with frailty persists into advanced old age (aged 85 years and over), indicating that survival beyond age 85, considered to be successful aging, is not

accompanied by relative immunity to the systemic effects of chronic low-level inflammation [21].

Diminished physical performance is a core component of the frailty phenotype, so it is not surprising that chronic inflammation was linked to worse performance on the 6-minute walk test in a research cohort of 60 men and women (mean age, 77 years) with systolic heart failure [22]. Across different chronic illnesses, CRP and interleukin-6 (IL-6) have been independently associated with worse scores on a composite measure of function (Short Physical Performance Battery), showing lower grip strength, longer time to complete 5 chair stands, and longer time to complete a 4-m walk [23]. In the Health, Aging, and Body Composition (ABC) study, 2081 men and women (mean age, 74 years) were followed for up to 30 months for incident self-reported mobility limitation, defined as difficulty walking ¼ mile (403 m) or walking up 10 steps. Baseline laboratory tests included CRP, IL-6, and tumor necrosis factor alpha (TNF-α). For each unit increase in standard deviation in CRP, IL-6, and TNF-α, there was a 19%, 20%, and 9% increased adjusted risk ratio, respectively, of mobility limitation. For CRP, IL-6, and TNF-α in the upper tertile (> 2.54 mg/L, 2.42 pg/mL, and 3.72 pg/mL, respectively), the adjusted risk ratio increases were 33%, 65%, and 13%, respectively. The incidence of severe mobility limitation increased linearly with the number of concurrent high inflammatory markers [24]. In the InCHIANTI study of aging, levels of IL-6 and IL-IRA (an anti-inflammatory cytokine) were significantly associated with worse physical performance scores after adjustment for demographic factors and selected comorbidities, medications, and laboratory values [25].

Inflammation and Geriatric Depression

Five major epidemiological studies have focused on the relationship between serum inflammatory markers and depressive symptoms in older adults [26]. A possible pathway by which pro-inflammatory cytokines like IL-6 and TNF-α cause depressive symptoms is through the stimulation of the hypothalamic-pituitary-adrenal axis, leading to increased cortisol and resulting fatigue, anorexia, weight loss, sleep disturbances, and reduced psychomotor activity [27]. Among 2879 persons aged 70–79 years, those with a depressed mood had significantly higher levels of TNF-α, IL-6, and CRP. Having high levels of all 3 biomarkers was associated with a 2.40 increased odds ratio of a depressed mood, compared to no high markers (95% CI 1.27–4.53) [27].

Depression in older adults also predicts incident disability. In the Health ABC study, older subjects were classified into three trajectories based on annual Center for Epidemiologic Studies Short Depression scale (CES-D10) scores: non-depressed, mildly depressed, and depressed. After adjustment for demographic and lifestyle variables and comorbidity, a clear dose-response relationship between longitudinal depression and incident disability was seen in men and women, with depressed individuals more than twice as likely to develop disability than those who were not depressed [28]. Thus, inflammation appears to contribute to disability directly as well as indirectly through its association with depressive symptoms. Future research must tease out whether depression is truly causative or an epiphenomenon of ongoing inflammation. The complex interrelationships between aging, inflammation, multimorbidity, frailty, and depression (see Fig. 1.5) underscore the importance of multimodal interventions for age-associated depressive syndromes that target comorbid conditions in addition to the depressive disorders.

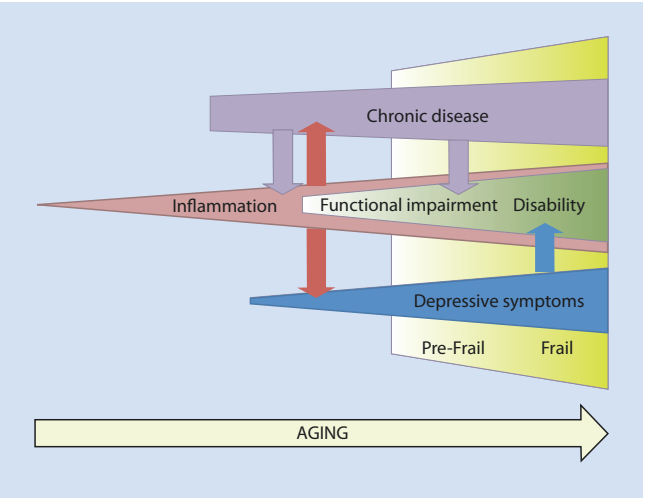

Fig. 1.5 The complex interrelationships among aging, inflammation, multimorbidity, frailty, and depressive disorder

Teaching Point

A complex web of interactions has been found linking age-associated inflammation and chronic disease to depression, functional impairment, and frailty.

1.1.5 Telomere Length, Inflammation, and Multimorbidity

Significance of Telomeres and Aging

Repeated nucleotide sequences (TTAGGG) called telomeres form a protective cap at the ends of chromosomes to prevent chromosomal shortening and loss of critical DNA during cell division. Telomeres are protected by the enzyme telomerase, but in most cells telomerase activity is insufficient to prevent loss of the integrity of telomeres, resulting in progressive shortening during the normal aging process. When the shortening reaches a critical level, errors in DNA transcription result in cellular senescence and cytopathology, in turn contributing to cell death (apoptosis) and increased oncogenic potential [16, 29]. Diseases of accelerated aging that are linked to inflammation, such as cardiovascular disease and type 2 diabetes mellitus, have been associated with greater telomere shortening, as have inflammatory environmental exposures like cigarette smoking. Negative risk factors for cardiovascular disease, such as higher high-density lipoprotein (HDL) and lower blood pressure, have been associated

with slower telomere shortening in the longitudinal 1934–1944 Helsinki Birth Cohort Study, whereas unintentional weight loss was associated with relatively accelerated telomere shortening [30].

In meta-analysis, certain psychiatric disorders in adults have shown a robust statistical association with telomere length, including depressive disorders, posttraumatic stress disorder, and anxiety disorders [31, 32]. The implication is that these psychiatric conditions may independently contribute to accelerated aging through telomere shortening, although establishing a causal link will require large longitudinal studies, and adjustment must be made for potential confounders like smoking. Telomere shortening has been associated with cognitive impairment, hyperphosphorylation of tau, and beta-amyloid deposits in the brain [33], where activated microglia and inflammatory cytokines can be found [34]. Whether the inflammation causes telomere shortening, whether they induce a positive feedback loop to amplify each other, or whether the two independently co-occur remains unsorted.

Teaching Point

Telomeres, a protective cap of a repeated sequence of nucleotides at the end of chromosomes, shorten with age, chronic inflammation, and several common chronic diseases. Shortened telomeres have been associated with mood disorders and neurocognitive decline.

1.1.6 Aging in Individual Organ Systems and Implications for Disease and Treatment

The Aging Nervous System

Morphological and Metabolic Changes in the Brain

In cross-sectional analyses, total brain volume declines in old age, with a 0.45% per year drop in whole brain volume after age 79. Gray matter tends to decline linearly with a loss of 0.11−0.18% per year. White matter declines in a nonlinear fashion [35].

White matter hyperintensities seen on T2 FLAIR MRI brain imaging are believed to reflect small vessel ischemic changes that many consider part of normal advanced aging but which also are associated with vascular risk factors like hyperlipidemia, hypertension, and type 2 diabetes mellitus [36, 37]. In turn, white matter hyperintensities are linked not only to the risk of ischemic vascular neurocognitive disorder but also to major neurocognitive disorder due to Alzheimer disease, suggesting a relationship between small vessel ischemia and beta-amyloid formation [36]. In healthy individuals, longitudinal MRIs demonstrate the dynamic nature of white matter hyperintensities, which sometimes remain stable, occasionally regress, and often progress, depending in part upon the severity of vascular risk factors and how aggressively they are treated [38]. Functional brain imaging shows reduced brain metabolic activity with aging that is unevenly distributed within brain regions and correlates well with reductions in gray matter volume [39].

Teaching Point

Gray and white matter decline in advanced old age, leading to a drop in brain volume. White matter hyperintensities accumulate in late life as part of normal aging as well as diseases associated with vascular risk. White matter hyperintensities have been associated both with vascular and Alzheimer disease-related neurocognitive disorder.

Cognitive Changes with Aging

In normal aging, general skills and knowledge, procedural (motor) memory, implicit (automatic) memory, memory retention, fund of knowledge, vocabulary, attention, object perception, and the ability to perceive abstractions like similes largely tend to be preserved into advanced old age. However, problem solving, processing speed, episodic memory, rate of learning, memory retrieval, verbal fluency, three-dimensional perception, and most domains of executive functioning tend to decline (Table 1.1) [40].

Teaching Point

In normal aging, problem solving, processing speed, episodic memory, rate of learning, memory retrieval, three-dimensional perception, and many domains of executive functioning decline.

Changes in the Peripheral Nervous System

Psychotropic medication use [41] and depressive disorders alone [42] are two of numerous factors that contribute to the falls experienced annually by over one third of adults 65 years and older, resulting in 2.6 million nonfatal fall-related injuries in the United States in 2000 [43]. The high incidence of falls stems in part from age-related changes in the central and peripheral nervous systems that affect balance, coordination, and the speed and adequacy of motor response to avert a fall. In older persons, peripheral vibration sense declines more rapidly than touch and pain, and the sensitivity of light touch decreases. In older adults, myelinated nerve fibers conduct signals more slowly, resulting in delay of transmission of sensory information from the feet and joints to the spinal cord, contributing to loss of balance. Mechanoreceptors in the joints, including the knees, hips, and neck, may become damaged from

Table 1.1 Cognitive changes in normal aging [40]

Cognitive domain	Definition	Examples	Trajectory
Intelligence			
Crystallized intelligence	Skills, knowledge, abilities that are well practiced and familiar Related to experience	Vocabulary, general knowledge	Stable or slight growth through 7th decade
Fluid intelligence	Problem solving and reasoning for new things	Executive function, judgment	Slow decline from third decade
Processing speed	Speed with which cognitive activities are performed	Slower performance on Trails B test	Slow decline from third decade
Attention			
Selective attention	Ability to focus only on relevant information	Driving	Slight decline in late life
Divided attention	Ability to multitask	Drive and carry on a conversation	Slight decline in late life
Memory			
Semantic memory	Fund of knowledge	Recall of US presidents after WWII	Late-life decline
Episodic memory	Memory for personally experienced events	Recall of last year's summer vacation	Slow decline throughout life
Implicit memory	Automatic triggered recall Procedural memory (motor memory)	Recall of tune and lyrics to national anthem How to ride a bicycle, play piano, or type on a keyboard	Generally stable throughout life
Memory acquisition	Learning new things	Studying a foreign language	Rate of acquisition declines with aging
Memory retention	Successful learning		Preserved with aging
Memory retrieval	Recall	Recalling recently learned new words	Declines
Language			
Verbal fluency and vocabulary	Word generation (phonetic and semantic fluency) and lexicon	Carrying on a conversation	Stable; vocabulary may improve with aging
Visual confrontation naming	Correctly naming a previously familiar object when presented with it	Seeing a pencil and calling it "pencil"	Stable with slow decline after age 70
Verbal fluency	Spontaneous word generation within a category	Naming as many words as possible beginning in "S" in 1 minute	Declines
Visuospatial abilities			
	Understanding space in 2 and 3 dimensions	Assembling a furniture kit, drawing a complex shape	Declines
	Object perception	Spatial perception when driving, recognizing faces	Stable
Executive functioning			
	Organize, plan, problem solve, self-monitor, mental flexibility	Planning and preparing a meal	Declines after age 70
	Response inhibition	Avoiding patterned responses inappropriate for situation, e.g., connecting 1–2–3, etc. When asked to connect the first number, first letter, and so on (1-A-2-B-3-C, etc.)	Declines
	Reasoning	Solving math problems	Declines
	Abstractions	Appreciate similarities (train and bicycle are modes of transportation); meaning of proverbs (people in glass houses, etc.)	Stable

1

osteoarthritic changes or lost because of joint replacement. This loss of peripheral sensation and proprioception substantially hampers postural control in older adults [44]. The response of the brain to postural perturbations requires motor signals to pass through the anterior horn cells of the spinal cord to the muscle. The number and diameter of motor axons in the spinal cord decline with age, as do the number of motor units (each unit representing a single motor neuron and all of its innervated muscle fibers). At the same time, the size of the motor unit increases, meaning that the remaining motor neurons innervate relatively more muscle fibers, resulting in coarser movements. Overall muscle mass declines 20–35% between the ages of 20 and 80, with a corresponding reduction in muscle strength that can be partially reversed with exercise. With aging, rapidly conducting fast-twitch (type II) muscle fibers drop out more quickly than the slower-conducting slow-twitch (type I) fibers, further retarding the motor response to postural disequilibrium [44]. Motor deconditioning occurs more rapidly in older adults, such that a few days of bedrest from acute illness can result in a substantial decline in muscle strength and gait safety. Both psychiatric and medical hospitalization thus can accelerate loss of strength as well as balance that is additionally threatened by the wide variety of psychotropic medications that are commonly prescribed. (See also ▶ Chap. 5.)

Teaching Point
Age-associated changes in the peripheral nervous system affect balance, coordination, and motor responses, thereby increasing vulnerability to falls. Psychotropic medications add to this increased risk of falling.

Aging and the Perception of Pain

The myelinated A∂ fibers mediate the immediate sensation of pain, whereas the unmyelinated, slower-conducting C fibers subserve the sustained pain that may follow. The numbers of both types of pain fiber decrease with aging, resulting in a diminished ability to detect pain, but when pain is detected, there is often a reduced pain tolerance. This decreased pain tolerance in older adults is believed to derive from central sensitization, which occurs in part from brain and spinal cord mast cell activation, especially in the thalamus, along with activation of microglia, leading to the release of inflammatory cytokines and a reduction in central inhibition of pain sensitivity [45]. In chronic pain syndromes, this may lead to an earlier requirement for opioids with their associated adverse effects in older patients (see also ▶ Chap. 16). Certain psychotropic medications, such as the serotonin norepinephrine reuptake inhibitors (SNRIs) and the gabapentinoids (e.g., gabapentin, pregabalin), may help reduce central sensitization [46–48], notwithstanding their own independent association with falls [41, 49].

Teaching Point
Changes in the central and peripheral nervous systems alter the perception of pain, with decreased peripheral pain sensitivity but greater overall perceived pain once the threshold for pain has been reached. The relatively greater perceived pain (i.e., lower pain tolerance) in older adults results from central sensitization.

1.1.7 Age-Related Changes in the Heart

Ventricular Function

Aging in the absence of cardiovascular disease is accompanied by thickening of the left ventricle and delayed diastolic relaxation (diastolic dysfunction) that reduces passive filling of the ventricles and necessitates greater reliance on atrial contraction. When the contribution of early passive filling (E) drops below the atrial component (A), diastolic dysfunction is diagnosed and is reported as an E/A ratio < 1 [50]. As a consequence of diastolic dysfunction, older patients are less tolerant of supraventricular arrhythmias in general, and atrial fibrillation in particular, and are therefore vulnerable to rate-related heart failure. In contrast, at rest, the left ventricular ejection fraction is preserved with aging.

Atrial Fibrillation and Cognitive Function

Atrial fibrillation confers an independent risk for major neurocognitive disorder independent of clinical stroke, and its annual incidence rises with age, from 1.9 per 1000 persons in women and 3.1 per 1000 in men below age 65 to 31.4 per 1000 in women and 38 per 1000 in men after age 85 [51]. In the Atherosclerosis Risk in Communities (ARIC) study (mean age, 76.9 years), persistent atrial fibrillation (defined as 100% atrial fibrillation during prolonged wireless electrocardiographic monitoring) was associated with significantly worse performance on multiple neurocognitive screens compared to participants with paroxysmal atrial fibrillation (1–6% of time in atrial fibrillation), after adjustment for history of clinical stroke [52]. This relationship extends to older patients with persistent atrial fibrillation and heart failure [53]. In patients diagnosed with atrial fibrillation, anticoagulation has been shown to be superior to antiplatelet therapy in minimizing decline in scores on the Mini Mental State Examination (MMSE), but anticoagulation has shown neither benefit nor harm in preventing the development of major neurocognitive disorder, based on meta-analysis [54].

Autonomic Changes

The aging heart is subject to a variety of neurohumoral changes that contribute to neurocardiovascular instability, chief among them a diminished baroreceptor reflex that results in an increased prevalence of orthostatic hypotension. Neurodegenerative disorders have an additive effect on age-related neurocardiovascular instability, which is particularly prominent in neurocognitive disorder due to Parkinson disease and Lewy body disease. It is also more common in major neurocognitive disorder due to Alzheimer disease and vascular disease, as well as in the pre-dementia state of mild neurocognitive disorder (also known as "cognitive impairment—no dementia"), compared to cognitively intact controls [55]. These autonomic changes can affect heart rate and blood pressure, resulting in increased susceptibility to bradycardia and syncope in patients who take acetylcholinesterase inhibitors [56].

Orthostatic Hypotension

Roughly 20% of adults aged 65 and older and approximately 30% of adults over age 75 experience symptomatic or asymptomatic orthostatic hypotension, and among frail seniors (e.g., those dwelling in skilled nursing facilities), the prevalence exceeds 50% [57]. The postural drop in blood pressure occurs when α1-adrenergic vasoconstriction fails to counteract postural venous pooling, especially in the visceral splanchnic system, and there is a corresponding inadequate compensatory rise in heart rate, leading to a drop in cardiac output. Postprandial hypotension, defined as a drop in systolic blood pressure of ≥ 20 mmHg, can occur 90 minutes after eating and was found in 67% of a sample of hospitalized older adults (mean age, 80 years) after consuming a standardized meal [58]. Orthostatic hypotension can cause postural light-headedness, syncope, loss of balance, falls, and fall-associated injuries and, if severe enough, can result in stroke or myocardial infarction. The polypharmacy prevalent among older patients includes multiple classes of medications, such as beta-adrenergic blockers, calcium channel blockers, other antihypertensives, and diuretics, which independently and additively contribute to as well as compound age-associated orthostatic hypotension. Many psychotropic medications have been strongly implicated in causing or exacerbating orthostatic hypotension, including (but not limited to) tricyclic antidepressants, trazodone, clozapine, quetiapine, olanzapine, ziprasidone, and haloperidol [59–61]. Lithium, whose renal toxicity involves impairment of the distal tubular response to vasopressin and resulting diabetes insipidus, can lead to volume depletion. Among 342 US veterans attending a geriatrics clinic, the prevalence of orthostatic hypotension rose monotonically with the number of potentially causative medications, from 35% among those receiving none to 65% among those taking 3 or more [62]. It is imperative that psychiatrists obtain an accurate list of current medications that could contribute to orthostatic hypotension and check for orthostatic blood pressure changes in their older patients before prescribing a psychotropic medication that could cause or exacerbate orthostatic hypotension.

Aging of the Cardiac Conduction System

More than half of patients 65 years and older will have an abnormal electrocardiogram (ECG), and nearly 20% of their ECGs show ST-T changes. The sinoatrial node (sinus pacemaker) loses pacemaker cells and the PR interval and QRS duration lengthen with age [63]. In older persons free of clinical cardiovascular disease, nearly 25% have a prolonged QRS duration of > 100 milliseconds, and of these, the majority are men. Over time, individuals with a prolonged QRS duration are more likely than those without prolongation to develop heart failure [64]. Given the prevalence of asymptomatic QRS duration prolongation in the seniors, drugs that block the cardiomyocyte sodium channels, especially tricyclic antidepressants, should be used cautiously, if at all. However, selective serotonin reuptake inhibitors (SSRIs) like fluoxetine and citalopram, although weaker sodium-channel blockers, can prolong the QRS duration and lead to cardiac arrest when doses are excessive [65]. With aging, the QTc lengthens linearly between the ages of 30 and 90, with a slightly higher slope of rise in men, although the QTc is consistently higher in women [66]. Consequently, SSRIs, SNRIs, haloperidol, droperidol, and the "atypical" antipsychotics, which prolong the QTc interval to varying degrees, have the potential for precipitating *torsades de pointes* and ventricular tachycardia. (See also ► Chap. 5.)

1.1.8 The Aging Lung

Without the help of tobacco or chronic asthma, aging by itself causes changes in pulmonary physiology, architecture, and function that can result in older patients, who are free of clinical lung disease, meeting the criteria for chronic obstructive lung disease stage 1. Emphysematous changes, marked by enlargement of alveoli without destruction of alveolar walls [67], and reduced elastic recoil lead to premature closure of the airways, causing the forced expiratory volume in 1 second (FEV_1) and forced vital capacity (FVC) to decrease with age, while the closing volume (CV) increases. The CV increases in the supine position and during general anesthesia. These changes translate into a higher residual volume and functional residual capacity, as seen in chronic obstructive pulmonary disease (COPD). The chest wall stiffens, adding to the work of breathing by the respiratory muscles (principally the diaphragm and intercostals). The age-related change in the proportion of type IIa muscle fibers impairs the strength and

1

endurance of the respiratory muscles. All of these changes affect oxygen transport. The net result of age-associated changes is a greater susceptibility to respiratory failure (i.e., hypoxemia) when acute or chronic pulmonary conditions, as well as pharmacological interventions that cause sedation or interference with respiratory drive (e.g., opioids, benzodiazepines), are superimposed [68]. Thus, sedating medications should be prescribed cautiously, especially at bedtime, in patients with known lung disease. Older inpatients with lung disease should have oxygen saturation monitored, especially when asleep. Obese patients can experience obesity-related hypoventilation due to the heaviness of their chest wall and should not sleep supine. Similarly, patients with COPD or severe asthma should be encouraged to sleep with their thorax elevated > 20° to minimize further deterioration in CV and to maximize the function of their diaphragms. Patients with kyphosis have the added burden of restrictive lung disease and need to sleep more upright or on their sides.

Teaching Points

- Aging itself causes structural and functional changes in the respiratory system that cause mild COPD-like changes, reduced oxygen transport and expiratory airflow, and increased vulnerability to the effects of medical and anatomical conditions that affect lung function.
- Sedating medications, especially those that can affect respiratory drive (e.g., opioids, benzodiazepines), may affect oxygenation, especially when taken at bedtime.
- A supine position can be harmful for patients with acute and chronic lung and thoracic disorders, such as:
  - Kyphosis
  - Morbid obesity
  - Moderate to severe COPD
  - Pneumonia
  - Other conditions that affect oxygen saturation
- Minimize bedrest for the older hospitalized patient including:
  - Encourage ambulation (supervised if fall risk or needing oxygen)
  - Encourage the use of the incentive spirometer if patient is able to cooperate
  - Up in chair as much as tolerated instead of lying in bed

1.1.9 The Aging Endocrine System

Thyroid Disorders

This section will focus on age-related changes in the neuroendocrine system that are germane to affective and cognitive changes in older patients. Hypothyroidism is not part of normal aging, but it is relatively common. The prevalence of hypothyroidism, defined as a thyroid-stimulating hormone (TSH) above the upper limits of normal, rises after the age of 60 and reaches nearly 5% in men and about 8% in women by age 70 [69]. It is beyond dispute that severe hypothyroidism impairs cognitive function, and it is considered one of the few "reversible" forms of major or mild neurocognitive disorders. More controversial is the impact of subclinical hypothyroidism, defined as an elevated TSH with normal levels of free thyroxine (T_4) and triiodothyronine (T_3). Pasqualetti et al. [70] performed a meta-analysis of 13 studies evaluating the effect of subclinical hypothyroidism on a composite endpoint of incident or prevalent major neurocognitive disorder (dementia), reduced MMSE, or reduced scores on intelligence tests in order to maximize statistical power. After stratifying by age (younger than 75 years, 75 years and older), they found that the younger hypothyroid patients were significantly more likely to show cognitive impairment than controls, whereas the older group did not show this effect. The reason for the age effect is unclear, but could reflect a greater prevalence of neurocognitive decline from other causes in the older age group, obscuring the effect of subclinical hypothyroidism. In a small clinical trial of 36 middle-aged women (mean age, 52 years) with mild hypothyroidism, treatment with levothyroxine reduced their TSH and increased T_4 levels while slightly improving verbal fluency on neuropsychological testing and slightly reducing depressive symptoms on the Hamilton Rating Scale for Depression [71]. Evidence is lacking for a positive relationship between subclinical hyperthyroidism and affective state in older men and women [72, 73].

In a large Israeli cohort of persons 65 years and older, 3.8% had subclinical hypothyroidism and 1% had subclinical hyperthyroidism. After adjustment for comorbid conditions, the hazard ratios (HR) for death over 10 years of follow-up, compared to euthyroid controls, were 1.93 for subclinical hypothyroidism and 1.68 for subclinical hyperthyroidism [74]. The physiological basis for this increased mortality remains unclear, but supports the conclusion that subclinical thyroid disorders in older adults can have harmful consequences.

Teaching Point

Subclinical hypothyroidism has been associated with cognitive impairment in patients under age 75, and both subclinical hypo- and hyperthyroidism are independently associated with an increased risk of mortality. More research is needed to assess the effect of treatment on cognitive outcomes. These associations should be considered in conjunction with other clinical symptoms and medical history before a decision is made to treat.

Sex Hormones, Aging, and Cognition

Estrogen Replacement Therapy in Postmenopausal Women

Historically, hormone replacement therapy following menopause was viewed as protective against the development of major neurocognitive disorder based on epidemiologic and

laboratory evidence. Most, but not all, case-control studies found a protective effect of supplemental estrogen, with risk reductions ranging from 40% to 60%. Animal studies reinforced the biological plausibility of a protective effect of estradiol, demonstrating facilitation of hippocampal long-term potentiation, showing neuroprotection in models of ischemia and oxidative stress, and showing reduced formation of beta-amyloid and the hyperphosphorylation of tau, the signature molecular events underlying Alzheimer disease-related neurocognitive disorder [75]. Contradicting this evidence, the landmark Women's Health Initiative Memory Study (WHIMS) demonstrated a harmful effect of hormone replacement therapy. Among 4532 postmenopausal women with a uterus, aged 65 and older, and free from probable major neurocognitive disorder at baseline, roughly half were randomized to receive oral conjugated equine estrogen (CEE) plus medroxyprogesterone, while the other half received a placebo. During at least 4 years of follow-up, the rate of probable neurocognitive disorder, based on standardized neuropsychological testing, was 45 per 10,000 person-years for the hormone replacement group, compared to 22 per 10,000 person-years for the placebo group (HR 2.05, 95% CI 1.21–3.48) [76]. Similar results were found for the 2842 women without a uterus taking unopposed CEE [77]. The greater incidence of neurocognitive decline in the CEE versus placebo group became evident after 2 years and continued for the entire period of extended follow-up to 8 years in both arms of the WHIMS study [77]. Various explanations have been put forward to explain the opposing results from the randomized, controlled trials and the prior observational studies. These have included selection bias (i.e., women with healthier lifestyles might have been more likely to take hormone replacement therapy) and recall bias (i.e., women with unrecognized mild cognitive impairment might not accurately recall hormone use). In addition to WHIMS, several randomized, controlled trials of estrogen replacement therapy in women with major neurocognitive disorder due to Alzheimer disease failed to show any cognitive benefits compared to placebo [75].

An important limitation of WHIMS is that participants received *oral* estrogen. Randomized, controlled trials of hormone replacement therapy in postmenopausal women have shown that oral estrogen, regardless of the compounds assessed, increases serum markers of clotting activation while decreasing antithrombotic clotting factors. In contrast, trials using transdermal estrogen have not shown clotting activation [78]. WHIMS did not differentiate between major neurocognitive disorder due to Alzheimer disease and vascular disease, and thus it remains unknown whether the increased risk of neurocognitive disorder with hormone replacement therapy results from vascular disease, due to increased clotting from the oral formulation, or from an inherent effect of estrogen on the postmenopausal brain. It is unknown whether there is a neuroprotective effect of transdermal estrogen. The current recommendation is that hormone replacement therapy of any type should *not* be administered to women over age 65. This blanket recommendation against all hormone replacement therapy in older women because of the increased risk of neurocognitive disorder based on a clinical trial of oral hormone replacement therapy poses a conundrum for the consulting psychiatrist. It is appropriate to recommend discontinuing hormone replacement therapy in women who are being evaluated for mild or major neurocognitive disorder. If the woman is cognitively intact and taking oral hormone replacement therapy, a recommendation for discontinuation also should be made. Given the paucity of data on the long-term neurocognitive effects of *transdermal* estrogen, it is a matter of clinical judgment whether the potential benefits outweigh the potential risks for the individual patient.

Teaching Point

Based on a large randomized, controlled trial, oral estrogen replacement therapy in postmenopausal women has been associated with a roughly twofold increased risk of neurocognitive disorder, compared to placebo. Whether this increased risk is due to the activation of clotting factors resulting from hepatic metabolism of the oral estrogen remains unknown. There are insufficient data regarding the risk of neurocognitive disorder in postmenopausal women taking transdermal estrogen, which does not activate clotting factors. Current guidelines recommend against any estrogen replacement therapy in women over age 65 years.

Neurocognitive Effects of Testosterone in Older Men

Testosterone and Cognition

Data from the Baltimore Longitudinal Study of Aging (BLSA) show that total testosterone and bioavailable testosterone (approximated by the free testosterone index, calculated as total testosterone/sex hormone binding globulin) decline steadily from the third decade onward (see ◘ Fig. 1.5), such that by the 7th, 8th, and 9th decades, 20%, 30%, and 50% of men, respectively, meet criteria for hypogonadism, defined as a total testosterone of < 11.3 nmol/L (325 ng/dL) or a free testosterone index < 0.153 (total testosterone [nmol/L]/sex hormone binding globulin [nmol/L]) [79]. The frequent co-occurrence of low testosterone and cognitive decline in older men has confounded the assessment of a causal relationship between the two. In the Concord Health and Aging in Men Project (CHAMP), 853 men (mean age, 77 years at baseline) were followed for 5 years [80]. Among those free of major neurocognitive disorder at baseline, 11% experienced a significant decline in cognition, defined as a drop of ≥ 3 points on the MMSE. After adjusting for age, depression, years of education, and body mass index (BMI), changes in total testosterone, dihydrotestosterone, and calculated free testosterone were independently associated with cognitive decline. However, causality remained indeterminate because of failure to adjust for other conditions known to be associated with incident major neurocognitive disorder, such

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as hypertension and diabetes mellitus. Other longitudinal studies have shown variable associations between testosterone and cognitive decline. In 574 men between the ages of 32 and 87 years from the BLSA followed for a mean of 19.1 years, higher levels of free testosterone index (a measure of bioavailable testosterone) were associated with a reduced risk of developing major neurocognitive disorder due to Alzheimer disease. (For every 10 nmol/nmol increase in free testosterone index, there was a 0.74 hazard ratio of major neurocognitive disorder due to Alzheimer disease [81].) In a sub-study of the Osteoporotic Fractures in Men study, 1602 men aged 65 and older underwent measurements of sex steroids and changes in performance on an expanded Modified Mini Mental State Exam (3MS) and the Trails B test. Neither total testosterone nor free testosterone index was associated with cognitive decline, although the period of follow-up was relatively short, compared to the BLSA. Studies of testosterone supplementation in hypogonadal, cognitively intact men suggest that visuospatial cognition and verbal memory may be enhanced. In several small randomized trials in men with mild cognitive impairment or Alzheimer disease-related neurocognitive disorder, the effects of testosterone supplementation on cognition appear promising [82]. However, the recent Testosterone Trials (TTrials) have shed new light on the safety and efficacy of testosterone replacement for older men with low androgen. The Cognitive Function Trial, 1 of 7 planned TTrials, randomized 788 men aged 65 and older from 12 US academic medical centers to testosterone replacement titrated to a normal level for young men or to a placebo gel, also "titrated" as needed to give balanced titration schedules for the treatment and control groups. All participants were age 65 years and older, with a mean age of 72.5 years, and to be eligible, all participants had to have a serum total testosterone of < 275 ng/dL and to have a formal diagnosis of age-associated memory impairment. The principal outcome measure was verbal memory tested by delayed paragraph recall, but an additional battery of standardized self-reported questions and standardized neuropsychological tests was administered. After 1 year, verbal memory, visual memory, spatial ability, and executive function were statistically similar between the two groups, suggesting that testosterone supplementation in hypogonadal older men does not improve early cognitive loss [83]. However, the subjects with age-associated memory impairment may have represented a mixed group comprised of those beginning a progressive neurocognitive disorder and those falling within the spectrum of "normal" cognitive aging. Additionally, the duration of treatment may have been too short to discern a statistically significant difference between the testosterone and placebo groups.

Testosterone and Depression

The effects of testosterone supplementation on mood in eugonadal and hypogonadal men (regardless of age) are variable [82]. In a well-designed analysis in 278 middle-aged US male veterans (mean age, 63 years), the 2-year incidence of a diagnosed depressive disorder was 21.7% in hypogonadal men (defined as a total testosterone consistently ≤ 200 ng/dL [≤ 6.94 nmol/L] or free testosterone ≤ 0.9 ng/dL [≤ 0.03 nmol/L]), compared to 7.1% in eugonadal subjects. Compared to eugonadal subjects, the hypogonadal men were 4.2 times as likely to develop depression [84]. In a small randomized, controlled trial, hypogonadal men over age 50 years with subthreshold depression received either placebo or testosterone gel. After 12 weeks, depressive symptoms as measured on the Hamilton Rating Scale for Depression decreased significantly. In the subsequent 24-week open-label phase in which all subjects received testosterone replacement, the group originally given placebo had a significant drop in the Hamilton Rating Scale for Depression score by week 24 that was comparable to the score in the group continuing testosterone [85]. These data suggest that hypogonadism in older men is a risk factor for depression and that testosterone replacement can ameliorate depressive symptoms. However, further evidence from larger clinical trials is required before psychiatrists can routinely recommend testosterone supplementation in depressed older men. Testosterone therapy appears relatively safe and has not been shown to cause *de novo* cancer of the prostate [86]. Total testosterone and free testosterone have not been associated with incident cardiovascular disease [87] or ischemic stroke [88], although dihydrotestosterone appears to have a U-shaped relationship with the risk of ischemic stroke, with low as well as high values statistically associated with cerebrovascular accidents [88]. Recent data from the TTrials show that a year of treatment with testosterone gel was associated with significant growth of non-calcified coronary plaque volume, although there was no increase in coronary events [89]. In a retrospective cohort study, 8808 men aged 40 and older with androgen deficiency and ever prescribed supplemental testosterone (injection, oral, topical) were compared to 35,527 men never prescribed testosterone. The men who had been prescribed testosterone were 33% less likely to experience a cardiovascular outcome over a median follow-up of 3.2 years [90].

Teaching Point

In hypogonadal men, data suggest that testosterone supplementation may slightly enhance cognitive performance and may be beneficial in men with major or mild neurocognitive disorder due to Alzheimer disease, but does not improve cognitive function in age-associated memory impairment. More convincing data exist for an association between hypogonadism and depressive disorders in older men, as well as for the amelioration of depressive symptoms with testosterone replacement therapy. Based on current epidemiologic data, testosterone replacement does not increase the risk of prostate cancer or incident cardiovascular disease.

1.1.10 Clinically Relevant Age-Associated Changes in Kidney and Liver Function

For clinicians, the relevance of age-associated changes in the liver and kidney largely relates to alterations in drug metabolism and duration of action (pharmacokinetics). With aging, liver volume declines between 20% and 40% with a corresponding reduction in hepatic blood flow, such that in adults 65 years and older, blood flow is reduced to approximately 35% of that in adults aged 40 years and younger. Importantly, the mass of functioning hepatocytes declines in both structure and function, with decreased numbers and efficiency of mitochondria, leading to reductions in ATP production, polyploidy, and accumulation of lipofuscin pigments, consisting of aggregates of denatured proteins that reduce cell survival [91]. Phase I metabolism, consisting of oxidation, reduction, and hydrolysis and mediated by the cytochrome P450 family, undergoes age-related reduction in activity, although phase I metabolism may be compound-specific [92]. Phase II metabolism, consisting of glucuronidation and sulfation, is generally considered to be unaffected by aging, although changes in protein binding of drugs may influence phase II activity, contributing to reduced age-related phase II clearance of drugs like acetaminophen (paracetamol), valproic acid, and naproxen [92].

The glomerular filtration rate (GFR) begins to decline at age 30–40 at a rate of about 0.75 ml/minute/year in conjunction with a decline in renal mass and an approximately 30% loss in the number of glomeruli by age 75 years. This decrease in renal function appears to be part of normal senescence, although common conditions like hypertension, diabetes mellitus, and atherosclerosis may accelerate the decline [93]. Drugs that are cleared by the kidney consequently may require an adjustment in dosage in older persons. Serum creatinine alone poorly predicts renal function in older adults because of an age-associated decline in lean body mass and a consequent reduction in total body water. The result is an increased plasma concentration of hydrophilic drugs. Even in non-obese older adults, there is an increase in total body fat, causing an increased volume of distribution and half-life of lipophilic drugs. (See ▶ Chap. 5.) ◘ Table 1.2 summarizes age-related changes that affect the pharmacokinetics of drugs [94].

Because of the inaccuracy of using creatinine alone, several formulae have been developed to estimate GFR [95]. The Cockcroft-Gault equation (CGE) estimates creatinine clearance (Cl_{cr}) without adjustment for body surface area:

$$\mathrm{Clcr}\left(\mathrm{ml/minute}\right)=\frac{\left(140-\mathrm{age}\left[\mathrm{years}\right]\right)\times\left(\mathrm{body\ weight}\left[\mathrm{kg}\right]\right)}{0.815\times\mathrm{serum\ creatinine}\left(\mu\mathrm{mol/L}\right]}$$

(Multiply result by 0.85 for women because of average lower muscle mass.)

The CGE appears valid up to age 100 years but also tends to underestimate the Cl_{cr} in very old individuals. Compared to the gold standard of Cl_{cr} based on excretion of the ethylenediaminetetraacetic acid (EDTA), the CGE has the lowest area under the curve of the estimating equations [95]. The Modification of Diet in Renal Disease (MDRD) formula estimates GFR adjusted for a standard body surface area of 1.73m^2:

$$\mathrm{Clcr}\left(\mathrm{ml/minute}\right)=186\times\mathrm{serum\ creatinine}\left(\mathrm{mg/dL}\right)^{-1.154}\times\mathrm{age}\left(\mathrm{years}\right)^{-0.203}$$

(Multiply by 0.742 for women.) The CKD-EPI (*Chronic Kidney Disease* Epidemiology Collaboration) equation is an updated version of the MDRD formula taking into account race and sex:

$$\mathrm{Clcr}\left(\mathrm{ml/minute}\right)=\left(\frac{\alpha\times\left(\mathrm{serum\ creatinine}\left[\mathrm{mg/dL}\right]\right)}{\beta}\right)^{\gamma}\times\left(0.993\right)^{\mathrm{age}}$$

α accounts for the following values for race and sex:

Black women = 166; Black men = 164; White or other women = 144; White or other men = 141.

β takes on the following values based on sex: Females = 0.7; males = 0.9.

The exponent γ takes on the following values based on sex and serum creatinine:

Females: creatinine ≤ 0.7 mg/dL = −0.329; creatinine > 0.7 mg/dL = −1.209.

◘ **Table 1.2** Summary of age-related changes that affect the pharmacokinetics of drugs

Physiologic change	Pharmacokinetic consequence
Decreased serum albumin	Increased free fraction in plasma for highly protein-bound acidic drugs
Increased alpha-1-acid glycoprotein	Decreased free fraction of alkaline drugs
Decreased lean body mass Decreased total body water	Increased plasma concentrations of hydrophilic drugs
Increased body fat	Increased volume of distribution and $T_{1/2}$ of lipophilic drugs
Decreased hepatic blood flow	Potentially decreased first-pass metabolism
Decreased hepatic mass	Phase I metabolism (CYP oxidation, reduction, hydrolysis) slightly decreased Phase II metabolism (glucuronidation, acetylation, sulfation) *preserved*
Decreased renal blood flow and GFR	Decreased renal elimination

Adapted from Hirsch et al. [94] (With permission of Springer Nature)

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Males: creatinine ≤ 0.7 mg/dL = −0.411; creatinine > 0.7 mg/dL = −1.209.

Calculators for these formulae are available on the Internet and on applications for smart phones and tablets (e.g., MedCalc: ► http://www.medcalc.com/gfr.html).

1.1.11 Sarcopenia of Aging

The loss of muscle mass and function with aging, termed "sarcopenia," results from an imbalance between anabolic stimuli such as insulin-like growth factor and atrophy induced by activation of the ubiquitin proteasome and myostatin pathways, affecting primarily the fast-twitch (type II) motor fibers [96]. Exercise and testosterone can slow or partially reverse the sarcopenia of aging, while a sedentary lifestyle, decreased testosterone, age-associated mitochondrial dysfunction, decreased protein synthesis, reduced protein and energy intake, and chronic inflammation promote it [96]. The long-term consequence of sarcopenia is loss of mobility, with decreased gait speed, difficulty standing from a low chair or toilet, difficulty climbing stairs, easy fatigability, increased risk of falls, and frailty. These in turn lead to dependence in physical instrumental activities of daily living and eventually basic self-care tasks like transferring and bathing. The Fried construct of frailty (see ► Sect. 1.1.3), in which sarcopenia plays a major role, has been associated with a greater than fourfold risk of anxiety and depressive symptoms in community-dwelling Irish men and women age 60 years and older, after adjusting for age, sex, and history of clinical depression and anxiety requiring pharmacotherapy [97].

1.2 Case Studies

This section will use case-based studies to emphasize the impact on older adults of age-related changes in physiology, which affect the vulnerability of older adults to acute and chronic disease, adverse effects from medications, neuropsychiatric illness, including neurocognitive decline, and other diseases.

1.2.1 Case 1

Case 1 History

Mrs. A. is a 79-year-old obese widow living alone, with a long-standing history of recurrent major depressive disorder since her 40s, for which she has been on fluoxetine 20 mg daily for many years. She has been followed for hypertension since her mid-50s and 10 years ago was diagnosed with type 2 diabetes mellitus and hyperlipidemia. At the age of 72, she tripped over a curb and sustained a right radial fracture, leading to the diagnosis of osteoporosis. Worsening pain in her knees has limited her walking for several years, causing her to socialize less frequently with her friends. In the last year she has had increasing difficulty arising from her sofa and toilet, more from weakness than pain, and has sustained two falls in the bathroom, one causing her to go to the emergency department for a gash to her forehead when she fell in the shower. She is now afraid of falling and does not like to walk without her walker, but is embarrassed to be seen with it in public. For the past year, she has had swelling of the ankles that worsens during the day but resolves overnight. However, in the past 3 months the swelling has worsened and she was started on the diuretic, furosemide. Although still obese, Mrs. A. has lost 9 kg (19.8 lbs) in the last 11 months, complaining that she has lost interest in eating. Since the addition of furosemide, she has had several episodes per week of urinary incontinence, characterized by intense urgency followed by involuntary micturition if she cannot reach the bathroom in time. An echocardiogram, obtained by the consulting cardiologist, showed a normal left ventricular ejection fraction and grade II (moderate) diastolic dysfunction plus mild left atrial enlargement. A chemistry panel from the same visit revealed a creatinine of 1.2 mg/dL (106 μmol/L; normal upper limit). Mrs. A.'s incontinence, coupled by worsening vision from macular degeneration and glaucoma, has led her to limit her driving to trips to the local supermarket, and she relies upon her daughter living nearby to drive her to doctors' appointments. Because of complaints of difficulty falling and staying asleep, her primary care physician prescribed zolpidem 5 mg at bedtime as needed.

Mrs. A. calls her daughter because of worsening shortness of breath and a productive cough for 1 week, beginning 3 days after she babysat her granddaughter, who had a cold. When the daughter arrives 6 hours later, she finds her mother seated in her recliner, soaked in urine, and unable to stand without her legs buckling. She repeatedly asks her daughter where her (Mrs. A.'s) husband is, although he has been deceased for 3 years. Her daughter calls an ambulance and Mrs. A. is transported to the emergency department of the local medical center, where her medical history is accessed on the electronic medical record. Her problem list includes depressive disorder, type 2 diabetes mellitus, heart failure with preserved ejection fraction (HFpEF), stage II chronic kidney disease, osteoarthritis of the knees, osteoporosis, macular degeneration, and history of falls. Her listed medications include fluoxetine 20 mg daily, metformin 800 mg twice daily, glyburide 5 mg daily, lisinopril 40 mg daily, amlodipine 10 mg daily, oxybutynin 15 mg extended release daily, timolol ophthalmic drops 0.25% 1 drop OU daily, latanoprost ophthalmic solution 1 drop OU at bedtime, alendronate 70 mg weekly, acetaminophen (paracetamol) 325 mg/hydrocodone 5 mg tablet (1 tablet up to 3 times prn daily for knee pain), zolpidem 5 mg at bedtime prn, and an over-the-counter vitamin with lutein for her macular degeneration. Her daughter reports that her mother also regularly takes over-the-counter ibuprofen 1–2 times per day.

On examination, Mrs. A. was alert, confused, and crying because her husband could not be located. Her weight by bed scale was 81 kg (178.25 lbs) with a height of 1.5 m (4.92 ft), corresponding to a BMI of 36 kg/m^2. Her blood pressure was 166/84 mm Hg, her heart rate was 118 beats per

minute and irregularly irregular, and her respiratory rate was 22 breaths per minute with a room air oxygen saturation of 87%. A complete blood count (CBC) showed a white blood cell count of $14 \times 10^3/\mu L$ ($14 \times 10^9/L$) and a hemoglobin of 11 g/dL (110 g/L). A comprehensive chemistry panel revealed a sodium of 133 mEq/L (133 mmol/L), potassium of 3.4 mEq/L (3.4 mmol/L), magnesium of 1.5 mg/dL (0.75 mmol/L; low), a creatinine of 1.7 mg/dL (150 μmol/L; high), an arterial blood lactate of 1.07 mg/dL (0.119 mmol/L), and an elevated random blood sugar of 240 mg/dL (13.3 mmol/L). A chest roentgenogram (chest X -ray) showed a left lower lobe infiltrate with air bronchograms and interstitial edema with cephalization of her pulmonary vessels, consistent with pneumonia and acute heart failure. Her electrocardiogram (ECG) showed atrial fibrillation at a rate of 115 beats per minute with non-specific ST-T wave changes in the inferior leads. Serial troponins drawn 2 hours apart were 0.08 and 0.07 ng/mL (0.08–0.07 μg/L; upper limit of normal is 0.04 μg/L).

She is diagnosed with a left lower lobe pneumonia, atrial fibrillation, demand coronary ischemia, and delirium, and admitted to a telemetry bed. She is begun on intravenous antibiotics for a community-acquired pneumonia, metoprolol for her atrial fibrillation, and intravenous furosemide for her heart failure. Her lisinopril is held but the amlodipine is continued. She is given supplemental magnesium and potassium by mouth. A low dose of long-acting insulin glargine is ordered for bedtime administration with rapid-acting insulin aspart to be given according to a sliding scale before meals.

When evaluated by the consulting psychiatrist, she is dressed in a hospital gown with disheveled hair and appears anxious, with repeated hand-wringing. She is alert and mildly agitated (Richmond Agitation-Sedation Scale—RASS +1) and keeps interrupting the interviewer to ask where her husband is. She intermittently becomes distracted and yells, "What are you doing to me? I want my husband!" while she tries to get out of bed. Her responses to questions are disorganized and frequently unrelated to the question, and she incorrectly states the year is 1990 and that she's at the police station. When she is asked to tap her hand on the bed rail when she hears the letter "A" in a string of letters, she claps her hands to all the letters and continues to clap her hands when asked why she is in the hospital. The psychiatrist confirms the diagnosis of delirium and requests a 24-hour sitter and a bed alarm.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What age-related physiologic changes contributed to her functional decline?

? Question 2. What age-related changes contributed to the development of urinary incontinence, inability to walk, and delirium because of a pneumonia?

Case 1 Answers

Case 1 Answer 1 (Question 1—What age-related physiologic changes contributed to her functional decline?)

It is difficult to disentangle disease-associated contributors to her functional decline from age-related physiologic changes, in part because disease and age-related changes may worsen each other. Mrs. A. suffered from multimorbidity, including diabetes mellitus, hypertension, hyperlipidemia, and obesity ("metabolic syndrome"), each of which is common among older adults and considered to be an accelerator of the normal aging process. Her metabolic syndrome predisposed her to atherosclerosis and ischemic heart disease. She also had osteoarthritis, made worse by her obesity. Atherosclerosis and diabetes mellitus contributed to underlying inflammation that may in turn have contributed to her frailty syndrome. Her obesity and hypertension likely played a role in her diastolic dysfunction and her risk of atrial fibrillation. Her medical conditions, to which were added declining visual acuity from macular degeneration and glaucoma, contributed as physiologic stressors to her depressive disorder. Her medical conditions led her to become deconditioned, further exacerbating her isolation and depressive disorder.

These medical conditions would not have had the same impact on her functional status or trajectory of functional decline were it not for underlying physiological changes caused by the aging process. From a cardiovascular standpoint, age-associated diastolic dysfunction already predisposed her to congestive heart failure. Although not considered part of normal aging, her rapid atrial fibrillation more readily led to congestive heart failure because of age-associated ventricular stiffness. She did not have underlying lung disease, but her obesity (BMI of 36 kg/m^2) likely led to obesity hypoventilation syndrome and predisposed her to respiratory failure. On top of that, age-associated pulmonary changes independently added to her pulmonary risk by being associated with loss of alveolar cells (and therefore reduced oxygen transport) and reduced elastic recoil of the airways, leading to a reduced FEV1, FVC, and closing volume. This chapter does not discuss the aging immune system, but lower immune defenses combined with age-associated pulmonary changes placed her at higher risk for pneumonia.

Postmenopausal estrogen deprivation contributed to Mrs. A.'s osteoporotic radial fracture, but the fracture would not have taken place without a fall. Allegedly she tripped on a curb, but other age-associated factors may have contributed. Age-related slowing of myelinated nerve conduction may have contributed to her loss of balance. In the very old, the motor response to loss of balance is delayed due to fewer motor units in the spinal cord and fewer and thinner motor axons. The coarser movements caused by larger motor units (surviving motor neurons innervating relatively more muscle fibers) likewise may have contributed to the inadequacy of her motor response to the trip. If she had just gotten out of a car, orthostatic hypotension, affecting approximately 30% of individuals age 75 and

older, may have caused light-headedness that contributed to her stumble. Her weaker legs may not have been able to compensate for her loss of balance. The age-associated loss of lean body mass (sarcopenia) also contributed to her deconditioning and difficulty walking and arising from low seats. Age-associated central sensitization to pain may have exacerbated her perception of pain in her knees, further limiting her mobility. If Mrs. A. had not eaten for many hours, the glyburide she was taking for diabetes mellitus could have contributed to hypoglycemia, adding to any light-headedness she might have experienced prior to the fall and affecting her balance at home. Because it is renally cleared, glyburide would be expected to have a longer half-life in older individuals because of the age-associated decline in renal mass and GFR. Mrs. A. regularly took ibuprofen, a nonsteroidal anti-inflammatory drug (NSAID), for control of her arthritis pain. NSAIDs inhibit cyclooxygenases 1 and 2, reducing the synthesis of prostaglandins that dilate the afferent arteriole of the kidney in order to maintain GFR. With fewer functioning nephrons, the kidneys of older adults are more susceptible to a significant reduction in GFR due to NSAIDs than younger kidneys. With her intravascular volume reduced by daily furosemide, blood flow to her afferent kidney arterioles already may have been reduced. The addition of over-the-counter ibuprofen consequently may have led to renal injury.

Age-related changes in pharmacodynamics (a drug's actions within the body; see ▶ Chap. 5) may have contributed to Mrs. A.'s imbalance and fear of falling. Zolpidem (which acts on central GABA receptors) and hydrocodone both have been associated with falls. Oxybutynin, an anticholinergic medication for urinary urgency, affects central histamine-1 receptors; geriatric patients are more susceptible to delirium from centrally acting anticholinergic medication, as well as from opioids.

Case 1 Answer 2 (Question 2—What age-related changes contributed to the development of urinary incontinence, inability to walk, and delirium because of a pneumonia?)

Although poorly understood, normal aging is associated with decreasing resilience to physiological stressors, including behavioral (e.g., posttraumatic stress disorder), environmental (e.g., urinary tract infection), and internal (e.g., flare of an autoimmune disorder) stressors. Some of this loss of resilience has been attributed to damage at the organ, cellular, and molecular levels. For example, repeated exposure to reactive oxygen species from chronic inflammation or environmental sources may damage DNA, which in the mitochondria is irreparable, leading to age-associated mitochondrial dysfunction. Without resilience within and among interacting organs to maintain homeostasis (normal functioning) in the presence of physiological stressors, organs can decompensate, even those not directly linked to the affected organ. Thus, a pneumonia or urinary tract infection might lead to incontinence, delirium, and falls. The search for a common pathway for multiple organ-system dysfunction, such as increased circulating levels of cytokines, continues.

Case 1 Analysis Mrs. A. likely meets the phenotypic definition of frailty, using ≥ 10% involuntary weight loss in 1 year as a low-weight equivalent (as described in the original Fried criteria) [98]. We should be concerned about a relapse of depression, given the association of frailty with incident depression. Her frailty should raise concern about future cognitive impairment and prompt regular screening. As is so often the case in the geriatric population, risk factors may be multifactorial. Apart from her history of type 2 diabetes mellitus and hypertension, both risk factors for ischemic vascular neurocognitive disorder, she has new-onset atrial fibrillation and risk of vascular neurocognitive disorder from thromboembolic ischemic stroke. Moreover, her delirium increases her risk of cognitive decline [99]. (Also see *Case 2 Analysis* for a synopsis of age-related physiology and pathology.)

1.2.2 Case 2

Case 2 History

Dr. M. is an 84-year-old retired orthopedic surgeon who is referred to geriatric psychiatry by his primary care internist for evaluation of forgetfulness and an increase in irritability and angry outbursts, as reported by his wife. The patient cancels his first appointment, but makes his rescheduled appointment after being promised by his internist that this is a routine screening evaluation for cognitive function to ensure that it is still safe for him to drive.

Dr. M. is accompanied by his wife. He is a tall, lean man wearing an expensive cardigan with visible food stains. Although clean-shaven, there are several unshaven patches below his mandible and beneath the chin. The belt on his khaki slacks is pulled to the second-to-last notch. He is polite but a bit haughty and asks the psychiatrist where he trained, making a point that he himself trained at McGill and the Mayo Clinic and published more than 75 articles during his career. Dr. M. denies that there is anything wrong with his memory beyond what would be expected with a man of his age. Behind him his wife shakes her head vigorously.

Review of Dr. M.'s past medical history reveals that he has a history of rate-controlled chronic atrial fibrillation, peripheral vascular disease with stable claudication, an elevated but stable prostate-specific antigen of 11 ng/mL, benign prostatic hypertrophy, and spinal stenosis in the lumbar region with moderately severe chronic low back pain intermittently radiating down the back of his left leg. He smoked 1/2 pack of cigarettes per day for 40 years but quit at age 60. He reports drinking 1 glass of wine most nights with dinner. On review of systems, Dr. M. admits to feeling tired much of the time and getting fatigued after walking several blocks. He denies dyspnea on exertion, edema, orthopnea, paroxysmal nocturnal dyspnea, or chest pain or pressure.

His medications include metoprolol succinate 50 mg daily, apixaban 5 mg daily, atorvastatin 40 mg daily, tamsulosin 0.8 mg at bedtime daily, hydrocodone/acetaminophen (paracetamol) 5 mg/325 mg three times a day as needed for back pain, and gabapentin 300 mg at bedtime.

On cognitive status testing with the Montreal Cognitive Assessment (MoCA), he scores 25 out of 30, failing to draw a cube or to set the time correctly on clock draw. He fails one simile because his interpretation is too concrete, and he misses 2 of 5 items on recall while correctly identifying them after cueing. His Geriatric Depression Scale score is 2 out of 15 (no significant depressive symptoms), but on the informant-based Cornell Scale for Depression in Dementia, completed by his wife, his score is 14 out of 38 possible points, suggestive of possible depressive disorder. He shows no abnormal motor or cranial nerve findings on neurological exam, and there is no cogwheel rigidity. On the Up and Go Test, he has to rock in his seat and push off with his hands to stand up and then has to hold on to his wife's shoulder for 10 seconds before starting to walk. His wife remarks that this often happens when he stands up quickly and states he has fallen twice getting out of bed to urinate at night. Walking in the hall, Dr. M.'s gait shows normal stride length and arm swing, although his posture is slightly stooped. However, he is slow to turn 180°, doing so *en bloc* with 4 steps and having to steady himself against the wall with one hand.

Recent laboratory studies reveal normal electrolytes except for a blood urea nitrogen of 26 mg/dL (9.28 mmol/L; high) and a serum creatinine of 1.33 mg/dL (117.6 μmol/L; high). His albumin was 3.2 g/dL (32 g/L; low) and his hemoglobin was 11.3 g/dL (113 g/L; low). Thyroid-stimulating hormone and vitamin B_{12} levels were within normal limits. Brain magnetic resonance imaging performed a month earlier showed mild cortical atrophy and scattered periventricular white matter changes both described as consistent with age.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. What age-related changes could be contributing to Dr. M.'s impaired cognitive performance and depressive symptoms?

? Question 2. Is there any additional work-up that would be helpful?

? Question 3. What recommendations would you make to the primary care physician?

Case 2 Answers

Case 2 Answer 1 (Question 1—What age-related changes could be contributing to Dr. M.'s impaired cognitive performance and depressive symptoms?)

Although he does not carry a high burden of white matter disease, cerebrovascular disease must be considered in the differential diagnosis, especially given the history of atherosclerotic peripheral vascular disease. Although there is no evidence of prior stroke, chronic atrial fibrillation has been associated with more rapid cognitive loss compared to paroxysmal atrial fibrillation or absence of arrhythmia. In developing a differential diagnosis, there are important clues in the history and exam. He reports feeling weak and has difficulty arising from a chair. He also has to steady himself on first standing, has fallen recently, and was unsteady when turning on the Up and Go Test. Orthostatic hypotension, which affects approximately 30% of older individuals after age 75, may be occurring. His weakness may be multifactorial. With aging there is loss of lean body mass (muscle), leading to reduced physical performance, but low testosterone may contribute to this weakness and affects approximately 50% of men in his age group. Hypogonadal levels of testosterone have been associated both with cognitive impairment and depressive symptoms, although there is insufficient clinical trial data to support treating *asymptomatic* hypogonadism. The patient's mental status also could be affected by medications, including the gabapentin and opioid. His wine consumption also may be a confounder and could be greater than he admits.

Case 2 Answer 2 (Question 2—Is there any additional work-up that would be helpful?)

Orthostatic vital signs are clearly indicated and should be obtained lying, sitting, and after standing for approximately 4 minute. Although the heart rate in atrial fibrillation can respond to sympathetic stimuli, he is on a beta-blocker and therefore might not increase his heart rate. A serum total testosterone and free (active) testosterone would be appropriate laboratory tests. The latter can be calculated by using the total testosterone, serum albumin, and the sex hormone binding globulin (see ► section Testosterone and Cognition). Adding free testosterone is important, because sex hormone binding globulin increases with age and thus may blunt the expected decline in total testosterone. A low albumin, to which approximately 50% of circulating testosterone is bound, allows more testosterone to be in the unbound, free state, although testosterone's binding to albumin is weaker than to sex hormone binding globulin. If a recent electrocardiogram (ECG) is not available, one should be obtained in anticipation of recommending an SSRI or SNRI antidepressant.

Case 2 (Continued)

Orthostatic vital signs reveal a supine blood pressure of 110/72 mmHg; pulse of 64 beats per minute and irregular, dropping to 92/58 mmHg; and pulse of 68 beats per minute and irregular, after standing for 4 minute. An ECG shows atrial fibrillation at an average rate of 68 beats per minute and a QTc of 450 milliseconds, at the upper limits of normal for a man. A week later his laboratory results return, showing a total testosterone of 190 ng/dL (6.59 nmol/L) and confirming a diagnosis of hypogonadism.

Case 2 Answer 3 (Question 3—What recommendations would you make to the primary care physician?)

Because the opioid and gabapentin potentially could contribute to his cognitive impairment, it would be ideal if they

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could be stopped, replacing them with safer alternatives. It is appropriate to make a recommendation to start acetaminophen (paracetamol) 650 mg 3–4 times daily and to reserve the opioid for severe, breakthrough pain. (See also ► Chap. 16.) In general, older adults have slightly higher nociceptive thresholds but have worse pain tolerance than younger individuals due to central sensitization. SSRIs and SNRIs may help to reverse the central sensitization. Dr. M. is on medication that may exacerbate orthostatic hypotension, including the selective alpha-blocker tamsulosin and metoprolol. Gabapentin may contribute to "dizziness" (see ► Chap. 5), which is problematic, given his fall history and orthostatic hypotension. Consideration therefore could be given to starting an SNRI like duloxetine, which could replace his gabapentin for the neuropathic pain. His QTc is borderline, but an SNRI is not contraindicated, provided the QTc is monitored during escalation of therapy.

Given the potential contributors to Dr. M.'s impaired cognition, including depression, it may be premature to diagnose his neurocognitive disorder or to prescribe a cognitive enhancer like a cholinesterase inhibitor. The prevalence of neurocardiovascular instability with an impaired baroreceptor reflex rises in advanced old age and is increased in neurodegenerative disorders like Alzheimer disease and Lewy body disease. The cholinesterase inhibitors can induce bradycardia and have been associated with a greater risk of falls (see also ► Chap. 5). His heart rate presently is in the 60s and does not increase despite a significant drop in blood pressure. It would be appropriate to recommend physical therapy for strengthening, balance training, a home safety check, and assessment for durable medical equipment (see ► Chap. 2).

Case 2 Analysis As seen in Case 2 (also illustrated in Case 1), changes in physiology accompany aging and directly affect the vulnerability of older adults to acute and chronic disease, adverse effects from medications, and neuropsychiatric illness, including neurocognitive disorders. As adults enter their 7th decade and beyond, *reduced resilience* at the organ-system and cellular levels to physiological stressors like infection can lead to concurrent dysfunction in multiple organ systems. Loss of resilience contributes to *frailty*, a construct that has been defined by investigators as a quantifiable measure and which is both linked to, yet distinct from, disability and multiple comorbidities (multimorbidity). Becoming frail has been associated with an increased risk of depression and neurocognitive decline.

Markers of low-level chronic inflammation increase with age, and chronic inflammation may contribute to the development of frailty as well as to depression. Depression, in turn, predicts development of disability, even after adjustment for demographic and lifestyle variables as well as comorbidity. Chronic inflammation and aging itself have been linked to shortening of telomeres, and the loss of these protective repeated nucleotide sequences at the ends of chromosomes contributes to alterations in DNA and resulting transcription and translation defects, leading to cellular apoptosis. In epidemiological studies, robust associations have been found between telomere length and depression, posttraumatic stress disorder, and anxiety, as well as between telomere length and cognitive impairment and the markers of Alzheimer disease—hyperphosphorylated tau and deposits of beta-amyloid.

As in Case 2 (as well as in Case 1), alterations in organ-system structure and function occur as part of the aging process. In the brain, both gray and white matter are lost, with a 0.45% per year drop in whole brain volume starting in the 8th decade. These changes are accompanied by declines in problem solving, processing speed, episodic memory, rate of learning, memory retrieval, verbal fluency, three-dimensional perception, and executive functioning; these age-associated deficits fall under the rubric of *age-associated memory impairment,* considered part of normal aging. The peripheral nervous system also experiences a decline, due both to normal aging and to deterioration related to chronic diseases like osteoarthritis. Motor function declines due to loss of motor units and slowed conduction, as well as to loss of muscle (lean body) mass, termed *sarcopenia.* The consequences of these peripheral changes are reduced strength, declining physical performance, reduced balance, and an increased risk of falls. Reductions in the numbers of peripheral pain fibers in old age slightly increase the threshold for pain, but once pain is detected, older adults tend to experience greater pain, compared to younger individuals. This is due, in part, to *central sensitization* to pain, which is poorly understood but believed related to intracerebral inflammatory processes mediated by microglia and inflammatory cytokines.

With aging, the heart's ventricles become stiffer and take longer to relax during diastolic filling (termed diastolic dysfunction). A rapid heart rate, as seen in supraventricular arrhythmias like atrial fibrillation, consequently is less well tolerated and can lead to heart failure. Even in the absence of clinical strokes, persistent atrial fibrillation is more likely than paroxysmal atrial fibrillation to lead to declines in neurocognitive performance, and anticoagulation for atrial fibrillation does not reduce the risk for major neurocognitive decline. Neurocardiovascular instability occurs frequently in old age, contributing to orthostatic hypotension, which affects nearly 20% of persons aged 65 and older. Age-associated changes occur in the cardiac conduction system, with loss of pacemaker cells in the sinoatrial node and increases in the PR, QRS, and corrected QT intervals. Many psychotropic medications can aggravate changes in one or more of these cardiac intervals, increasing the risk of life-threatening arrhythmias and cardiac events.

In the lung, aging mimics the changes seen in chronic obstructive pulmonary disease (COPD), with connective-tissue changes resulting in loss of alveoli and elastic recoil of the smaller airways, leading to relatively earlier collapse of airways during forced and tidal expiration. The thorax also becomes stiffer with age. These changes increase the vulnerability of older adults to respiratory compromise and failure.

Hypothyroidism, although not part of normal aging, is common, affecting nearly 5% of men and 8% of women by

age 70 years. There have been few studies of the effects of subclinical hypothyroidism in the geriatric patients; thus far, robust evidence is lacking for an effect on either cognition or depressive symptoms. The loss of circulating estradiol after menopause has been linked with subtle and mild neurocognitive deficits that are clinically insignificant, but oral hormone replacement therapy has been associated with a roughly twofold increase in risk of neurocognitive decline, based largely on data from the Women's Health Initiative. In men, testosterone and bioavailable (free) testosterone decline beginning in the third decade, such that by age 70, about 20% of men are hypogonadal. Some but not all epidemiological studies evaluating testosterone and cognition suggest a possible relationship between hypogonadism and risk of neurocognitive disorder. Hypogonadal men have an approximately fourfold risk of developing depression over 2 years, compared to men with normal testosterone levels, after adjustment for confounders. Preliminary data from small, randomized controlled trials suggest that testosterone supplementation in mild cognitive impairment or early Alzheimer disease-related neurocognitive disorder may slightly improve cognitive function. Randomized trial data suggest that testosterone replacement in middle-aged and older hypogonadal men can significantly improve depressive symptoms on standardized depression scales. However, more clinical trials are necessary before testosterone replacement therapy can be recommended for hypogonadal men with either an early neurocognitive disorder or depression.

The kidney and liver are the principal sites of drug metabolism, and both organs undergo age-related declines in function. Among persons aged 65 and older, hepatic blood flow is reduced by approximately 65%, compared to adults aged 40 and younger. Mild reductions in the phase I metabolism of drugs—oxydation, reduction, and hydrolysis, principally by the P450 cytochrome family—can affect the concentration and half-life of drugs undergoing phase I metabolism. In contrast, phase II metabolism, consisting of glucuronidation and sulfation, remains largely unaffected, although changes in protein binding may affect the phase II metabolism of some drugs, notably acetaminophen (paracetamol), valproic acid, and naproxen. In the kidneys, the glomerular filtration rate (GFR) begins to decline around the age of 30 as glomeruli drop in number. Because creatinine is derived from the breakdown of muscle and muscle mass declines with aging, serum creatinine may remain within normal limits in spite of a declining GFR. Equations have been derived to estimate GFR in older adults, including the Cockcroft-Gault equation, the MDRD formula, and an updated version of the MDRD called the CKD-EPI. These equations have been provided in the text and are available as online calculators and as applications for handheld computers. Age-related changes in body composition affect drug distribution as well as elimination. Hydrophilic drugs are distributed in the body's water compartment. The age-associated decline in lean body mass is accompanied by a decline in total body water, resulting in an increased plasma concentration of hydrophilic drugs. As lean body mass (principally muscle) declines, there is an increase in total body fat, causing an increased volume of distribution and half-life of lipophilic drugs.

Age-associated changes in physiologic function must be recognized and factored into the assessment of risk factors for and treatment of neuropsychiatric morbidity in older patients. Most older patients seen by psychiatrists will have multiple comorbidities treated by multiple medications. The dynamic interplay between medical and psychiatric comorbidities and the potential interactions and adverse effects of medications due to age-associated physiologic changes contribute to the challenges faced by the geriatric psychiatrist.

1.3 Key Points: Physiology and Pathology of Aging

- Frailty is a quantifiable measure which is both linked to, yet distinct from, disability and multiple comorbidities (multimorbidity); becoming frail has been associated with an increased risk of depression and neurocognitive decline.
- Markers of low-level chronic inflammation increase with age, and chronic inflammation may contribute to the development of frailty as well as to depression.
- Depression, in turn, predicts development of disability, even after adjustment for demographic and lifestyle variables as well as comorbidity.
- Chronic inflammation and aging itself have been linked to shortening of telomeres, and the loss of these protective repeated nucleotide sequences at the ends of chromosomes contributes to alterations in DNA and resulting transcription and translation defects, leading to cellular apoptosis.
- Robust associations have been found between telomere length and depression, posttraumatic stress disorder, and anxiety, as well as between telomere length and cognitive impairment and the markers of Alzheimer disease-related neurocognitive disorder.
- Alterations in organ-system structure and function occur as part of the aging process.
- In the brain, both gray and white matter are lost, with a 0.45% per year drop in whole brain volume starting in the 8th decade.
- The peripheral nervous system experiences a decline, due both to normal aging and to deterioration related to chronic diseases like osteoarthritis, while motor function declines due to loss of motor units and slowed conduction, as well as to loss of muscle (lean body) mass, termed sarcopenia.
- Reductions in the numbers of peripheral pain fibers in old age slightly increase the threshold for pain, but once pain is detected, older adults tend to experience greater pain, compared to younger individuals.
- With aging, the heart's ventricles become stiffer and take longer to relax during diastolic filling (termed diastolic dysfunction).
- Neurocardiovascular instability occurs frequently in old age, contributing to orthostatic hypotension, which

affects nearly 20% of persons aged 65 and older. Many psychotropic medications can aggravate changes in one or more of these cardiac intervals, increasing the risk of life-threatening arrhythmias and cardiac events.
- In the lung, connective-tissue changes result in loss of alveoli and elastic recoil of the smaller airways, leading to relatively earlier collapse of airways during forced and tidal expiration. The thorax also becomes stiffer with age.
- Hypothyroidism, although not part of normal aging, is common, affecting nearly 5% of men and 8% of women by age 70 years.
- The loss of circulating estradiol after menopause has been linked with subtle and mild neurocognitive deficits that are clinically insignificant, but oral hormone replacement therapy has been associated with a roughly twofold increase in risk of neurocognitive decline, based largely on data from the Women's Health Initiative.
- Testosterone and bioavailable (free) testosterone decline beginning in the third decade, such that by age 70, about 20% of men are hypogonadal. More clinical trials are necessary before testosterone replacement therapy can be recommended for neurocognitive disorder or depression.
- The kidney and liver are the principal sites of drug metabolism, and both organs undergo age-related declines in function.
- Age-associated changes in physiologic function must be recognized and factored into the assessment of risk factors for and treatment of neuropsychiatric morbidity in older patients.

1.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following contributors to reduced physical performance in older adults is *not* part of normal physiologic aging?

A. Loss of lean body mass
B. Age-associated thyroid dysfunction
C. Mitochondrial dysfunction
D. Age-associated changes in the cardiac conduction system
E. Decreased number of motor units in the anterior horn of the spinal cord

Answer: B

Thyroid disorders are not part of normal aging, although the prevalence of hypothyroidism rises after age 60 and affects approximately 5% of men and 8% of women by age 70. Lean body mass declines from about the age of 30. Mitochondrial DNA is not repaired, and damage from free radicals and other toxic insults reduces the number and ATP production of mitochondria. Age-associated changes in the conduction system include prolongation of the PR, QRS, and QTc intervals, and maximum exertional heart rate declines steadily with age, which can be estimated with the formula: Maximum heart rate = 220-(age in years). With aging, the number of motor units declines, while the size of the motor units (which refers to the number of myocytes innervated by the motor axon) increases. Therefore, the correct answer is statement B.

MCQ 2. Which of the following statements regarding drug metabolism in older adults is true?

A. Referring to Case 2, Dr. M. had a serum creatinine of 1.33 mg/dL (117.6 μmol/L). Because of his tall height and lean body habitus, Dr. M.'s serum creatinine of 1.33 mg/dL reflects mild chronic kidney disease, which should not significantly affect the elimination of renally cleared drugs.
B. Because of age-related changes in hepatic function, all drugs principally metabolized by the liver experience delayed elimination in older adults.
C. Men and women experience similar changes in hepatic and renal clearance of drugs in old age, and no adjustment for sex is therefore necessary for estimating the creatinine clearance in men and women.
D. Age-associated prolongation in the elimination of renally cleared drugs is a result of a decline in the glomerular filtration rate (GFR) from loss of glomeruli and reduced renal mass.
E. Total body water increases with age, as demonstrated by the increased incidence of peripheral edema in older patients.

Answer: D

The GFR declines at the rate of approximately 0.75 ml/minute/year starting between the ages of 30 and 40 as a result of loss of glomeruli and renal mass. Dr. M.'s serum creatinine of 1.33 mg/dL translates into an estimated creatinine clearance (Cl_{cr}) of 41 ml/minute using the MDRD equation, placing him in chronic kidney disease stage 3B, or moderately severe chronic renal insufficiency. Because of the loss of muscle mass with aging, serum creatinine in older adults underestimates renal function. Consequently, a validated equation like the MDRD must be used to estimate the Cl_{cr}. Therefore, statement D is the correct answer. In the liver, phase I metabolism of drugs, consisting of oxidation, reduction, and hydrolysis, declines with age *pari passu* with reductions in the mass, structure, and function of hepatocytes. However, for the most part phase II metabolism (glucuronidation and sulfation) remains unaffected. Because women have a smaller muscle mass than men, an adjustment for female sex is required for estimating the GFR. Total body water declines with age because most of the body's water is contained in soft tissues like muscle. Peripheral edema is more commonly seen in older patients because of age-related dysfunction of the valves inside large lower-extremity veins, leading to venous stasis, as well as to the increased prevalence of heart failure in older adults.

MCQ 3. Which of the following statements about the aging nervous system is *not* true?

A. All cognitive skills, including memory, fund of knowledge, problem solving, object perception, and executive functioning, decline after the age of 70, resulting in a corresponding rise in the incidence of degenerative neurocognitive decline.
B. Myelinated sensory nerve fibers conduct signals more slowly in older adults, contributing to problems with balance.
C. The loss of muscle mass with aging is accompanied by a greater dropout of fast-twitch fibers than slow-twitch fibers.
D. The increased prevalence of orthostatic hypotension in older adults is a direct consequence of age-related changes in neurohumoral responsiveness.
E. Small vessel ischemia within the cerebral cortex contributes to the production of beta-amyloid formation.

Answer: A

Fund of knowledge, vocabulary, attention, object perception, ability to abstract, procedural (motor) memory, automatic memory, and general skills and knowledge tend to be preserved with aging (see Table 1.1). In contrast, problem solving, processing speed, episodic memory, rate of learning, memory retrieval, verbal fluency, three-dimensional perception, and most domains of executive functioning decline. Thus, statement A is untrue. Myelinated sensory fibers as well as motor axons tend to conduct signals more slowly, leading to slower perception of and motor response to sensory stimulation. This accounts in part for a decrement in balance in older adults, as evidenced by increased postural sway when standing with feet together and eyes closed, compared to younger adults. Fast-twitch (type II) muscle fibers experience a greater loss than slow-twitch (type I) muscle fibers, contributing to the impaired motor response to postural disequilibrium. With aging, neurohumoral changes directly lead to neurocardiovascular instability and impaired baroreceptor responsiveness, contributing to orthostatic hypotension. Research has demonstrated that chronic white matter ischemia can provoke the production of intracerebral beta-amyloid, which therefore is not a pathognomonic feature of major neurocognitive disorder due to Alzheimer disease.

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Comprehensive Geriatric Assessment

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2

2.1 Background

2.1.1 Overview

Comprehensive geriatric assessment is defined as a multidisciplinary diagnostic and treatment process that identifies medical, psychosocial, and functional limitations of a frail older person in order to develop a coordinated management plan [1]. The geriatric assessment differs from a standard medical evaluation by emphasizing functional capacity, quality of life, and a holistic approach to the older adult. It requires evaluation of multiple issues, including physical, cognitive, and other psychiatric components, as well as social, financial, environmental, and other components that influence an older adult's health [2]. In many settings, the comprehensive geriatric assessment process relies on a core team consisting of a clinician, nurse, and social worker and may also draw upon an extended team of physical and occupational therapists, nutritionists, pharmacists, dentists, and other clinicians. Core components of comprehensive geriatric assessment that should be evaluated during the assessment process are as follows: cognition, mood, functional ability, physical health, medication review, and social supports [1, 2].

2.1.2 Cognition and Mood

Early diagnosis of neurocognitive, depressive, anxiety, and other psychiatric disorders can be beneficial in facilitating timely access to services and medications. In addition, it can also help in the management of other physical and functional issues. Assessment of cognition and mood falls within the mental status examination, and psychiatrists will already be familiar with the common screening tests, diagnoses, and management.

2.1.3 Functional Ability

Functional status refers to a person's ability to perform tasks required for daily living and is a key component of the geriatric assessment. This information is important for planning, for monitoring response to therapy, and for determining prognosis. Activities of daily living (ADL) are tasks of self-care and include dressing, bathing, toileting, transferring, continence, and feeding. Instrumental activities of daily living (IADL) are tasks that are required to live independently (e.g., housework, meal preparation, medication administration, managing finances, and using a telephone and other communications devices). Deficits in the ability to safely complete tasks may signal a worsening disease process or the need for additional assistance.

Teaching Point

The level of functional impairment may be determined by self-report, proxy report, and/or direct observation. Two commonly used instruments to assess functional ability include the Katz ADL scale (Table 2.1) and the Lawton IADL scale (Table 2.2) [3, 4].

2.1.4 Physical Health

The geriatric assessment incorporates all aspects of a conventional medical history as well as topics specific to older adults, including vision, hearing, urinary/fecal continence, nutrition, fall prevention, and polypharmacy.

Vision and Hearing

Common causes of visual impairment in older adults include presbyopia, cataracts, age-related macular degeneration, glaucoma, and diabetic retinopathy [5]. Presbycusis is a common chronic condition in older adults affecting one-

Table 2.1 Basic activities of daily living [3]

Function	Independent, no difficulty	Independent but having some difficulty	Independent, having lots of difficulty	Can't do	Getting some help	Getting lots of help	Who helps?	Cause(s) for difficulty or dependence
Bathing								
Dressing								
Toileting								
Transfer								
Feeding								

Instructions: Place a check in each column that characterizes the patient. If the patient cannot perform or is having difficulty with a self-care task, ask the patient why he or she is having difficulty and who helps with the task. Patients who cannot perform or have lots of difficulty with a task, and who do not have someone who regularly assists them with it, have an unmet care need and may need referral to the social worker

Table 2.2 The Lawton Instrumental Activities of Daily Living Scale [4]

	Score
A. *Ability to use telephone*	
1. Operates telephone on own initiative; looks up and dials numbers	1
2. Dials a few well-known numbers	1
3. Answers telephone but does not dial	1
4. Does not use telephone et all	0
B. *Shopping*	
1. Takes care of all shopping needs independently	1
2. Shops independently for small purchases	0
3. Needs to be accompanied on any shopping trip	0
4. Completely unable to shop	0
C. *Food preparation*	
1. Plans, prepares, and serves adequate meals independently	1
2. Prepares adequate meals if supplied with ingredients	0
3. Heats and serves prepared meals or prepares meals but does not maintain adequate diet	0
4. Needs to have meals prepared and served	0
D. *Housekeeping*	
1. Maintains house alone or with occasional assistance	1
2. Performs light daily tasks such as dishwashing, bed making	1
3. Performs light daily tasks but cannot maintain acceptable level of cleanliness	1
4. Needs help with all home maintenance tasks	1
5. Does not participate in housekeeping tasks	0
E. *Laundry*	
1. Does personal laundry completely	1
2. Launders small items, rinses stockings, etc.	1
3. All laundry must be done by others	0
F. *Modes of transportation*	
1. Travels independently on public transportation or drives own car	1
2. Arranges own travel via taxi, but does not otherwise use public transportation	1
3. Travels on public transportation when assisted or accompanied by another	1
4. Travel limited to taxi or automobile with assistance of another	0
5. Does not travel at all	0
G. *Responsibility for medications*	
1. Is responsible for taking medication in correct dosages at correct time	1
2. Takes responsibility if medication is prepared in advance in separate dosages	0
3. Is not capable of dispensing own medication	0
H. *Ability to handle finances*	
1. Manages financial matters independently (budgets, writes checks, pays rent and bills, goes to bank), collects, and keeps track of income	1
2. Manages day-to-day purchases but needs help with banking and major purchase	1
3. Incapable of handling money	0

Instructions: Circle the scoring point for the statement that most closely corresponds to the patient's current functional ability for each task

third of individuals over age 65 and is characterized by loss of acuity to high-frequency sounds that can affect comprehension of sibilant ("hissing") sounds like "sh" and "ch." Poor vision and hearing can adversely affect older adults' independence, can lead to isolation and loss of pleasurable stimulation, and have been associated with depressive symptoms [6]. The whispered voice test is an easy test to perform at the bedside to ascertain how well the patient can hear the examiner, with sensitivities and specificities ranging from 70 to 100% [7]. To perform the whispered voice test, the clinician should stand at arm's length behind the patient and whisper a combination of numbers and letters that the patient is asked to repeat. With high-frequency-loss presbycusis, lower-pitched, concussive tones like "k" and "d" may be heard better than high-pitched, sibilant ones. Thus, asking the patient to repeat a sibilant-heavy phrase like, "*Sh*e was *ch*astised at *ch*urch for *ch*anting and *sh*outing and was *hu*shed," may help uncover high-frequency hearing loss. It is not uncommon for family members to express concern over a patient's memory when, in fact, the patient could not hear properly. Older patients who report complex visual hallucinations without other signs or symptoms of psychosis or major neurocognitive disorder should be screened for visual impairment. Complex visual hallucinations in the presence of substantial visual impairment characterize the Charles Bonnet syndrome. There has been debate whether the Charles Bonnet syndrome represents a *forme fruste* of a major neurocognitive disorder, but the research to date has been inconclusive because of the lack of adequately powered prospective studies [8].

Urinary Incontinence

Urinary incontinence affects approximately 15–30% of community-dwelling older adults, and its prevalence rises to 50–75% of persons in institutions. This symptom often goes unreported due to a reluctance to discuss the condition. Urinary incontinence can have significant medical and psychosocial consequences, including urinary tract infections, decubitus ulcers, and restriction of activities.

Teaching Point
In many cases, urinary incontinence may be a key feature in deciding upon nursing home placement.

Urinary incontinence, frequently but inconsistently, has been associated with depressive disorders in older women, depending upon the incontinence screening instrument used and the population studied [9]. Given its potential psychosocial impact, urinary incontinence can be an important, potentially treatable contributor to depressive symptoms. Screening for its presence should be performed when a depressive disorder has been diagnosed in an older adult, especially an older women. Because of the sensitivity of the topic, discrete introductory questions are advisable, followed by more directed questions utilizing a brief, validated screening instrument like the Incontinence Severity Index [10] (see ◘ Table 2.3). An assessment of urinary incontinence should include the evaluation of fluid intake, cognitive function, mobility, and medications [11, 12]. ◘ Figure 2.1 describes the four principal types of urinary incontinence, common causes, and their relationship to common medications, including psychotropics.

◘ Table 2.3 Screening for urinary incontinence

Screening questions:
Do you ever not make it to the toilet in time?
Do you wear a pad or other garment because you are afraid of leaking urine?
Evaluation of severity [10]
A. How often do you experience urinary leakage?
– Less than once a month
– One or several times a month
– One or several times a week
– Every day and/or night
B. How much urine do you lose each time?
– Drops or little
– More
Severity index: Multiply the results of A and B
1–2: slight
3–5: moderate
6–8: severe

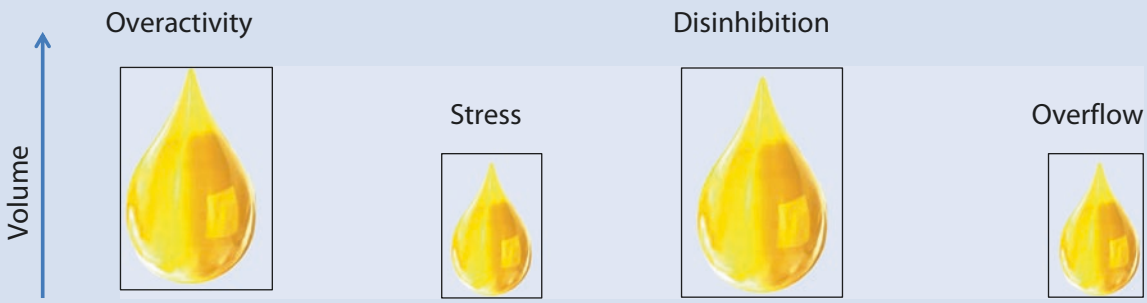
Nutrition

Screening for nutritional status is an important part of the comprehensive geriatric assessment, as unintentional weight loss and inadequate micronutrient intake are common in older adults. In one study, the prevalence of malnutrition in hospitalized older adults was over 38% [13]. There are numerous risk factors for undernutrition and malnutrition in older adults, and a high body mass index due to obesity can mask underlying protein-calorie malnutrition, micronutrient deficiency, and low muscle mass (sarcopenia). Poor dentition, dysphagia, chronic inflammation, acute and chronic illness, psychiatric (including neurocognitive) disorders, functional dependence, and medications can adversely affect appetite, taste, and ability to ingest adequate kilocalories to prevent weight loss or an imbalance of essential micronutrients. Older adults meeting criteria for frailty (see ▶ Chap. 1) commonly have multiple micronutrient deficiencies [14].

Folate deficiency is common in older adults due to reduced dietary intake or age-associated reduction in gastric acid production, leading to intestinal malabsorption; this problem can be caused or worsened by inhibitors of gastric acid production (e.g., proton-pump inhibitors). Anticonvulsants also can contribute to folate deficiency [15]. Studies have found an association between low serum folate and the development of minor and major neurocognitive and depressive disorders, although folic acid supplements have not been shown to reverse or stop cognitive decline [15].

Major neurocognitive disorders constitute an especially important risk factor for malnutrition due to associated neurological changes that affect olfaction, taste, swallowing, and the cognitive skills required to obtain and ingest adequate amounts of nutrient energy sources (see ◘ Fig. 2.2) [16]. Patients who have reduced calorie intake also likely have inadequate micronutrient intake and should receive an adult multivitamin with trace minerals or a commercial nutritional supplement, which usually contains the recommended amount of vitamins and trace minerals.

Teaching Point
Psychiatrists should be aware that some systemic medical conditions, such as advanced chronic kidney disease, heart failure, and liver failure, can influence the safe amount of some minerals and macronutrients. Thus, the recommendation for a nutritional supplement should be done in conjunction with the patient's primary care physician.



Definition: Strong urge to void at relatively low bladder volume with short interval between urge and involuntary voiding.

Volume: Bladder contents

Frequency: Intermittent, dependent on reaching critical bladder volume

Causes:

- Idiopathic
- Irritation, like UTI
- Prostatic hypertrophy

Worsened by:

- Inability to reach toilet in time 2° immobility
- Diuretics
- Cholinesterase inhibitors
- Lithium

Definition: Failure of internal sphincter to prevent leakage of urine during valsalva maneuver, e.g., from cough.

Volume: Small to moderate

Frequency: Intermittent

Causes:

- Women: pelvic laxity from childbirth
- Pelvic surgery
- Men: urological surgery like transurethral resection of prostate

Definition: Uncontrollable reflex bladder emptying, often without warning.

Volume: Bladder contents

Frequency: Intermittent, dependent on reaching full bladder volume triggering reflex

Causes:

- Brain injury, like stroke
- Advanced major neurocognitive disorder
- Transient CNS dysfunction, like delirium

Definition: Pressure from high bladder volume exceeds pressure of internal sphincter, causing leakage.

Volume: Small

Frequency: Continuous, whenever bladder volume exceeds critical level

Causes:

- Spinal cord injury, peripheral neuropathy
- Obstruction
- Bed rest
- Pain and cold (increased α-adrenergic activity)
- Anticholinergic medication (e.g., tricyclic antidepressants, first generation antihistamines)

Fig. 2.1 The four principal types of urinary incontinence

Because inadequate nutrition is associated both with neuropsychiatric disorders and their treatment in older patients, clinicians should screen for risk factors for malnutrition. This can be done efficiently using a brief, validated screening tool like the five-item Mini Nutritional Assessment (Short Form) [17]. Although copyrighted, it is available for free download and clinical use (▶ http://www.mna-elderly.com/mna_forms.html).

Falls

Approximately one-third of community-dwelling older adults fall at least once per year, with many falling multiple times. Falls are a leading cause of hospitalization and injury-related death in older adults. The US Centers for Medicare and Medicaid Services considers falls a quality indicator for hospital operations and does not reimburse hospitals for patient injuries resulting from nosocomial falls. Falls are associated with delirium and may be the result of lower extremity weakness, cerebellar or vestibular dysfunction, peripheral or autonomic neuropathy, neurodegenerative disorders (e.g., Parkinson disease), visual impairment, orthostatic hypotension, prior stroke, cardiac arrhythmias, and/or the effects of medications. All classes of psychotropic medications have been associated with falls, with a combined 78% increased risk compared to patients not taking a psychotropic drug [18]. In many cases, there is more than one contributing factor. Patients who fall require an evaluation to assess for injury as well as the etiology.

Although amnesia for the fall often limits the accuracy of the history [19], as much information as possible should be obtained from the patient and any witnesses in order to ascertain preceding symptoms (e.g., lightheadedness) and the exact circumstances surrounding the fall. Vital signs should be obtained immediately. Loss of consciousness, even if transient and not accompanied by injury, must be evaluated. Once the patient has been ruled out for injuries (see below), lying, seated, and standing blood pressures should be obtained to evaluate for orthostatic hypotension.

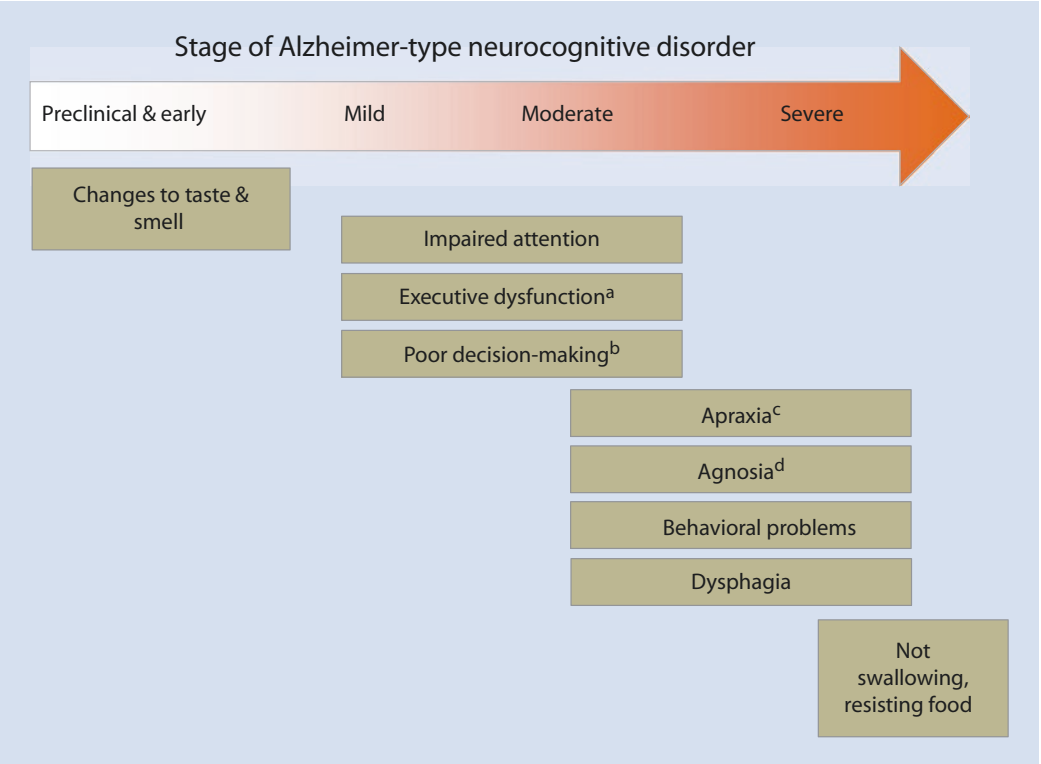


Fig. 2.2 Factors involved in the development of nutritional deficiencies in major neurocognitive disorders. [a]Examples: shopping, preparing food; [b]Examples: unhealthy food choices, forgetting to eat; [c]Example: loss of ability to manipulate eating utensils; [d]Not recognizing food as food [16]

An electrocardiogram with rhythm strip should be obtained; if an explanatory arrhythmia for loss of consciousness is not revealed, the patient will require telemetry and thus admission to a medical ward. The most common causes of syncope in geriatric patients include orthostatic hypotension, neurally mediated syncope ("vasovagal syndrome"), carotid sinus syndrome, and arrhythmias [19].

A careful neurological examination is mandatory for all fallers, looking for new, abnormal neurological signs and symptoms that may suggest stroke or intracranial bleed. As part of the motor exam, the patient also should be assessed for musculoskeletal injuries, and the ability to bear weight and walk without new or worsened pain should be assessed.

Because cervical spinal injury can occur without evidence of spinal cord injury, in an unwitnessed fall, the patient's neck should be immediately immobilized in a rigid collar, pending obtaining cervical spinal X-rays. Following head trauma, intracranial bleeding can occur insidiously, delaying the development of neurological symptoms for hours to days. Computed tomography (CT) of the brain is therefore recommended—and *must* be obtained if the patient is taking an anticoagulant. If a head CT is not available, nurses should perform frequent neurological checks (evaluating level of consciousness and gross motor and cognitive function) for at least 48 hours.

Gait stability should be assessed following the fall to determine if a new walking aid and/or physical therapy should be prescribed:

- Can the patient stand without pushing off with his/her hands? If not, the quadriceps muscles may be weak, constituting a risk factor for future falls.
- With the patient 1 step in front of a chair (for safety if he/she falls backward), can the patient stand with feet together and eyes closed for 10 seconds without holding on for support? If no, proprioceptive, vestibular, or cerebellar function may be affected. Does the patient tend to fall backward when attempting to stand? If so, check for other signs of parkinsonism.
- What does the gait look like? Look for stride length and arm swing, posture (stooped vs. erect), ability to walk in a straight line vs. staggering, reaching out to touch walls or furniture for support (reflecting a fear of falling), and the stability of the 180° turn to return to the original location.

2.1.5 Medication Review

The majority of older patients admitted to psychiatric units and general hospitals have multiple comorbidities and are prescribed multiple medications. In an epidemiological

sample, 80% of US veterans with unplanned hospitalizations (mean age, 76 years) were taking ≥ 5 drugs at the time of admission [20]. The Australian National Census of Medicines Use determined that nearly 50% of women and 35% of men aged 75 years and older took 5 or more medications in the previous 24 hours, underscoring the prevalence of polypharmacy in older adults [21]. Patients are usually continued on their prescribed outpatient medical regimen for "stable" chronic conditions not directly affected by the admitting diagnosis. However, medications prescribed to older patients may not necessarily be the most appropriate, effective, or safest for them.

In addition to a medication reconciliation (*what the patient says they are taking* versus *what the patient has been prescribed*), a thorough medication review for appropriateness should be conducted. Drugs with anticholinergic properties can cause cognitive impairment ranging from subtle changes detectable only by neuropsychiatric testing to frank delirium. Even drugs with individually weak anticholinergic activity (e.g., furosemide, digoxin) can add to the overall anticholinergic burden. Antihypertensive medications and diuretics can contribute to orthostatic hypotension. (For more discussion on potentially inappropriate medications in older adults, see ▶ Chap. 5.) It may be necessary to contact the primary care physician if a review of the medical record does not elucidate the rationale for a medication that may appear to be inappropriate.

2.1.6 Social Supports

Screening questions regarding formal and informal social supports as well as financial resources may be helpful in designing realistic management plans. Caregivers should also be interviewed to assess the level of caregiver stress and the potential of burnout. Vulnerable older adults should also be screened for potential elder mistreatment.

2.1.7 Focused Geriatric Physical Examination

The ability to perform a basic physical examination remains an essential part of the psychiatrist's skill set, and it is essential that the psychiatrist be able to evaluate acute systemic medical conditions or exacerbations of chronic ones in order to determine if the patient requires an urgent internal medicine consultation or visit to the emergency department. Although it is impossible to review the entire physical examination, this section will emphasize important clinical findings that are more commonly encountered in older patients.

Vital Signs

The screening blood pressure should be checked in a seated position after the patient has had a chance to rest. Anxiety related to medical care can increase the blood pressure (so-called white coat hypertension), so, if initially high, it should be checked again after the interview. Taking the pulse for at least 30 seconds will increase the ability to detect an irregular rhythm. Blood pressure may be overestimated in geriatric patients due to calcification in their blood vessels that cannot be compressed. This is known as "pseudohypertension" and should be suspected if dizziness develops after antihypertensives are begun or doses are increased to treat elevated systolic BP [22]. Patients over age 65 should be evaluated for orthostatic hypotension due to its high prevalence, as it may affect the choice of psychotropic medication or reflect a need to refer back to the primary care physician. The blood pressure and pulse first are measured with patient in the supine position and then after standing for 3–5 minute. If systolic blood pressure falls ≥ 20 mm Hg or the diastolic blood pressure falls ≥ 10 mm Hg while standing, compared to the supine values, orthostatic hypotension is diagnosed. The failure of the pulse to rise by ≥ 10 beats per minute in the presence of orthostatic hypotension also indicates autonomic dysfunction, unless the patient is taking a beta-adrenergic blocker. Measuring the patient's current weight and comparing to baseline values can identify significant weight loss or gain; both may be indicators of psychiatric illness and/or its treatment. A respiratory rate greater than 20 breaths per minute indicates tachypnea and should prompt a measure of oxygen saturation, even if the patient denies dyspnea.

Head and Neck Examination

Inspection of the mouth can provide important clues about the patient's hydration status, self-neglect, self-image, and ability to chew. Missing, broken, or carious teeth may reflect self-neglect or neglect by others and can adversely affect nutrition. If the patient is missing teeth or is edentulous, ascertain if the patient has a well-fitting dental appliance or dentures. Inspect the tongue for normal papillae. A red, smooth, beefy-looking tongue suggests B_{12} or folate deficiency. Dryness of the mucus membranes may indicate volume depletion, sicca syndrome (inability to generate adequate saliva), or the use of anticholinergic medication. In patients complaining of headache, tender scalp, and/or weakness or achiness in the shoulders, the temporal arteries should be palpated for tenderness or nodularity which may indicate temporal arteritis, which is a vision-threatening condition requiring immediate referral to the emergency department or an ophthalmologist for evaluation and possibly temporal artery biopsy. Vision should be checked either with a wall-mounted Snellen chart or a handheld pocket card in both eyes with corrective lenses in place. If the visual acuity is < 20/100 corrected in either eye, the patient's vision is severely impaired, which can impact gait safety and increase fall risk. Bifocal and trifocal lenses distort vision when the patient looks down and can be a risk factor for falls.

Cardiopulmonary Examination

In patients with shortness of breath, the use of intercostal and neck strap muscles (accessory muscles) and worse shortness of breath when reclining indicate higher medical acuity and require urgent internal medicine evaluation. Pursed-lip breathing (i.e., exhaling with the lips close together as if blowing up a balloon) helps to keep the airways open and is a sign of severe bronchospasm or chronic obstructive lung disease. If the patient stops and bends forward to catch their breath (known as the "tripoding" sign), acute respiratory distress should be assumed and the patient immediately evaluated. At a minimum, the psychiatrist should be able to recognize the important key visual and auscultated lung findings (Table 2.4).

Auscultation of the heart permits more accurate assessment of an irregular pulse as well as detection of murmurs, rubs, and gallops. Although accurate auscultation of heart murmurs in the stable patient has become less important with the increased availability of echocardiography, it is important to recognize new or worsened murmurs in patients presenting with a suspected myocardial infarction or experiencing new or acutely worse heart failure. Measurement of the jugular venous pressure may be very useful in determining volume status. To measure the patient's venous pressure, the clinician should examine the veins on the right side of the neck, as they have the most direct route to the heart. An elevated jugular venous pressure is defined as the top of the internal jugular vein pulsations which are more than 3 cm above the sternal angle, with the neck and torso raised to 30° above the horizontal. The internal jugular vein is located lateral to the carotid artery. Inspection of the neck for the internal jugular pulsation is facilitated by shining a light obliquely against the neck from the side, which allows the internal jugular pulsations to be seen under the skin. Unlike the single pulsation of the carotid, the internal jugular pulsation is characterized by three separate waves, which produce a fluttering.

If heart failure is suspected, the feet and ankles should be inspected for edema. It is important to press gently over the tibia or malleoli for up to 40 seconds to fully displace the interstitial fluid before rating the edema from trace to 4+.

Abdominal Examination

Patients who are unable to assume and maintain the supine position (e.g., kyphoscoliosis, cardiopulmonary disease) may give the appearance of having abdominal distension. It is important to remember that not all abdominal pain denotes pathology inside the peritoneal cavity. When the patient

Table 2.4 A psychiatrist's mini-primer on essential lung findings

Sign	Description	Significance
Accessory muscle use	Strap muscles of the neck are employed to lift up the lung; intercostal muscles separate ribs to allow lung expansion	Significant air trapping, seen in advanced chronic obstructive pulmonary disease, severe asthma, or respiratory failure with hypoxemia
Tripoding	Patient has to lean forward and lean on knees to catch breath	Sign of respiratory distress
Ronchi	Gurgling sounds on inspiration or expiration	Fluid in airways, suggesting patient cannot cough out airway secretions, a sign of respiratory distress
Wheezes	Musical sounds on expiration. Important to note when in expiration they are heard: Throughout or just part way? How loud are they? Where are they?	Indicates bronchospasm. Holo-expiratory more serious than end-expiratory. Loud holo-expiratory wheezes indicate decent air movement. Softer holo-expiratory wheezes can indicate very severe bronchospasm preventing enough airflow to produce the wheezes. Localized wheezes could be a sign of a foreign body aspirated into an airway or a sign of a focal pneumonia
Crackles (aka rales)	Very fine, late-inspiratory crackles (rales; like Velcro™ being peeled open or the sound of hair being twirled) indicate the popping open of alveoli (air spaces)	Can be heard in pulmonary edema or early pneumonia
	Fine, holo-inspiratory crackles (rales)	May indicate interstitial fluid (pulmonary edema) or another interstitial process
	Coarse crackles	Can indicate airspace consolidation, as in a pneumonia
Egophony	As the patient says "Eeeeee," the sound goes from "Eeeee" to "Ahhhhh" or "Aaaaa"	Indicates airspace consolidation consistent with pneumonia. A pleural effusion will produce decreased sound but not conversion of "E" to "A"
Decreased breath sounds	A localized area of decreased breath sounds compared to the rest of the lung fields	Indicative of airspace consolidation, pleural effusion, or a section of the lung not receiving air from the bronchi (e.g., pneumothorax)

complains of abdominal pain, the location of the pain should be assessed by gentle, deep palpation. In older, frailer patients, intraperitoneal pathology may not immediately localize and the patient may simply complain of diffuse pain or discomfort; the physical exam may facilitate localization. Pain which is made worse when the hand is pulled away (rebound tenderness) suggests peritonitis and is a medical emergency. Early on, geriatric patients with peritonitis may lack classic peritoneal signs of rebound and guarding. Pain in the right upper quadrant may reflect liver or gallbladder inflammation. An involuntary gasp as the right upper quadrant is firmly pressed (Murphy's sign) suggests cholecystitis. If the pain is reproduced with fairly superficial pressure, the patient should be asked to sit up. If tensing the abdominal muscles worsens the pain, an abdominal wall hernia should be suspected and the affected area gently probed with a finger, feeling for a defect in the abdominal wall.

Pain that radiates from the flank to the groin, especially if it comes in waves and is very intense, may reflect passage of a kidney stone and, if severe, should prompt immediate referral for internal medicine evaluation and either an ultrasound or computerized tomogram of the abdomen. If urinalysis is readily available, it should be obtained to look for hematuria and crystals. Pain that seems localized to the side, beneath the rib cage, especially if the patient is thin, could reflect "floating rib syndrome." In floating rib syndrome, the pain is worsened by lateral bending of the trunk or coughing/sneezing and can be reproduced by hooking the examiner's fingers under the rib cage. It is usually caused by the 12th (floating) rib poking the oblique muscle and tissue adjacent to it. Although uncomfortable, the floating rib syndrome is not a medical emergency.

In some thin older adults, a normal aorta is palpable, but the vessel and pulsations do not extend laterally. Most abdominal aortic aneurysms are palpable as a pulsatile mass and their lateral width can be measured on physical examination. For patients with symptoms of constipation, palpation may reveal hard, palpable stool in the ascending, descending, and sigmoid segments of the colon.

Lower Extremity Examination

On general observation, look for swelling at the ankles, feet, and legs (see previous discussion). In patients who are bedbound, edema may also be present in the sacral and coccygeal areas. Lower limb edema that is symmetric in both limbs may indicate right heart failure. Unilateral swelling may represent venous thromboembolism, and if the patient also has concurrent complaints of chest pain or dyspnea, then consider an urgent evaluation for pulmonary thromboembolism.

Neurological Examination

The neurological examination seeks to identify asymmetric neurological findings suggestive of local pathology or multifocal disease. The neurological examination is an integral part of neurocognitive testing and can provide important clues to the etiology of neurocognitive disorders, fall risk, and neurotoxicity from medications (e.g., lithium, anticonvulsants). The examination consists of the mental status examination (which is discussed elsewhere), cranial nerves, motor exam, sensory exam, and tests of coordination, gait, and reflexes. Proper interpretation of the neurological exam requires an understanding of normal findings in the healthy older adult. It is beyond the scope of this chapter to review all parts of the neurological exam.

Level of Consciousness

The neurological examination of the unconscious patient is by necessity brief and focused and the goal is to determine underlying etiology. The Glasgow Coma Scale (GCS) is commonly utilized to assess the severity of impaired consciousness both on initial and subsequent assessments. Mild brain injury is classified as GCS $\geq$ 13, moderate injury as GCS 9–12, and severe with GCS $\leq$ 8, which may require intubation [23]. Note that a depressed GCS can reflect excessive sedation as well as brain injury.

Cranial Nerves (CN)

On routine examination, testing olfaction (CN I) is often omitted. A diminished sense of smell occurs in half of individuals aged 65 and older. Notably, deficits in odor identification occur early in the course of major neurocognitive disorder due to Alzheimer disease, with neurofibrillary tangles appearing in the entorhinal cortex. An impairment of odor identification (a sort of olfactory agnosia) precedes the onset of cognitive symptoms and predicts progression from mild cognitive impairment to syndromal neurocognitive disorder due to Alzheimer disease [24]. Thus, neurological examination of older patients presenting with cognitive impairment should include a test of smell using a substance readily identified by its odor, such as fresh, ground coffee.

Near and distant vision (CN II) should be tested in both eyes, as vision affects critical life skills (e.g., reading, driving), and older patients may not report impairment. Bedside assessment of visual fields is performed by confrontation testing (finger counting) in the four quadrants of each eye separately. With aging, the size of the pupil for a given amount of ambient light becomes smaller, increasing intraocular light scatter and reducing spatial contrast. From a practical standpoint, this impairs nighttime driving and seeing in the dark, contributing to the risk of nighttime falls [25].

Fundoscopy can reveal causes of visual loss such as cataracts, optic atrophy, as well as optic disc edema. Impairment of the optic nerves or entrapment of ocular muscles by infiltrative processes (e.g., Graves' ophthalmopathy) is revealed on examination of extraocular movements. Nystagmus (rhythmic side-to-side, up-and-down, or rotatory motion of the eye with fast and slow components) can be seen due to vestibular (peripheral) disease (e.g., Meniere's disease, positional vertigo from otolith) and from pathology in the central nervous system (e.g., vestibular nucleus, cerebellum).

Facial motor function and sensation can be assessed by examining the facial (CN VII) and trigeminal (CN V) nerves. CN VII controls taste on the anterior two-thirds of the tongue and controls the muscles of facial expression. CN V is responsible for sensation in the face and also controls oral muscles

used in biting and chewing. The face should be inspected for symmetry and the examiner should test the ability to close the eyelids against resistance. The patient should be asked to purse their lips, blow out their cheeks, and show their teeth. Knowledge of neuroanatomy permits the differentiation of Bell's palsy, a peripheral neuropathy, from acute ischemic stroke. Fibers of CN VII that control the lower half of the face fully decussate (crossover) in the brain stem to the side opposite their hemispheric origin, whereas half of the fibers of CN VII that control the upper half of the face (eyes and forehead) decussate, while the other half remain on the same side. This means that in an acute stroke involving CN VII, the patient retains the ability to close both eyes and wrinkle the forehead symmetrically, even though one-half of the lower face remains paralyzed. In contrast, peripheral injury to CN VII affects one-half of the entire face.

The psychiatrist may be asked to evaluate a patient with the rapid onset of unilateral facial paralysis, consisting of inability to close the eye, drooping of the corner of the mouth, and loss of the nasolabial fold. In the absence of any other acute neurological abnormality, the facial paralysis most likely represents Bell's palsy, an idiopathic injury of the ipsilateral CN VII. Other symptoms may include loss of taste on the anterior two-thirds of the tongue as well as either decreased hearing or hyperacusis in the ipsilateral ear. Contrast-enhanced head computed tomography or magnetic resonance imaging of the head can be performed and a formal neurological consultation obtained if differentiating Bell's palsy from stroke cannot be done with certainty. Glucocorticoids remain the mainstay of treatment for Bell's palsy, and symptoms can persist for months.

Hearing (CN VIII) can be crudely tested by whispering in each ear while covering the other ear. Cranial nerves IX and X are tested in tandem and manage the gag reflex and palatal movement, respectively. Ask the patient to say "Ahhh" or to pant (driving the base of the tongue to the floor of the mouth) and look for smooth upward palatal movement. CN XI is tested by asking the patient to shrug their shoulders (trapezius muscles) and turn their head (sternocleidomastoid muscles) against resistance. To test cranial nerve XII, ask the patient to stick out their tongue and observe for fasciculations and tongue deviation. If there is unilateral weakness, the tongue will deviate toward the weaker side.

Motor Exam

The motor examination first consists of inspection, looking for *fasciculations* (fine, intermittent contractions of muscle visible beneath the dermis) and muscle bulk. Benign causes of fasciculation include caffeine, beta-adrenergic agonists, and anticholinergic medications used over a long period of time. *Tone* is defined as the resistance of a muscle to passive movement and can be rated as increased, normal, or decreased. Testing for tone in the upper extremities can be performed by brisk supination of the relaxed forearm. Increased tone can be described as spastic or rigid. Corticospinal spasticity leads to resistance to flexion or contraction that releases toward the end of the motion, analogous to opening a folding pocket knife, leading to the descriptor "clasp-knife" spasticity. Rigidity is a velocity-independent "lead pipe" response that affects the flexor and extensor muscles equally and is associated with parkinsonism. Parkinsonism also is associated with cogwheel rigidity, consisting of a ratcheting or stuttering sensation as the joint resists, permits, resists, and permits movement along the arc of flexion or extension. This stuttering often can be visualized as well as felt. The examiner grasps the hand in a handshake and, after asking the patient to let the hand muscles go limp, then supinates and pronates the wrist. Above the elbow, the examiner places a thumb on the biceps tendon while flexing and contracting the arm. Muscle *strength* testing identifies patterns of weakness between upper and lower extremities and right and left sides. The six-point Medical Research Council (MRC) grading scale is commonly used to describe strength:

- 0—No contraction
- 1—Muscle contraction but no movement
- 2—Can move but not against gravity
- 3—Can move against gravity but not resistance
- 4—Weak movement against resistance
- 5—Normal power

Manual muscle testing is limited by the cooperation of the patient, and the examiner's arm strength easily can be overwhelmed by the more powerful leg muscles, allowing mild-moderate weakness to be missed even with "5/5" strength. Manual muscle testing consequently is not sensitive for detection of mild lower extremity weakness that can affect mobility and increase the risk of falls. A neurological examination is not complete without asking the patient to stand from a seated position and walk. With the patient seated in a standard armless chair, ask the patient to fold their arms across the chest and then stand. If the patient must rock back and forth to gain momentum to stand, or must push off with their hands, there is significant weakness in the quadriceps muscles.

Teaching Point

Pain or severe arthritis of the hip or knee can produce a pseudo-weakness of the hip and knee muscles that can be mistaken for intrinsic muscle weakness. That stated, patients with symptomatic hip or knee arthritis commonly have lower strength in the affected limb.

Abnormal Muscle Movements

Myoclonus Myoclonus represents involuntary muscle activity that appears as a sudden, brief jerk. The etiology of myoclonus can be broken down into essential, physiological, epileptic, and symptomatic [26]. Essential is a nonprogressive, rare, and largely autosomal-dominant form of myoclonus. Physiological myoclonus is benign myoclonus that can be recognized in most healthy individuals. The prototypic physiological myoclonic jerk is the hiccough, and patients commonly report spontaneous jerks during sleep (hypnic jerks) or while awake and at rest. Fatigued muscles after exercise may spontaneously jerk. Epileptic myoclonus, as the name implies, occurs as part

of a seizure disorder. The jerks may remain isolated without progression into a full seizure, can sometimes be induced by specific stimuli, and may occur as part of *epilepsia partialis continua*. Under symptomatic myoclonus is subsumed a long list of etiologies, of which the most important types in older adults include congenital and acquired spinocerebellar degeneration, neurocognitive disorders, central nervous system infections, metabolic disturbances, delirium/encephalopathy following physical injuries, direct nervous system damage, and miscellaneous causes that include paraneoplastic syndrome and hereditary startle response.

Asterixis Asterixis is effectively the opposite of myoclonus (a spontaneous motor contraction) and instead consists of a brief loss of muscle tone in agonist muscles, followed by a compensatory twitch of the antagonistic muscles. Asterixis usually is bilateral and most commonly seen in advanced cirrhosis, usually in the presence of hepatic delirium/encephalopathy. However, it also can be seen in severe azotemia from advanced kidney disease. It may occur as a neurotoxic side effect of anticonvulsants, principally phenytoin, valproic acid, and carbamazepine, and has been described as a toxic reaction to barbiturates, benzodiazepines, metoclopramide, lithium, and the antibiotic ceftazidime. Hypomagnesemia and hypokalemia may also cause asterixis. Focal brain lesions, particularly in the thalamus, can produce unilateral asterixis [27].

Tremor Tremor is the most common movement disorder and is characterized by an involuntary, rhythmic movement. Clinicians often have difficulty distinguishing a resting tremor, the hallmark of Parkinson disease, from essential tremor. Differentiating features are shown in Table 2.5. A resting tremor occurs when the body part is fully supported against gravity without voluntary motor activity. An action tremor presents during voluntary movement of the body part and can be subdivided into five types [28]:

- Isometric tremor: when a limb muscle contracts isometrically against an immovable object (e.g., the examiner's hand that is resisting the movement), a tremor in the contracting muscle group occurs.
- Task-specific tremor: the tremor is induced or increased by a specific movement.
- Postural tremor: a tremor emerges when the appendage tries to hold a position against gravity, exemplified by a tremor induced by extending the arms.
- Kinetic tremor: the tremor emerges during a voluntary movement of a limb and continues, without change in amplitude, through the entire movement.
- Intention tremor: the tremor increases in amplitude as the appendage approaches its target.

Miscellaneous Pathological Movements Other involuntary movements can be identified during the motor exam. Clonus consists of an involuntary rhythmic movement at a joint when the muscle is stretched and represents a hyperactive stretch reflex. Clonus can extinguish after several beats or be sustained.

Table 2.5 Differentiating features of Parkinson disease-related tremor and essential tremor [28]

Clinical feature	Parkinson tremor	Essential tremor
Tremor		
Improves with alcohol consumption	No	Frequently
Sidedness	Begins unilaterally, progresses to bilateral	Bilateral in upper extremities
Phase of movement	Resting (common) Sustained voluntary movement against gravity Prominent when walking	Visible with voluntary movement and when limb held against gravity (e.g., outstretched arms) Resting in severe cases Quiescent with walking
Frequency	4–6 Hz	7–12 Hz
Other sites for tremor	Mouth, tongue, legs Normal voice	Head (titubation—side to side or up and down) May have tremulous voice
Other features		
Family history	Rare	Frequent
Handwriting	Micrographia with decreasing size of movements while drawing a spiral	Sloppy, with sine-wave-like strokes throughout drawing of a spiral
Face	Mask-like facies Blunted emotional expression (seems sad all the time) Reduced blink rate	Normal facial expression and blinking
Gait	Stooped posture Shortened stride length Reduced and often asymmetrical arm swing	Normal gait

It is invariably pathologic after ten beats. Dystonia consists of inappropriate muscle contractions arising from aberrant motor impulses from the central nervous system and can present as abnormal posturing, that is, sustained, abnormal, and frequently painful contractions of muscle groups. Dystonic reactions are frequently seen as a result of an idiopathic reaction to dopamine-blocking drugs, such as antipsychotics and metoclopramide, or as a result of brain injury (e.g., cerebral palsy, severe hypoxic injury). Dyskinesias are distinguished from dystonia by more flowing, large involuntary movements without tonic contraction of muscle groups. They can be part of the spectrum of movement disorders induced by chronic dopamine blockade by antipsychotics (tardive dyskinesia) or from long-term use of

2

dopamine agonists and thus often is seen as a complication of more advanced Parkinson disease. Within the spectrum of dyskinesias, chorea is an involuntary, writhing movement arising from dysfunction in the basal ganglia due to inherited, autoimmune, pharmacologic, or metabolic disturbances [29].

Coordination and Gait

Cerebellar function does not change during normal aging. Ischemic stroke and degeneration from chronic ethanol ingestion are the most common causes of cerebellar dysfunction in older adults. In psychiatric patients, irreversible cerebellar damage can occur from lithium toxicity; in the geriatric patient, lithium levels in the usual therapeutic range have been associated with cerebellar dysfunction. Chronic use of anticonvulsants, either for epilepsy or as treatment for bipolar disorder, also may lead to cerebellar dysfunction. Pan-cerebellar dysfunction may result from a form of multisystem atrophy and can occur as a paraneoplastic syndrome. Examination of cerebellar function involves testing the trunk for balance and the limbs for coordination. Limb ataxia is assessed by the finger-to-nose test in the upper extremities and the heel-to skin test in the lower extremities. For patients with cerebellar ataxia, there may be dysmetria (overshooting or undershooting of the intended target). Truncal imbalance from cerebellar dysfunction or peripheral neuropathy requires the patient to assume a broader stance to maintain balance. Cerebellar dysfunction impedes the ability to perform a tandem gait, and during ambulation the patient shows a wide-based gait with truncal imbalance, mimicking acute ethanol intoxication. Such a gait can become chronic with alcohol-related cerebellar degeneration. The latter affects the paleocerebellum and thus tends to occur without an accompanying intention tremor.

Patients with parkinsonism or other neurodegenerative processes involving the basal ganglia and related motor pathways can have postural dysequilibrium, characterized by redirection of the legs and trunk to a centrally reset, displaced center of gravity. As a result, the patient may have difficulty standing because of placing the feet too far forward or tend to lean backward when upright, leading to backward falls with high risk of closed head injury. When walking, patients try to compensate for their incorrect center of balance by bending forward at the waist. Historically, these patients or their family report having a tendency to fall back into the chair when they attempt to stand. Gait assessment is also discussed in ▶ section Falls. Two structured gait assessments are commonly performed in comprehensive geriatric assessment, the Up-and-Go test and the Tinetti Gait and Balance test, which is open access. The Up-and-Go is a quick, qualitative test of gait and balance. The patient is asked to stand from a seated position without using their arms, walk 10 feet (3 m), turn, return to their seat, and sit down. With the patient instructed to walk at their usual pace, the examiner checks for unsteadiness, loss of balance, grabbing at the walls, staggering, shuffling, using an assistive device (if any) improperly (e.g., carrying cane), and whether they turn en bloc (in a series of short steps rather than pivoting on 1 foot). Taking more than 12 seconds to complete the entire Up-and-Go test predicts falls. The Tinetti test divides balance into nine components and gait into seven components, each of which is scored and added together. Higher scores reflect better performance. Out of a possible 28 points, ≤ 18 corresponds to a high fall risk, 19–23 an intermediate risk, and ≥ 24 low risk [30].

Reflexes

Deep tendon reflexes (DTR) are routinely tested and the results are described based on their presence or absence and whether or not they are symmetrical. These reflexes tend to diminish with aging, and it is often necessary to use reinforcement techniques (e.g., teeth clenching, grasping the fingers of each hand, and pulling) to bring out reflexes that appear absent or diminished. The National Institute of Neurological Disorders Myotatic Reflex Scale grades reflexes as follows:

- 0—Absent
- 1—Trace response or reinforcement required
- 2—Reflex in lower half of normal range
- 3—Reflex in upper half of normal range
- 4—Reflex greater than normal, including clonus

Reflexes that are significantly diminished or absent suggest peripheral nerve disease. Hyperreflexia is abnormal in older patients and suggests a brain lesion in the motor cortex or damage along the spinal pyramidal tract above the level of the spinal motor nerve arising from the anterior horn. Although hyperreflexia can be associated with hyperthyroidism, this association is seen less in older, compared to younger, patients. Unilateral hyperreflexia may be a residual finding from prior stroke. Sustained rhythmic beating at a joint during forceful flexion (e.g., the ankle) indicates clonus. Up to 3–4 beats can be within normal limits. Non-sustained clonus will extinguish after 5–10 beats and sustained clonus lasts > 10 beats; both are pathologic.

Babinski Reflex The extensor plantar response is not part of normal aging and its presence suggests an interruption in the corticospinal tract (e.g., stroke, mass lesion, spinal cord compression). To test the reflex, the patient should first be placed in the supine position. Using a thumbnail, key, thin stick, or the pointed tip of a neurological reflex hammer, gently stroke along the lateral aspect of the sole starting near the heel, and sweep upward in an arc across the base of the toes to the first metatarsal head. The normal response is a downward flexion of the toes. The classic abnormal response is the up-going great toe with or without spreading of the rest of the toes.

Teaching Point

Be careful to avoid producing pain or tickling the patient in order to avoid a withdrawal response, which often involves extension of the big toe and can be mistaken for a positive Babinski reflex. Rubbing the knuckles down the shin or running the key or sharp object strictly on the lateral aspect of the foot often can induce the plantar response with tickling the patient.

Primitive Reflexes Primitive reflexes (frontal release signs) are present in infancy and disappear with development of the central nervous system. The six reflexes include the snout, palmo-mental, glabellar, sucking, rooting, corneo-mandibular, and grasp. Reappearance of these reflexes may occur in late life both in normal older adults and in certain disease conditions. For example, an abnormal glabellar tap may be seen in neurodegenerative conditions such as more advanced neurocognitive disorder and Parkinson disease. The reflex is elicited by tapping the area above the nose on the forehead (glabella) at 1-second intervals. In a normal patient, the blink reflex will occur after each tap for several repetitions and then extinguish. In a patient with frontal lobe injury or Parkinson disease, this blinking does not extinguish.

Sensory

Spinothalamic (pain, temperature, and light touch), dorsal column (vibration, proprioception, and touch localization), and hemispheric (graphesthesia) sensory functions should be assessed. The stimulation should be applied lightly and should be compared bilaterally as well as distally versus proximally. Vibration sensation is reduced in the lower limbs of normal older adults and may not be attributable to disease. Loss of proprioceptive position sense in the great toes is pathologic and can occur in B_{12} deficiency or after peripheral nerve injury. With the patient's eyes closed and the patient instructed not to move the toe, the examiner grasps the great toe on the sides and moves it up and down several times before asking the patient if the toe is "up or down." The test should be repeated several times to ensure consistency of response (correct or incorrect localization). There are age-related increases in sensory thresholds for sensory modalities, but these changes are not clinically apparent on bedside testing.

The Romberg tests evaluate sensory (proprioceptive) function of the feet and require healthy dorsal columns of the spinal cord. With the patient standing with the feet together just in front of a chair next to a wall in case they should lose balance, the examiner asks the patient to shut their eyes. Romberg's *sign* is excessive swaying or falling with the eyes closed. This test is enhanced by pushing the sternum forcibly (calibrated to the patient's size and estimated strength), while the patient has their eyes closed. A positive Romberg test indicates peripheral neuropathy and/or delayed motor reflexes arising from midbrain or motor-tract degeneration (e.g., Parkinson disease) and/or slowed motor conduction.

2.1.8 Special Challenges with Geriatric Patients

Atypical Presentation

Most older patients present with the *typical* signs and symptoms of an illness, but an increased proportion present *atypically* [31, 32]. An atypical presentation may take several forms:

1. *Failure to manifest many of the usual and expected features of a disease process.* Examples include lack of cough and sputum production or even leukocytosis with a pneumonia, lack of the typical rhinorrhea, nasal congestion, and sore throat with influenza and the absence of chest pain with acute coronary ischemia. Using ambulatory electrocardiographic monitoring, asymptomatic ("silent") coronary ischemia can be detected in > 30% of geriatric patients with known coronary heart disease. The incidence of silent coronary ischemia is higher in older diabetics with coronary heart disease [33].
2. *Symptoms apparently unrelated to the involved organ system.* A disturbance in an organ system that is remote from the involved organ may be the first presentation of an acute illness in a frail, older patient. For example, central nervous system dysfunction manifesting as delirium, falls, and/or urinary incontinence may be the clinical presentation of pneumonia. Physical signs and symptoms developing from pathology in a seemingly unrelated organ system are thought to arise from the inability of the patient, as an integrated organism, to respond to physiologic challenges to homeostasis due to reduced physiologic reserve and resilience. A variation of this phenomenon is acute dysfunction in a previously damaged but functionally recovered organ when exposed to severe physiologic stress. For example, a patient with no apparent residua from a previous stroke may appear to be experiencing a recurrence of the same signs and symptoms of that stroke during the stress of sepsis. A patient with well-compensated heart failure may experience an exacerbation of heart failure because of a respiratory infection.
3. *Nonspecific symptoms.* Nonspecific symptoms do not readily suggest a specific cause. A patient experiencing a myocardial infarction may only complain of acute fatigue or nausea rather than crushing substernal chest pressure. A woman with a urinary tract infection may simply feel tired without complaints of dysuria and frequency. A patient with acute appendicitis initially may complain of generalized abdominal discomfort, nausea and vomiting, or merely loss of appetite instead of classic right lower quadrant pain.
4. *Presentation of symptoms due to failure to mount an appropriate physiologic response.* Age-associated dysfunction in one or more organ systems may prevent an adequate compensatory response to a stressor that would mitigate symptoms. For example, otherwise healthy older adults may not feel thirsty and drink enough water to correct a hyperosmolar state from volume depletion due to a blunting of the normal thirst response to volume [34], making older adults susceptible to hypotension, lightheadedness, and acute kidney injury from illnesses that cause volume loss (e.g., diarrhea) or reduced intake (e.g., gastroenteritis). Roughly 30% of older adults have impaired vasoconstriction during assumption of an upright posture,

leading to orthostatic hypotension [35], typically defined as a drop of 20 mm Hg in systolic blood pressure or 10 mm Hg of diastolic blood pressure upon standing. The result may be lightheadedness or syncope. When the upright posture is maintained for more than 3 minutes, the prevalence of orthostatic hypotension rises to as high as 40% [36]. Orthostatic hypotension may be worsened by the failure of the heart rate to increase cardiac output due either to conduction-system disease or autonomic dysfunction. These maladaptive age-related changes can be worsened further by medications that affect an organ's compensatory response (e.g., beta-adrenergic blockers that prevent compensatory tachycardia).

The Older Psychiatric Patient as Poor Historian

The history alone is sufficient to arrive at an accurate diagnosis in approximately 20% of patients admitted to a medical inpatient service. The history coupled with the physical examination yields an accurate diagnosis in 80% of cases [37]. However, psychiatric (including neurocognitive) disorders can impair history taking and delay diagnosis, with potentially dire consequences for the patient. An accurate informant who is knowledgeable about the patient and the circumstances leading up to the present constellation of symptoms therefore becomes critical. Psychiatric patients may develop strong beliefs about the cause of symptoms, potentially misdirecting the workup or causing the clinician to dismiss the symptoms as fictitious.

2.2 Case Studies

In older adults with psychiatric illness and often comorbid chronic systemic medical conditions, the medical, functional, and psychosocial statuses are essential elements to address in the assessment process in order to inform the development of the medical and nonmedical components of the treatment plan to maximize overall health with aging. The following two cases reflect the interplay of common elements of the comprehensive geriatric assessment.

2.2.1 Case 1

Case 1 History

Ms. C. was the 67-year-old chief food and wine critic for the major newspaper of a large metropolitan area. Over the years she had had a tendency to engage in periodic binge eating of food in favored restaurants (though she remained moderate in her wine consumption), which resulted in obesity, diabetes mellitus, and hyperlipidemia, for which her internist prescribed glipizide, metformin, and atorvastatin. She also had been taking the proton-pump inhibitor, lansoprazole, for a number of years to manage severe heartburn. Following the periods of over-indulgence, she usually became morose and sullen for several days, but after one of her bingeing episodes, she developed a major depressive episode requiring psychiatric hospitalization. She was diagnosed with bipolar II disorder and placed on divalproex 1000 mg at bedtime for mood stabilization and sertraline 100 mg daily. Although her food consumption normalized, she had difficulty losing weight and controlling her blood glucose and eventually required insulin glargine at bedtime and insulin aspart at mealtime, with discontinuation of glipizide.

One morning she awoke and was horrified to see that the right side of her face from the forehead to the chin was sagging. She could not close her right eye or curl the right side of her mouth into a smile. She went immediately to the emergency department, fearful that she had had a stroke. There, her neurological examination was completely normal except for right-sided facial droop. She could not furrow the right half of her forehead or close her right eye on command. The emergency physician ordered a non-contrast computerized tomogram of her brain, which was negative for evidence of an acute stroke, but did reveal moderate periventricular white matter disease, considered above average for her age. She was given an aspirin and admitted overnight for observation. By morning, the facial droop had improved considerably, and she was able to close her right eye two-thirds of the way. She was told to take an 81 mg aspirin daily, an ophthalmic lubricant to prevent corneal damage, and was discharged home with follow-up with a neurologist.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. Is this a stroke, transient ischemic attack, or Bell's palsy?

? Question 2. Can you create a differential diagnosis for the decline of Ms. C.'s career following her Bell's palsy?

? Question 3. What is your differential diagnosis for her falls, and what might these recommendations have been?

Case 1 Answers

Case 1 Answer 1 (Question 1—Is this a stroke, transient ischemic attack, or Bell's palsy?)

Ms. C. experienced an acute onset of right facial paralysis involving the upper as well as lower half of her face. Half of the fibers of the seventh cranial nerve that ultimately innervate the forehead and eye muscles cross the brain stem to the opposite side and innervate the opposite side of the face; the other half innervate the ipsilateral side. The fibers ultimately innervating the lower half of the face only travel to the opposite side. Thus, in a unilateral stroke affecting one of the CN VII tracts within the central nervous system, the patient should retain the ability to wrinkle the forehead and close both eyes while having hemi-paralysis of the face. The remainder of Ms. C.'s neurological exam was within normal

limits. Thus, it is highly likely that she experienced Bell's palsy and was fortunate to achieve rapid improvement within 24 hours. Bell's palsy stems from idiopathic inflammation of the peripheral portion of the CN VII, and so the entire side of the face is affected. Often, resolution can take months. Corticosteroids may reduce the inflammation and hasten recovery; she did not receive any.

Case 1 (Continued)

After returning home, Ms. C. was distressed to find that the sensitivity of her taste had precipitously declined, such that most foods that she tasted seemed bland unless she heavily seasoned them. At first she did not realize the fault was hers, and wrote scathing reviews about several restaurants and collected, in return, surprised comments from readers who praised the food. She lost interest in food and began to focus on restaurants' ambience. She went out less often and wrote fewer reviews and was put on probation by the editorial staff. She once again became moody and sullen and her psychiatrist increased the sertraline to 200 mg per day. She used to write eloquently, with pithy, image-full descriptions of food and wine, but the quality of her writing deteriorated. She visited an ear, nose, and throat specialist who did formal testing of her sense of taste and found that it had returned to normal. Ms. C. complained that she still could not smell the food or could not recognize their odors, which was her rationalization for abandoning her famous descriptions like, "A voluptuous flan with perfectly seared brown sugar, imparting a decadent caramel flavor that embraced the tongue like a passionate lover...." One year after Bell's palsy had resolved, Ms. C. was fired from the newspaper.

Case 1 Answer 2 (Question 2—Can you create a differential diagnosis for the decline of Ms. C.'s career following her Bell's palsy?)

The differential diagnosis must include relapse of a major depressive episode. Certainly this affected her ability to write her column, as did her hypogeusia. CN VII subserves taste on the anterior two-thirds of the tongue and likely altered her taste perception for weeks. The loss of taste likely contributed to her recurrent depressive episode. However, after her taste returned, based on objective testing, the quality of her writing continued to be poor. She attributed this to a gradual deterioration in her sense of smell, which is almost as important as taste for a connoisseur and critic of fine food. However, another explanation exists. Alterations in odor perception occur early in neurocognitive disorder due to Alzheimer disease and can be found well before clinical symptoms develop. Reduced sense of smell commonly goes unnoticed by patients and is rarely checked by physicians. However, this is something a food critic would notice. An alternative explanation for the worsening quality of her columns is mild cognitive impairment or major neurocognitive disorder. Her white matter disease may have made her more vulnerable to concomitant neurocognitive disorder due to Alzheimer disease and/or vascular disease.

Case 1 (Continued)

Two months after she was fired, Ms. C.'s psychiatrist referred her for comprehensive neuropsychiatric testing, which found that she was performing at a lower-normal IQ level and suspected that she was in the very early stage of a neurocognitive disorder. Around this time she began experiencing intolerable burning pain in her feet, which her internist diagnosed as diabetic peripheral neuropathy and prescribed gabapentin, which was slowly titrated to the maximum dose of 600 mg three times daily. After she reached this dose, she began to lose her balance when walking and turning and experienced three major falls over the course of 2 months, one resulting in a Colles' wrist fracture and another in facial trauma including a broken nose. For each event she was seen in the emergency department, and her ethanol level each time was zero. She was referred to a geriatrician, who performed a thorough neurological exam. Her vibration sensation was very poor in her lower extremities. She could not hold a tandem or hemi-tandem stance with her eyes open and, when walking, tended to stagger and clutch the walls. A B_{12} level was obtained and she was prescribed a four-wheel walker with handbrakes. The geriatrician additionally made recommendations regarding her medications.

Case 1 Answer 3 (Question 3—What is your differential diagnosis for her falls, and what might these recommendations have been?)

Ms. C. began falling shortly after her gabapentin reached the maximum dose. Gabapentin is in the anticonvulsant family of drugs and can affect cerebellar function; it also is known to increase the risk of falls. In addition, she presumably still was taking the divalproex, also an anticonvulsant associated with increased fall risk. Finally, she was presumably still taking her sertraline, a selective serotonin reuptake inhibitor, which also has been independently associated with an increased risk of falls. On examination she had clear sensory neuropathy, which could affect her balance and gait. Finally, she had been taking a proton-pump inhibitor for years. The loss of an acid milieu in the stomach impedes absorption of vitamin B_{12} through intrinsic factor. Vitamin B_{12} deficiency further could have added to her peripheral neuropathy and might have contributed to her cognitive decline. The geriatrician's recommendations may have included:

- Vitamin B_{12} replacement.
- Stop the gabapentin and find safer ways to treat her neuropathic pain (e.g., around-the-clock acetaminophen (paracetamol)).
- Replace the sertraline with duloxetine, a serotonin norepinephrine reuptake inhibitor that may help both with her depressive symptoms and peripheral neuropathy.
- Physical therapy for gait and balance training.
- Home safety check for throw rugs, other fall hazards, and need for safety equipment such as grab bars in the shower.

Case 1 Analysis This case emphasizes the holistic approach required in the comprehensive geriatric assessment of the older adult. It illustrates how the evaluation of multiple issues, including physical and neuropsychiatric health, medication review, occupational, financial, environmental, and social components can all influence an older adult's health. A comprehensive geriatric assessment process relies on a core team consisting of clinicians, nurses, social workers, and physical and occupational therapists, nutritionists, pharmacists, dentists, and other specialty clinicians.

2.2.2 Case 2

Case 2 History

Mr. A. was an 86-year-old man who presented to his psychiatrist in early October for routine follow-up of major depressive disorder stemming from a difficult and costly lawsuit with neighbors stemming from roots from one of the neighbor's trees undermining the patient's foundation and the neighbor's refusal to contribute to the expensive foundation repair. He previously had been in fair health with well-compensated diastolic dysfunction, hypertension, a history of atrial fibrillation treated by ablation and a pacemaker, chronic constipation, a history of prostate cancer with resection with a rise in his prostate-specific antigen from 2 to 6.2 ng/mL over the past 6 months, and stage III chronic kidney disease. At baseline, he was able to walk slowly at least twice around the block without stopping; his walking was chiefly limited by sciatica in his left leg. At his last visit 2 months earlier, his depressive symptoms had improved. On presentation to the clinic, he complained of mild but worsening shortness of breath and dry cough after returning 4 days earlier from a Hajj to Mecca. He also reported mild diarrhea, with 2–3 loose stools daily for the previous 2 days; normally, he reported chronic constipation. He complained of feeling weak, had no appetite, and had recently refused most meals except for some yogurt and fruit in the morning. Mr. A. reported that he heard a few passengers coughing on the flight from Mecca to Paris, but no one near him seemed sick, and his wife was in her usual state of health. His medications at the time included bumetanide 1 mg twice daily, sertraline 50 mg every morning, metoprolol succinate 25 mg daily, gabapentin 100 mg every 8 hours for neuropathic pain related to sciatica, and vitamin D_3 1000 IU daily.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. How concerned should you be about Mr. A.'s shortness of breath and cough, and what sort of evaluation should you do?

? Question 2. What are the specifically "geriatric" features of this case thus far?

? Question 3. Do you have any concerns about the way he was managed?

Case 2 Answers

Case 2 Answer 1 (Question 1—How concerned should you be about Mr. A.'s shortness of breath and cough, and what sort of evaluation should you do?)

The differential diagnosis for Mr. A.'s new-onset asthenia is broad, ranging from a relapse of major depressive disorder resulting from the stress of travel and disrupted sleep patterns to new heart failure or an infection. Before simply referring him to his primary care physician, some medical triaging is important, some of which can be done without a formal physical examination. Much can be gleaned about his current functional status by observing him walk and arise from his chair. However, his baseline physical function, apart from reportedly being able to walk two blocks, is not known. Did he have baseline difficulty performing any of his physical IADLs or ADLs? At baseline how hard was it for him to stand from a chair, i.e., could he bound up quickly and easily, or did he have to regularly push off with his hands? A functional assessment emphasizing IADLs and ADLs, baseline mobility, and psychosocial support would have been appropriate to have on file but can be gleaned at this appointment. He was not coughing and did not appear ill, although he was moving slowly and complaining of fatigue, which is reassuring, but his oral intake had been poor while taking his daily furosemide. Because acute illness in older and especially frail individuals may not present typically, a limited physical examination including vital signs (including orthostatic blood pressure for increased sensitivity to intravascular volume depletion), evaluation of the oral mucosa, and auscultation of the heart and lungs is indicated.

Case 2 (Continued)

Mr. A.'s blood pressure was 102/68 mm Hg, heart rate 60 beats/minute and regular, temperature 38 °C (100.4 °F). His mouth appeared dry, corresponding to the patient speaking more "thickly" than usual and having to lick his lips frequently. Chest exam revealed very slight wheezing but no other adventitious sounds. His heart exam revealed a regular rate and rhythm with a soft, early-peaking 2/6 ejection murmur at the right base. Today he shuffles and seems unsteady on his feet, and he had had to rock back and forth and then get help from his wife while pushing with his hands to get out of the examiner's sofa. Normally he could arise with minimal pushing off, which the patient attributed to his knee osteoarthritis. A more extended social history revealed that his wife suffered from chronic shoulder and back pain and had a recent compression fracture resulting from a misstep on the Hajj. She was worried about being able to help her husband in this condition. Despite admonitions from the psychiatrist that the low-grade fever and low blood pressure could reflect a serious developing infection and that he should go see his primary care physician or go to the emergency department today, Mr. A. dismissed the idea, stating that he suspected he caught a virus while on the Hajj and just needed rest. He agreed to stop at the laboratory before leaving the clinic for a complete blood count, electrolyte panel, chest X-ray, and a urinalysis.

The results of the laboratory studies came back to the psychiatrist's office 36 hours later. Mr. A.'s white blood cell count was 8.7 K/mm3, and his chest X-ray showed mild cardiomegaly but no evidence of an infiltrate or heart failure. His chemistry panel was notable for a serum sodium of 128 mEq/L (128 mmol/L) and serum creatinine of 1.9 mg/dL/168 μmol/L (baseline 1.5 mg/dL/133 μmol/L). The urine dipstick was negative except for 2+ glucose. The psychiatrist called the patient's internist about the results, who in turn called the patient to go to the emergency department. His wife answered the phone (his mobile) stating that he already was there after experiencing more intense, nonproductive coughing and worsening shortness of breath, to the point that he had to sit up in his lounge chair to breathe and became dyspneic walking to the bathroom and had fallen twice.

In the emergency department, his temperature was 39.2 ° C (102.5 ° F), blood pressure 98/54 mm Hg seated, respiratory rate 28 breaths/minutes, and pulse 60 beats/minutes and regular. His oxygen saturation ($Sa0_2$) was 91% on room air. There was diffuse wheezing on lung exam that masked any other sounds, but the chest X-ray showed a small retrocardiac infiltrate. His serum sodium remained 128 mEq (128 mmol)/L, but his creatinine had now risen to 2.7 mg/dL (239 μmol/L). His ECG showed a fully paced rhythm with left bundle branch block and no acute ischemic changes. A serum troponin I as surveillance for cardiac injury was obtained and came back as 0.09 ng (μg)/L (upper limits of normal 0.04 ng/L). Mr. A. was lethargic and not able to answer questions coherently, with most of the history coming from his wife. He was empirically given azithromycin 250 mg and ceftriaxone 1 gm IV, bronchodilators, and 40 mg IV of prednisolone with a presumptive diagnosis of community-acquired bronchopneumonia, started on 5% dextrose in 0.9 normal saline, and admitted to the medical service on call, which continued the antibiotics, added oxygen at 2 L/minute as needed for a $Sa0_2 < 90\%$, ordered vital signs every 4 hours, as well as albuterol/ipratropium nebulizers every 4 hours up to every 2 hours as needed.

In the morning of hospital day 2, Mr. A. was delirious and agitated, with a RASS score of +1 (restless), for which he received olanzapine 5 mg (rapid-dissolving) with subsequent calming. He now required O_2 at 6 l/minute to maintain a $Sa0_2 \geq 90$ and his chest X-ray showed extension of his left lower lobe infiltrate, along with new pleural effusions and cephalization of his pulmonary vasculature, consistent with acute heart failure. A nasal swab for upper respiratory viruses came back positive for influenza A, and he was placed on respiratory isolation and begun on oseltamivir for the influenza. His troponin I peaked at 6.9 ng (μg)/L and he was given a diagnosis of a non-ST-elevation myocardial infarction. A serum albumin was 2.2 g/dL (22 g/L).

Case 2 Answer 2 (Question 2—What are the specifically "geriatric" features of this case thus far?)

Mr. A.'s initial presentation showed multiple atypical features. At the outset, his only symptoms of the "flu" were a low-grade fever and a dry cough. He did not have rhinorrhea, nasal stuffiness, headache, or sore throat. He also displayed the nonspecific symptoms of weakness, lethargy, and poor appetite. His diarrhea, in retrospect, was likely part of the acute influenza. Oseltamivir would have been more effective in blunting the course of his influenza and possibly could have averted secondary heart failure had it been administered early in the course, but because of the atypical presentation, influenza was not suspected until he worsened, despite antibiotics.

The heart failure typifies how dysfunction in one organ system can have an effect on another organ, in this case the effect of lung pathology on cardiac function. In addition, he began falling at home and later became delirious, demonstrating how remote organ systems (in his case, the brain) can be affected. Here, it is impossible to tease out whether the delirium arose because of the myocardial infarction, the influenza A bronchopneumonia, and/or multiple risk factors working additively or synergistically. Mr. A. had multiple risk factors for delirium, including age, acute infection, intermittent hypoxemia, and baseline depressive disorder.

Case 2 Answer 3 (Question 3—Do you have any concerns about the way he was managed?

When seen by his psychiatrist, Mr. A. admitted to poor oral intake, yet continued to take his bumetanide for compensated heart failure. He was hypotensive in the office. His psychiatrist should have stopped the diuretic and ordered the chemistry panel *statim* because of the risk of pre-renal azotemia and either hyponatremia or hypernatremia. The former was a possibility because he was on a loop diuretic plus a selective serotonin reuptake inhibitor (SSRI), which can cause the syndrome of inappropriate antidiuretic hormone (SIADH). If volume depleted, his kidneys, despite the baseline chronic kidney disease, would have avidly retained as much water as possible, and if he was losing salt from the diuretic and not taking enough in, he could become hyponatremic, especially if he was drinking some fluids. He also could have become hypernatremic if the water loss from the diuretic exceeded salt loss, his kidneys could not adequately retain water, and he was not ingesting enough salt or water.

In the emergency department, he already displayed the hypoactive form of delirium and was given high-dose corticosteroids, which could exacerbate the delirium. On the medical unit, no apparent mental status evaluation was done beyond that done in the emergency department, and no nonpharmacologic delirium preventive measures were employed. Moreover, he was placed in restraints when he became agitated, which likely aggravated his delirium and agitation. No sitter was obtained to minimize the use of restraints. The team also should have encouraged his wife to be at his bedside as much as possible and to recruit additional family members, if available, to provide frequent reorientation and reassurance.

At baseline the patient had mild mobility impairment and therefore was at extremely high risk for further deconditioning and loss of ADL independence. A mobilization program with physical therapy and occupational therapy should have begun as soon as the patient was able to cooperate, and he

should have been moved to a chair for all meals and as tolerated. He was malnourished at admission, and aggressive nutritional repletion should have been implemented early on with the help of a dietician, notwithstanding his delirium and concern for aspiration.

Case 2 (Continued)

The patient's pulmonary and cardiac status improved. The psychiatry consultation-liaison/psychosomatic medicine service provided consultation for his delirium and recommended the use of a sitter instead of restraints and haloperidol for delirium-associated agitation and educated his wife about providing gentle stimulation by conversing with him and playing simple card games when he was alert. They also encouraged that he be out of bed for meals. Although the patient became more behaviorally appropriate and able to engage in conversations, he remained intermittently disoriented to time and circumstance, and he demonstrated very poor short-term memory. His delirium by CAM-ICU assessment became negative on the 7th hospital day, but his Mini Mental State Examination score was 18/30 with 0/3 on short-term recall and errors on most of the orientation questions. Physical therapy became involved, but by discharge on hospital day 9, he was non-ambulatory, required moderate assistance for transfers, and required discharge to a skilled nursing facility for rehabilitation.

Case 2 Analysis This case illustrates how an older patient can present atypical signs and symptoms of an illness, which has taken several forms. He demonstrated a presentation of atypical symptoms due to failure to mount an appropriate physiologic response. This case demonstrates how dysfunction in one organ system could have an effect on another organ (i.e., lung pathology on cardiac and brain function). Age-associated dysfunction in one or more organ systems may have prevented an adequate compensatory response to a stressor that would have mitigated his symptoms.

2.3 Key Points: Comprehensive Geriatric Assessment

- Comprehensive geriatric assessment consists of the systematic evaluation of an older patient's functional and psychosocial status as well as their medical conditions; places special emphasis on the patient's ability to perform daily activities and on quality of life; and investigates through questions, objective testing, and systematic observation risk factors for, or causes of, common pathological conditions affecting older adults, including cognitive impairment, impaired mobility, falls, incontinence, and polypharmacy.
- Geriatric assessment explicitly looks for clinical manifestations of age-associated physiological changes, which can be harbingers of organ-system dysfunction and chronic disease, and tries to incorporate interventions that either mitigate these age-associated changes or help the patient to adapt to them.
- Older adults as they become frail are at risk for malnutrition from inadequate energy and micronutrient intake.
- Aging causes an inevitable decline in motor function, leading to impairments in gait and balance. However, strength and balance training can mitigate these declines.
- Standardized tests have been developed in geriatrics to systematically assess and quantify performance and can be used both as prediction tools and the basis for individualized interventions.

2.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Mrs. M. was a 74-year-old obese woman with severe obsessive-compulsive disorder, who was admitted for suicidal ideation with a clear plan. Her past medical history was notable for hypertension, hypercholesterolemia, osteoarthritis, and gastroesophageal reflux disease (GERD). Although taking a daily proton-pump inhibitor, she intermittently complained of substernal chest pain. ("I know it's my heartburn, and it's getting worse! Please give me something for it!") The on-call psychiatrist acquiesced and prescribed 30 mL of aluminum hydroxide/magnesium hydroxide antacid as needed, usually with relief of symptoms after 15–20 minutes. On hospital day 6, she was found unresponsive in bed at 6:00 AM. A "code blue" was called, but after 15 minutes of unsuccessful resuscitation efforts, she was declared dead. An autopsy revealed pathological features of acute and healing myocardial infarctions. What was the underlying cause of death in this case?

A. Stroke
B. Suicide
C. Peptic ulcer perforation
D. Pneumonia
E. Myocardial infarction

Answer: E

Mrs. M. had several vascular risks factors to indicate a possible cerebrovascular ischemic cause for her sudden death, but the pathological evidence *did not support* this conclusion. Sudden death is defined as any death that occurs less than 24 hours after the onset of first symptoms. She complained of epigastric pain which could have indicated a peptic ulcer complication, but this would unlikely result in sudden death. Aside chest pain, she did not present symptoms or signs of an acute respiratory illness such as pneumonia. Given the admission reason of suicidal ideation with a plan, a completed suicide would have been plausible. However, this was not supported by the pathology report findings. Mrs. M.'s frequent

chest pain represented an angina equivalent. Because the patient had a history of GERD, the psychiatrist assumed the patient's belief that she had heartburn was accurate; instead, the psychiatrist needed to take a careful history and perform an exam to rule out other causes of chest pain. The patient's underlying cause of death was acute myocardial infarction (statement E), which was supported by the autopsy findings.

MCQ 2. What is the correct statement about Charles Bonnet syndrome?

A. It indicates the presence of a psychotic disorder.
B. It occurs in major depressive disorder with psychotic features.
C. It occurs in major neurocognitive disorder with Lewy bodies.
D. It is associated with visual impairment.
E. It represents a *forme fruste* of a major neurocognitive disorder.

Answer: D

Complex visual hallucinations in the presence of substantial visual impairment characterize the Charles Bonnet syndrome (statement D). Onset of complex visual hallucinations in older adults without other symptoms of psychosis, mood, or neurocognitive disorder should be screened for visual impairment as it could indicate a diagnosis of Charles Bonnet syndrome (which will exclude the statements A, B, and C). However, there has been debate whether the Charles Bonnet syndrome represents a *forme fruste* of a major neurocognitive disorder, but the research to date has been inconclusive (statement E).

MCQ 3. Which of the following statements about urinary incontinence is *not* correct?

A. Prevalence is 15–30% of community-dwelling older adults.
B. Prevalence is 50–75% of older adults in institutions.
C. Urinary tract infections, decubitus ulcers, and restriction of activities are common complications.
D. It is a key feature in deciding upon nursing home placement.
E. It is associated with depressive disorders in older men.

Answer: E

Urinary incontinence affects 15–30% of community-dwelling older adults and 50–75% of persons in institutions (statements A and B). Urinary incontinence can have significant complications, including urinary tract infections, decubitus ulcers, and restriction of activities (statement C). Urinary incontinence may be a key feature in deciding upon nursing home placement in some cases (statement D). Urinary incontinence has been associated with depressive disorders in older women (but not in men as in statement E) depending upon the incontinence screening instrument used and the population studied; therefore, statement E is the correct answer.

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Neuroimaging in Clinical Geriatric Psychiatry

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3.1 Background

3.1.1 Introduction

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Associations of brain structure and function to behavior date as far back as the second and third century CE when the Greek physician, Galen of Pergamon, suggested that the brain plays a central role in control of perception, cognition, and memory [1]. Attempts by eighteenth-century German physicians, Franz Joseph Gall and Johann Gaspar Spurzheim, at linking specific brain areas to specific mental states gave rise to the pseudomedical field of phrenology, namely, the physical examination of the shape and surface of the skull as accurate indicators of psychological traits [2]. Although phrenology has long been debunked, Gall and Spurzheim's notion of functional localization of cerebral and cerebellar structures and associations of functional brain domains to behavior still hold true. Today more advanced techniques are available for assessing regional changes in the brain in relation to neurobehavioral disorders, in vivo, even down to molecular levels. Since the invention of radiography by Wilhelm Roentgen in 1895, there have been ongoing efforts by physicists and clinicians to optimize the validity of neuroimaging tools for diagnosing brain disorders. Early radiographic tools, using x-rays, included ventriculography and pneumoencephalography by Walter Dandy (a neurosurgeon) in 1918 and cerebral arteriogram by Antonio Egas Moniz (a neurologist) in 1927. In 1961, William Oldendorf invented computed tomography (CT) technology, which was applied to clinical use in 1973 as facilitated by Godfrey Hounsfield (an electrical engineer). Eventually magnetic resonance imaging (MRI) was introduced in the mid-1970s [3]. Since then, there has been a revolution of neuroimaging technology that has involved improvement in image resolution for better structural imaging in addition to the arrival of nuclear and molecular imaging, which allowed in vivo imaging of brain function, metabolism, and molecules. Psychiatry has been in the search for biomarkers to allow accurate diagnosis, identification of treatment targets, and monitoring disease process and treatment outcome markers for over a century with only modest success. Therefore, the arrival of neuroimaging, and especially functional and molecular techniques, has created huge excitement in the field as promising biomarker tools [4]. In psychiatry, neuroimaging has been used for three main purposes: (i) rule out (or in) brain lesions that could explain psychiatric symptoms, (ii) support the diagnosis of neuropsychiatric disorders associated with neurodegeneration (e.g., Huntington disease, Alzheimer disease), and (iii) explore neuroimaging correlates of other neuropsychiatric disorders (e.g., schizophrenia, bipolar disorders). Although geriatric psychiatry patients can present with "primary" psychiatric disorders, it is not uncommon for these patients to present with significant neurological comorbidities, and at times the psychiatric symptoms can be explained almost exclusively by the underlying neurological disorder. Therefore, brain imaging is often a significant part of the diagnostic work-up in geriatric psychiatry. In this chapter, we provide an overview of general anatomical landmarks that help interpret neuroimaging results; outline some of the changes considered "normal for age"; describe currently available neuroimaging modalities, their advantages and disadvantages, and their clinical utility; and outline potential future utility of emerging neuroimaging tools in this field. We will then provide examples where neuroimaging lend help in the diagnostic work-up of clinical cases.

3.1.2 Brain Structure and Networks

Neuroanatomical Landmarks

Detailed neuroanatomy is beyond the scope of this chapter. In this section we provide an overview of the anatomical organization of the brain, which will enhance the reader's ability to interpret neuroimaging reports in the context of clinical presentations. The brain is composed mainly of the following:

- Forebrain (prosencephalon)
  - Telencephalon
    - Cerebral hemispheres
    - Deep structures or nuclei
  - Diencephalon
    - Thalamus
    - Sub-thalamus
    - Hypothalamus
- Midbrain (mesencephalon)
  - Midbrain and colliculi (superior and inferior)
- Hindbrain (rhombencephalon)
  - Metencephalon
    - Cerebellum
      - Dentate nucleus
      - Vermis
      - Cerebellar hemispheres
    - Pons
  - Myelencephalon
    - Medulla oblongata

Cerebral hemispheres are composed of four major (frontal, temporal, parietal, and occipital) lobes. When examining brain surface from the lateral aspect, we can appreciate the landmark sulci and fissures that divide the cerebral hemisphere into different lobes. These include the oblique fissure that separates the frontal lobe from the temporal lobe anteriorly and temporal lobe from the parietal lobe posteriorly, in its depth lays the insular cortex, the central sulcus that separates the frontal lobe from the parietal lobe, and the parieto-occipital sulcus that separates the parietal lobe from the occipital lobe. From medial view, we can see the cingulate sulcus that separates medial prefrontal cortex from anterior and mid cingulum, the extension of the central sulcus that separates medial prefrontal cortex from the paracentral lobule, the parietal cortex, the parieto-occipital sulcus that separates medial aspect of parietal lobe (including the precuneus) from the medial aspect of the occipital lobe (cuneus), and the calcarine fissure that separates the occipital lobe (cuneus) from

medial aspect of the inferior temporal lobe (lingual gyrus). From this view, we can appreciate the limbic lobe including the sub-genual, anterior, mid, and posterior cingulate surrounding the corpus callosum, which has anterior portion (genu), mid portion and posterior portion (splenium), and medial temporal lobe structures including parahippocampal gyrus and uncus. The lateral ventricle, some of the caudate head, putamen, globus pallidus, thalamus, hypothalamus, fornix, and anterior and posterior commissures can be seen from this view, depending on the depth of the section.

It is often very difficult to appreciate the anatomy of the brain solely from neuroimaging, and readers interested in more familiarity with the neuroimaging anatomical correlates are advised to take advantage of several good web-based resources that give comprehensive overview of brain anatomy and imaging correlates, for example, Anatomy of the Brain from University of British Columbia (► www.neuroanatomy.ca, accessed October 27, 2016), The Brain from Top to Bottom from McGill University (► http://thebrain.mcgill.ca/, accessed October 27, 2016), and The Whole Brain Atlas from Harvard Medical School (► http://www.med.harvard.edu/aanlib/home.html, accessed October 27, 2016).

Cortical Cytoarchitecture Classification (Brodmann Areas)

One of the most influential works in neurology at the late nineteenth and early twentieth century is the work by Korbinian Brodmann. Brodmann, a German neurologist-psychiatrist, classified cortical areas in humans and mammals based on the cytoarchitecture using Nissl staining technique. He made important assertions regarding the evolution and development of the cortex and suggested that difference in cytoarchitecture translates to differences in functional correlates, a concept that continues to be very influential in clinical neuroscience disciplines including psychiatry, neurology, and neurosurgery. Brodmann areas are routinely reported on in neuroimaging research, which resulted in better understanding of functional correlates of these areas and their involvement in functional brain networks [5].

Full description of Brodmann areas is beyond the scope of this chapter. ◘ Table 3.1 summarizes anatomical and functional correlates of key Brodmann areas relevant to geriatric psychiatry.

For more details of Brodmann areas and their anatomical and functional correlates, the reader is referred to web resources, for example, Brodmann's Interactive Connectivity Map (► http://www.fmriconsulting.com/brodmannconn/intro.php, accessed October 29, 2016). ◘ Figure 3.1 illustrates a sample of neuroanatomical correlates using structural images (mainly MRI T1 images).

More recently, and due to advances in neuroimaging methodology, new cortical mapping and parcellation techniques have been suggested. A recent publication demonstrated that using multimodal MRI images from 280 participants in the Human Connectome Project (HCP) and by applying a semiautomatic neuroanatomical parcellation approach, the authors were able to delineate 180 distinct cortical areas per cerebral hemisphere. With a machine learning classifier software, they were able to classify 96.6% of cortical areas in a new human subject [6]. It is likely that future studies will utilize modern methods of parcellation and update functional correlates of cortical areas beyond Brodmann area's current description.

Functional Brain Networks

Advances in functional brain imaging, especially functional MRI (fMRI), diffusion tensor imaging (DTI), and positron emission tomography (PET), and the increased sophistication in image analysis methodology have allowed better understanding of the functional anatomy and functional connectivity between different brain areas and gave rise to large-scale neuronal networks, which can be studied in neuropsychiatry [7]. Consistent temporal correlation between different brain areas as seen in resting-state fMRI (rsfMRI), event-related fMRI, and PET scanning allows mapping of several brain networks. There are three main consistent large-scale networks that have significant evidence in neuropsychiatric disorders: default mode network (DMN), central executive network (CEN), and salient network (SN) [8]. The DMN is composed mainly of midline structures including medial prefrontal cortex and posterior cingulate cortex in addition to the precuneus and lateral parietal cortex. This network is usually active at rest and when the person is not engaged in any specific external task but rather in self-referential processes (introspection) [9–11]. The CEN, also referred to as frontoparietal network, is composed of lateral prefrontal and intra-parietal areas and is usually active in response to external tasks such as working memory and performing cognitive tasks [12, 13]. The SN, also referred to as anterior cingulo-insular network, is composed of the anterior insula (mainly on the right side) and the dorsal anterior cingulate cortex in addition to a loop of subcortical structures (areas in the striatum, globus pallidus, sub-thalamic nucleus, and thalamus) and is thought to be somewhat of a switch between the DMN and CEN as it attaches salience to stimuli and allows the person to "tune in" to what is more relevant to him/her [14, 15]. Advanced meta-analytic tools applied to the vast amount of structural and functional neuroimages have allowed better modeling of the core networks involved in several psychiatric disorders. The SN stood out as one network that is involved in several psychiatric illnesses. Deficiency in this network likely results in loss of "cognitive control" over emotional processes and a dysfunction in modulating the tension between inner drives and external demands, which is likely involved in the formation of different psychiatric symptomatologies. Understanding the deficiency in the SN network can lead to better therapeutic targets with brain stimulation and other modalities [16]. ◘ Table 3.2 summarizes major large-scale networks, their core structure, and main function.

Table 3.1 Key Brodmann areas and their anatomical and functional correlates

Brodmann area (BA)	Anatomical correlate	Function
BA10	Frontal pole, medial and lateral	Widely connected, complex social decision making and balancing
BA9	Dorsolateral prefrontal cortex, mainly lateral but some medial	Executive control area
BA8	Posterior to BA9 in lateral prefrontal cortex	Frontal eye field, executive function given its wide connections
BA6	Posterior portion of the lateral frontal area, just anterior to motor cortex	Motor initiation and programing, some language, memory and executive functions
BA46	Mid lateral prefrontal (middle frontal gyrus)	Involved in executive control of language (left) and in monitoring (right)
BA44, 45	Inferior aspect of lateral prefrontal area	Make Broca's complex, involved in language production (mainly in left dominant side) and some more complex aspects of language and pre-language behavior
BA47	Anterior inferior aspect of prefrontal area	Makes posterior part of orbital frontal cortex involved in language and social cognition
BA11	Base of the frontal pole	Connected to other limbic structures and to executive areas, involved in initiation of behavior
BA4	Precentral (part of frontal lobe)	Primary motor function
BA1, 2, 3	Postcentral (part of parietal lobe)	Primary sensory function
BA5 and 7	Superior parietal cortex	Association sensory-motor areas, involved in cortical sensory processing
BA40	Supramarginal, inferior parietal lobule	Complex cognitive processing, connected with frontal executive areas, part of central executive network
BA39	Angular gyrus, inferior parietal	Involved in complex tasks including language, calculation, and spatial orientation
BA21	Middle temporal	Involved in semantic, prosodic, and complex sound processing and deductive reasoning
BA41 and 42	Superior temporal	Primary auditory area
BA 13–16	Insula and temporal-insular junction	Part of salience network, involved in somatic representation, pain (posterior), and affective processing (anterior)
BA31	Posterior cingulate cortex	Part of the default mode network, involved in self-referential function
BA25	Sub-genual cingulate cortex	Involved in affective processing and depression
BA38	Temporal pole	Involved in emotional processing
BA37	Medial aspect of inferior temporal area	Facial recognition
BA28 and 39, BA35–36	Entorhinal area and perirhinal areas (medial temporal)	Memory and spatial function
BA17, 18, 19	Occipital cortex	Primary, secondary, and association visual areas
BA24, 32, and 33	Anterior cingulate cortex	Involved in salience network, connection between cognition and emotion, motivation

3.1.3 Age-Related Changes in Brain Structure and Brain Networks

With aging, several changes are expected in brain structure and function. In general, brain volume declines with age at a rate estimated at 0.5–1% per year. There is evidence on shrinkage of brain matter and enlargement of ventricles, but this pattern is heterogeneous with larger involvement of frontal and temporal cortices in addition to subcortical nuclei mainly the putamen, thalamus, and nucleus accumbens. This loss of gray matter volume is thought to be due to shrinkage of neurons and loss of dendritic spines and synapses

rather than neuronal loss per se. There is also evidence for loss of myelinated axon length by up to 50%. These changes correlated with age-related cognitive changes like decline in processing speed, executive function, and episodic memory [17]. (See ► Chap. 4.) In a study of 54 healthy volunteers aged 20–86 years, gray matter loss during adult life seemed to have linear relationship with aging, while white matter loss accelerates in middle age [18]. Although this study did not identify difference in the rate of gray and white matter atrophy between the sexes, an earlier study did show that age-related shrinkage in some central nervous system domains (e.g., sulci, lateral fissure, cerebrospinal fluid volume, and in parietal-occipital areas) is more prominent in males compared to females [19]. Although brain volume change has been considered "normal for age," there is evidence that gray matter volume loss might be overestimated and is in fact linked to future cognitive decline especially in the prefrontal area [20, 21].

Another change that has been considered as "normal for age" is an increase in white matter hyperintensities. It is estimated that one third of people over age 60 have white matter hyperintensities [22]. In addition to age, female gender, high

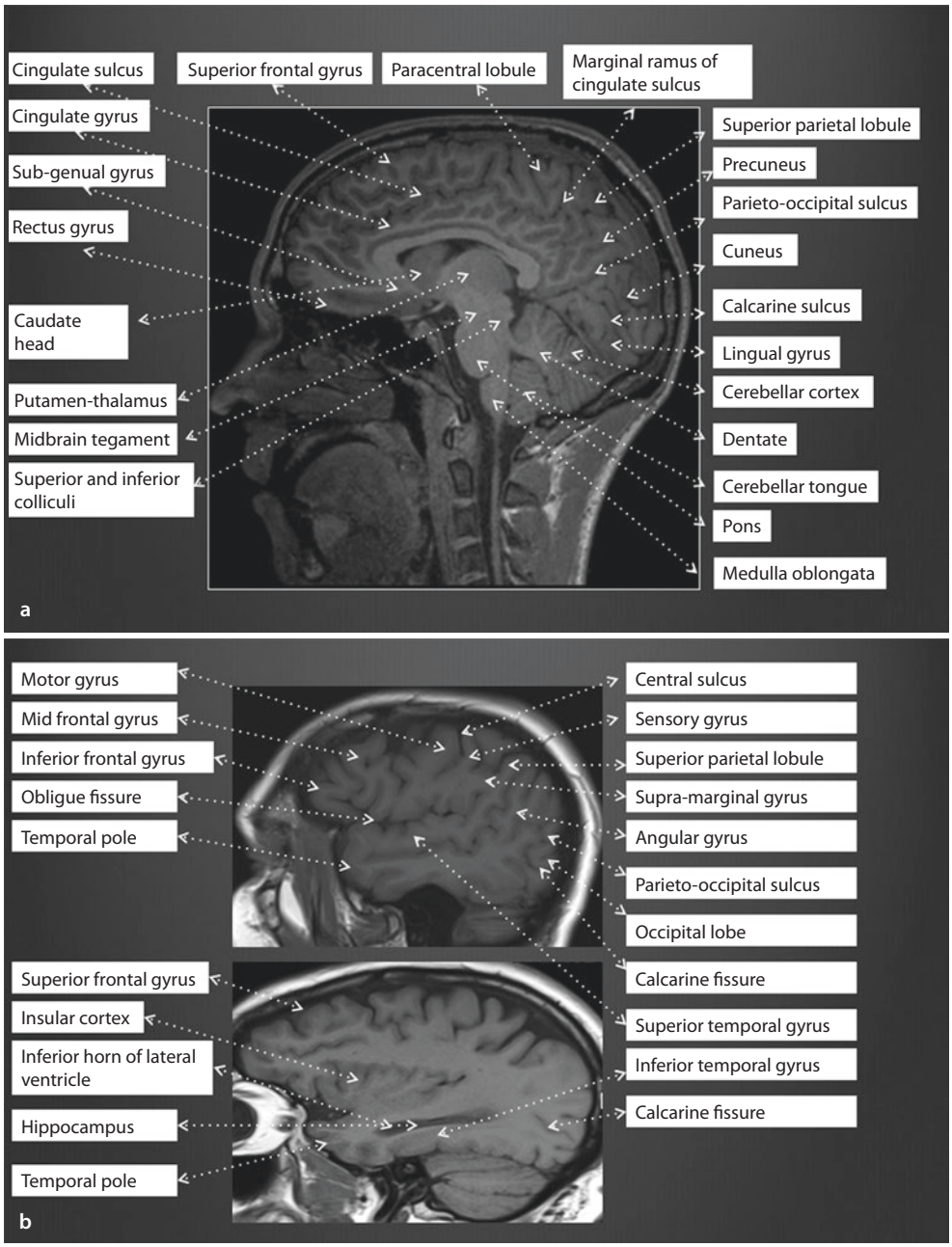


Fig. 3.1 Illustration of the main anatomical structures seen on T1 structural MRI images. **a** Medial view, **b** lateral view

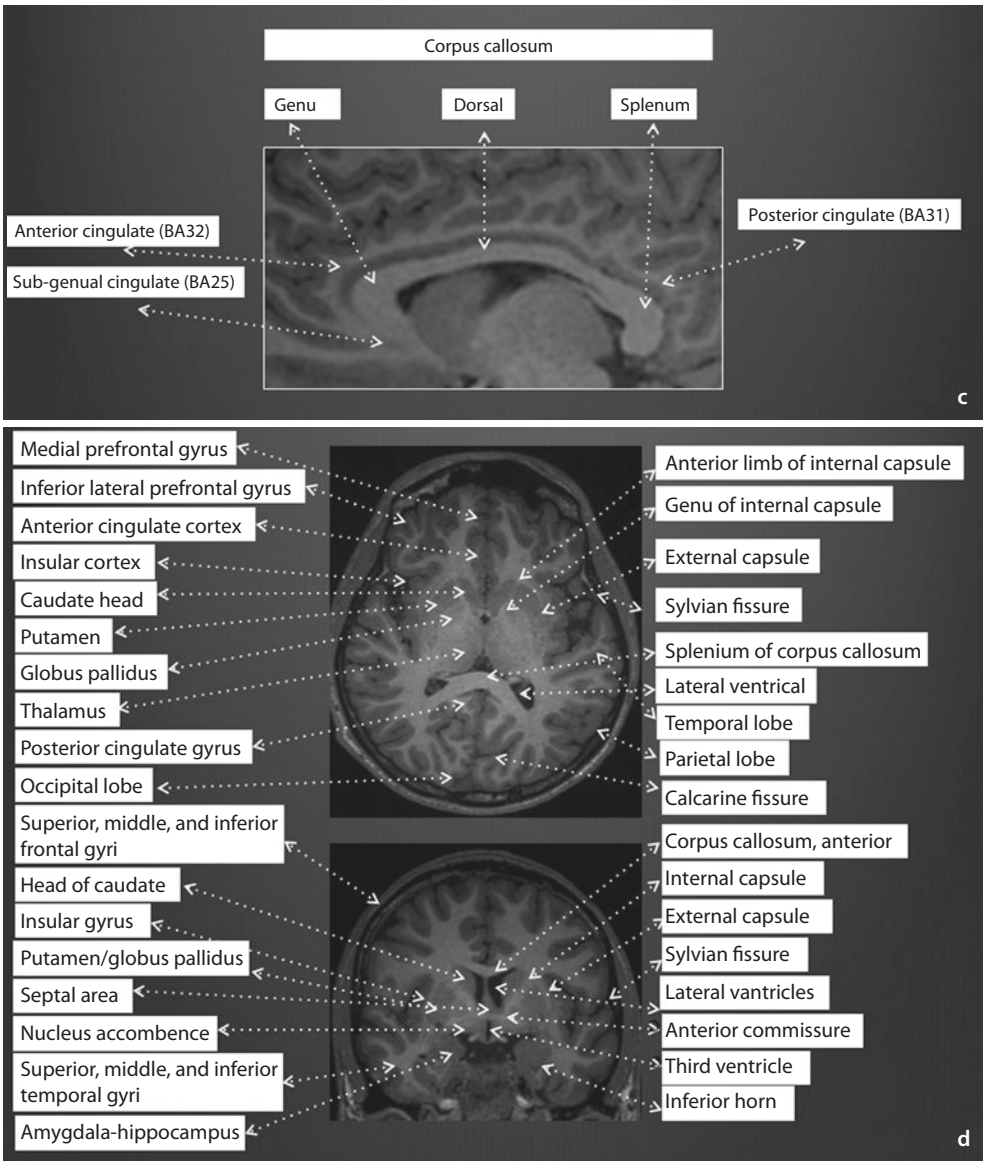


Fig. 3.1 (continued) **c** Closeup look at the cingulate gyrus with some Brodmann areas added for demonstration, and **d** transverse section (*upper*) and coronal section (*lower*) approximately at the level of the anterior commissure

Table 3.2 Summary of the three main large-scale networks, their structure, and function

Network	Anatomical structures	Function
Default mode network (DMN)	Medial prefrontal cortex (mPFC) Posterior cingulate cortex (PCC) Precuneus Lateral parietal cortex	Introspection Self-referential
Central executive network (CEN), aka frontal-parietal network (FPN)	Lateral prefrontal cortex (lPFC) Intra-parietal cortex (including inferior parietal lobule)	Extrospection Task-related Involved in cognitive tasks
Salience network (SN), aka anterior cingulo-insular network (aCIN)	Dorsal anterior cingulate cortex (dACC) Anterior insular cortex Subcortical loop: Striatum Globus pallidus Sub-thalamus Thalamus	Emotional network Switch between DMN and CEN based on salience to the individual Crossroad between several psychiatric illnesses

systolic blood pressure, and aortic atherosclerosis are other risk factors for white matter hyperintensities [23–25]. These changes in white matter can be seen in periventricular and/or in deep white matter locations. Despite relatively similar appearance on MRI (T2 and FLAIR sequences; see below for description), the nature of these lesions is somewhat heterogeneous in terms of histological nature including white matter infarction, gliosis, or plaques of demyelination [26, 27]. The appearance of periventricular white matter hyperintensities in terms of the irregularity of lesion edges is thought to be related to their histological nature, i.e., lesions with irregular edges tend to be ischemic in nature, while those with smooth edges are more related to gliosis and demyelination [28].

The above changes in brain structure likely contribute to modification in brain networks in old age. Detailed discussion of these changes is beyond the scope of this chapter. Briefly, there are two main lines of research into cognitive network activity and connectivity with aging: task-related fMRI and resting-state fMRI. Task-related fMRI involves obtaining brain activation pattern as it is related to a cognitive task (i.e., event-related, like working memory and episodic memory tasks). Several studies identified modification in fMRI BOLD (described below) signal during cognitive tasks in older compared to younger adults. Examples of these modifications include loss of cortical specificity (dedifferentiation), recruitment of wider network to achieve the same task (indicating compensation), and more involvement of frontal rather than posterior networks when performing the cognitive task. This sizeable literature resulted in several models to explain cognitive aging including scaffolding theory of aging and cognition (STAG) [29], system vulnerability view [30], and brain maintenance hypothesis [31].

Resting-state fMRI (rsfMRI) connectivity studies have the advantage of not being task-performance dependent, which makes them more feasible and less subject to variability. Converging evidence suggests reduction in connectivity in large-scale networks including DMN, SN, and CEN networks with aging. This change correlates with cognitive changes with aging and is likely the result of changes in brain structure described above (please see [32] for review).

3.1.4 Overview of Brain Imaging Modalities

This section describes the various clinical neuroimaging techniques currently used in management of geriatric psychiatry. Advantages and disadvantages of each imaging modality are outlined. Brief descriptions of emerging imaging tools reserved for research studies are highlighted.

Brain imaging techniques fall under two broad categories based on whether they are used for (1) structural or (2) functional imaging. In most clinical settings, structural imaging modalities are established primary care diagnostic tools for detecting changes in brain morphology, volume, and overall integrity. Computed tomography (CT) system and magnetic resonance imaging (MRI) are the key established modalities for clinical anatomical imaging. Recent technological advances in hardware instrumentation and software capabilities, notably in areas of image resolution, data storage, and image reconstruction, have allowed rapid increase in clinical adoption of functional imaging modalities. Single-photon emission computed tomography (SPECT) and positron emission tomography (PET) are now routinely used to characterize deficits in brain blood flow and glucose metabolism in psychiatric patients. Each imaging modality contributes to better understanding of neurobehavioral disorders.

Structural Brain Imaging

Computed Tomography (CT)

Computed tomography is a three-dimensional (3D) representation of x-ray absorption from different tissues in the brain. Put differently, brain CT scans are multiple x-ray images acquired around the head at multiple angles from top of the first cervical vertebra through the top of the calvarium, creating cross sections or "slices" of the brain. Most clinical CT scanners used in brain imaging are multislice CT scanners, developed in the late 1980s known as helical or spiral CT scanners. Helical CT scanners consist of a patient table and multiple arrays of thinly collimated scintillation detectors linked to a rotating x-ray tube, which is the source of x-ray beams. A patient lying on the imaging table is moved through the ring of detectors and x-ray tube, as the detector and x-ray tube rotate continuously around the patient in a helical or spiral fashion. The transmitted x-ray beam from the patient interacts with the crystal elements in each detector, and the radiation is converted to light, electronically amplified and finally converted to an electrical signal. The resulting CT image is a reconstructed 3D image of the signals in brain slices where each volume element (voxel) within a given slice contains the summed signal intensity (I) or attenuated values (μ) along the path of the x-ray beam.

$$I = I_0 e^{-\Sigma^{n}_{i=1} \mu i \Delta x}$$

I = transmitted x-ray intensity, I_0 = original x-ray beam intensity from the source, e = Euler's constant, μ = linear attenuation coefficient, and Δx = slice thickness.

The contrast between different tissue types is the varying signal intensities based on varying tissue densities. For instance, denser structures such as the bone appear bright on CT images because the bone attenuates more x-ray compared to thinner structures such as the ventricles, which appear almost as dark as air. A simpler way of quantifying the amount of x-ray attenuation in tissues is to relate each tissue linear attenuation coefficient, the fraction of x-ray beam absorbed, to a reference value such as the linear attenuation of water. Hence, clinical CT images are distribution of CT numbers expressed in Hounsfield units (HU), where the CT number is

$$\text{CT Number (HU)} = \left[\mu_{\text{tissue}} - \mu_{\text{water}}\right] / \mu_{\text{water}} {}^{*} K$$

K = contrast or scaling factor = 1000

The quality of CT images including spatial resolution, noise, and contrast resolution is closely related to the absorbed x-ray dose. In turn, CT dose is governed by the amount of x-ray delivered (measured in mill amperage, mA), quality of x-ray beam delivered (measured in peak kilovoltage, kVp), and the length of time the patient is exposed to the x-ray (measured in seconds) [33]. The amount of radiation given to a patient is measured and tightly regulated to ensure that overexposure leading to tissue damage is avoided. A measure of the quantity of deposited radiation energy including x-ray, gamma ray, beta, or alpha particles is called the absorbed dose. The unit of absorbed dose is gray (Gy) or in metric, rad (radiation absorbed dose). 1 Gy = 100 rad. In CT, dose exposure is estimated for each patient examination and related to several factors such as dose distribution of the beam intensity along the patient path, thickness of the beam collimation, the number of detectors, and the pitch, which is the distance the table travels per tube rotation [34]. For simplicity, a calculated absorbed dose reference level, referred to as the volume computed tomography dose index (CTDIvol), is provided on the scanner by the manufacturer for each scan when the appropriate imaging parameters are set. Table 3.3 outlines suggested imaging parameters for a routine CT brain scan applicable to geriatric psychiatry clinical indications. Note that most clinical CT scans of the brain do not require exogenous contrast enhancement, except in cases related to cerebrovascular disease or neuro-oncology. As such the use of contrast media is not included and will not be further discussed.

Table 3.3 Standard clinical CT brain imaging parameters[a]

Parameter	Description	Set value
Mode	Helical scanners can be operated in sequential or non-spiral mode, often referred to as axial mode or step-and-shoot. Helical offers faster imaging and less motion artifacts	Helical
kVp	Peak kilovoltage; the maximum voltage applied to the tube	120
mA	Tube current or the number of electrons produced by the tube per second. The lower the tube current the lower the dose	300
FOV	Vendor preset field of view (FOV); small, medium, or large body. For head, small body is used to maintain isotropic imaging and minimize radiation exposure	SFOV
Rotation time	The lower the rotation time, the lower the radiation dose but the higher the image noise	0.5 seconds
Pitch	Applies to helical CT; the distance the table travels in mm in one 360^0 tube rotation. The larger the pitch, the lower the patient dose	0.531:1
Speed (mm/second)	The table feed speed; how fast the table translates through the gantry per tube rotation in mm per second	10.62
CTDIvol (mGy)	CT dose index; the diagnostic reference level set by the American College of Radiology for brain imaging is 75 mGy	54.15
Image reconstruction	One with standard algorithm and second one with bone algorithm; thickness and interval = 5 mm	2

[a]This is based on typical imaging parameters used on a 32-multislice GE Healthcare CT scanner. Variations between vendors might exist. For more information, other vendors suggested CT brain imaging parameters (see AAPM Adult Routine Head CT Protocols Version 2.0 March 1, 2016) (► https://www.aapm.org/pubs/CTProtocols)

Teaching Point

In general for all forms of radiation, absorbed dose reduction can be achieved by minimizing the distance from the radioactive source, decreasing time exposed to the source, and increasing collimation thickness.

Magnetic Resonance Imaging (MRI)

Since the production of the first MR image of a live human nearly 40 years ago, MRI has rapidly advanced at a pace much faster than other imaging modalities [35]. The first human scan in July 1977, for instance, was an image of the chest acquired over 4 hours in a scanner twice the diameter and length of current clinical scanners (► http://www.smithsonianmag.com/). Today, a similar image can be acquired in less than 5 minutes with ten times better spatial resolutions. Over the past 40 years, the strength of the magnetic field has gone from 0.5 Tesla in the mid-1980s to 7 Tesla. Tesla (T) is a measure of the magnetic flux density. One Tesla is equivalent to 10,000 gauss (a measure of magnetic flux). For comparison, the earth's magnetic flux density is around 5×10^{-5} T or 0.5 gauss, and a refrigerator magnetic field strength is 0.005 T. Modern clinical MRI scanners have field strength of 1.5 T. MRI scanners used in clinical research can range from 3 T to 7 T.

The ability of MRI to produce high spatial resolution and good soft tissue contrast makes MRI appealing for investigating subtle anatomical (and to a larger extent, functional) abnormalities. An MR image of the brain is created when the head is exposed to the electromagnetic field produced by a strong MRI magnetic field. The human body is made up of large pools of hydrogen atoms (H^+, a component of water or H_2O), each consisting of one subatomic particle in the nucleus, called a proton. Hydrogen protons rotate freely around their own axes, in a manner similar to a toy-spinning top after it has been hit. When hydrogen atoms in the body are exposed to the strong magnetic field of an MRI, the protons are "magnetized," meaning the initial random nondirectional motion of their collective spins is now aligned with the direction of the MRI's magnetic field. In the case of a

patient lying on their back for a brain scan, majority of their hydrogen protons will line up in the direction of the head or feet when placed inside the magnetic field of the MRI scanner. The protons aligned in either the head or feet will cancel out, leaving a few protons that are not perfectly aligned to the MRI field. If the MRI radiofrequency pulse is applied to the remaining protons, it will cause the protons to spin at a certain frequency and in a given direction. When the radiofrequency pulse is removed, the hydrogen protons will return back to their natural orientation, releasing energy that is detected as MRI signals. This process is called relaxation. Thus, the MRI contrast in an image depends on the amount of relaxation of the hydrogen protons.

Hydrogen proton relaxation is measured using two MRI values, T1 and T2. T1 and T2 images are acquired using T1-weighted and T2-weighted pulse sequences, respectively (see suggested optimal imaging parameters in ◘ Table 3.4). Each imaging sequence is generated by manipulating two distinct timing parameters measured in milliseconds (ms), echo time (TE) and the repetition time (TR). Echo time refers to the time duration after application of a radiofrequency pulse and before readout or sampling of the MRI signal following proton relaxation. Repetition time is the time period between successive radiofrequency pulses. T1-weighted images are created by combination of a relatively short TE and TR times, producing brain images where tissues with bound hydrogen protons (such as fat) give off high signal and appear bright, while fluids containing large pools of free hydrogen protons such as cerebrospinal fluid (CSF) give off low signal and appear dark or black. This is because the free pool of hydrogen proton in CSF has not fully relaxed back to their natural state giving off only a small fraction of their maximal signal, before signal readout by the computer. The large difference between T1 values of CSF, gray matter, and white matter produces high tissue contrast necessary for evaluating areas of subtle changes in gray matter structure and volume. On the other hand, T2-weighted imaging is the reverse of T1, a combination of long TR and long TE. Fluids such as CSF are the brightest in T2 images, because their long T2 values are ideal for longer TE and TR times, ensuring that a larger fraction of their maximum signal is readout by the computer. T2 images are ideal for evaluating white matter lesions and intracerebral vascular changes such as hemorrhage, inflammation, and edema.

◘ Table 3.4 Standard T1 and T2 brain imaging sequences (at 3 T)

Sequence	Parameters
T1-weighted	TR/TE/T1 = 2000/2.96/900 milliseconds Flip angle = 9^0 Slices/slab = 176 FOV = 256 × 256 Acceleration factor = 2 Voxel size = 1.0 mm^3 isotropic Bandwidth = 240 Hz/Px Three-dimensional acquisition Total acquisition time = 4 minutes 8 seconds
T2-weighted FLAIR (fluid-attenuated inversion recovery)	TR/TE/T1 = 5000/395/1800 milliseconds Slices/slab = 160 FOV 256 × 256 Acceleration factor = 2 Voxel = 1.0 mm^3 isotropic Bandwidth = 781 Hz/Px Three-dimensional acquisition Total acquisition time: 5 minutes, 52 seconds

Note: 3 T scanner is twice the field strength of 1.5 T. Expect increased signal-noise ratio, temporal resolution (faster imaging), spatial resolution, T1 relaxation times, and specific absorption rates (amount of radiofrequency energy deposited per unit mass of tissue) compared to 1.5 T. Sequence parameters are optimized for a Siemens 3 T Verio MRI scanner. Imaging parameter names may vary with vendor
T1 = inversion time, time between a 180° and a 90° pulse for spin echo-based sequences
FOV = field of view in X (longitudinal) and Y (transverse) plane
Acceleration factor increases acquisition speed by a set factor value
Bandwidth is the frequency range allowed in the MRI signal in hertz per pixel (Hz/Px)

Teaching Point
The large difference between T1 and T2 values of CSF, gray matter, and white matter produces the high tissue contrast necessary for evaluating changes in brain structure and volume.

Other combinations of TR and TE are possible, each producing varying tissue contrasts. For example, a short TE and long TR will produce a proton-density weighted image. Advanced imaging sequences such as arterial spin labeling (ASL), used to directly measure cerebral blood, or blood-oxygen-level-dependent (BOLD) MRI, for relating changes in deoxyhemoglobin to brain function, are advanced variations of T1/proton-density-weighted and T2-weighted sequences, respectively. ASL and BOLD are increasingly gaining clinical relevance especially for mapping of functional brain networks in populations with major neurocognitive disorders [36] and localizing eloquent regions in epilepsy patients [37]. ASL is a noninvasive MRI-based perfusion imaging technique where the inflow of magnetized blood spins from the neck is measured downstream in the brain, a short time after arrival. The cerebral blood flow (CBF) images from ASL scans are similar to CBF images from PET measurements of radiolabeled ^{15}O-water tracer [38]. Regional CBF measurement with ASL also correlates well with regional cerebral metabolic rate measurement using ^{18}F-FDG PET in normal healthy adults [39–41] and Alzheimer disease patients [42, 43]. These observations suggest that these noninvasive and radiation-free MRI techniques are ideal for detecting and long-term monitoring of functional changes in the brain.

In the interim, clinically available T1- and T2-weighted imaging sequences can provide added quantitative

information beyond qualitative visual inspections currently practiced. Statistical modeling techniques can be applied to T1 and T2 images to reveal subtle regional differences over time within an individual or groups of patients or between patients and controls [44]. Voxel-based morphometry (VBM) and cortical thickness mapping (CTM) are automated techniques for segmenting T1 or T2 images and statistical mapping of local changes in gray matter or white matter concentration, cortical shape, and cortical thickness. Clinical T1 scans can be readily analyzed using open-source and free-for-use software such as Statistical Parametric toolbox (SPM, University College, London, UK, ► www.fil.ion.ucl.ac.uk/spm/) and FMRIB Software Library (Oxford University, Oxford, UK, ► http://fsl.fmrib.ox.ac.uk) for VBM analysis or Free Surfer (Harvard University, Boston, USA, ► https://surfer.nmr.mgh.harvard.edu) for CTM. Several VBM and CTM studies in large cohorts of individuals over the human life span have revealed temporal patterns of age-related brain atrophy [45, 46] and distributed patterns of atrophy related to neurodegenerative disease [47, 48]. It is evident that VBM and CTM could also serve as sensitive diagnostic biomarkers for detecting, characterizing, and quantifying neurobehavioral disease progression.

Contraindications for Structural Imaging

MRI and CT are complimentary structural imaging tools. In certain cases one modality could be preferred over the other. Contraindications and advantages for each imaging tools are outlined in ◘ Table 3.5. In general, both CT and MRI are poor at handling metallic objects embedded within the skull, jaw, or brain. Surgical aneurysm clips, orthodontic implants, and dental crowns create signal voids in MRI and streaking artifacts from x-ray beam hardening and scatter in CT images. Known allergic reactions to MRI contrast media for evaluation of vascular lesions, neoplasms, stroke, and inflammation may permit the use of a complimentary non-contrast CT scan. Evaluation of bone-related neoplastic processes or evaluation of cortical ossicles is better obtained from CT scans compared to MRI.

◘ Table 3.5 Comparison of structural brain imaging modalities

	CT	MRI
Radiation burden	1 scan (~2.2 mSv/year)[a] is less than the average annual radiation dose from natural background radiation (3.1 mSv/year)[a]	None
Tissue contrast	Good soft tissue contrast	Excellent soft tissue contrast
Scan time	Faster, order of seconds to less than 1 minute; less prone to patient motion	Slow; few minutes long for each sequence; prone to patient motion
Claustrophobia	Relatively larger bore; easier for claustrophobic-prone patients	Smaller enclosed bore; sedation may be offered
Trauma-friendly	Yes	In certain cases; transfer from emergency room to MRI-safe monitoring devices and intravenous lines are required
Metallic implant contraindication	Safe to scan; metallic streaking artifacts might exist	Conditional-safe; thorough screening is required before admitting patient to MRI suite

[a]NCRP Report No. 160, Ionizing Radiation Exposure of the Population of the United States. Available at ► www.ncrponline.org, Accessed November 19, 2016

Functional Brain Imaging: SPECT and PET

The primary role of functional imaging in neuroradiology has long been recognized as a means of detecting subtle disease-related brain changes. Patterns of functional brain abnormalities serve as biomarkers for detecting and characterizing brain disorders and often precede deficits in cognitive function, which in turn precede structural abnormalities [49]. The fundamental understanding that brain function is related to local changes in cerebral blood flow (CBF) or glucose metabolism (CMRglc) is central to the use of functional imaging techniques such as PET and SPECT in evaluation of functional deficits. Earlier measurements of brain function in humans used invasive serial sampling of arterial/venous blood during continuous inhalation of inert gas mixtures to measure changes in global CBF [50] or linked indirect changes in blood volume from cortical surface pulsations measures to task-evoked brain responses [51]. The advent of nuclear engineering following World War II led to discoveries of safe radioisotopes capable of capturing in vivo local changes in CBF or CMRglc, revolutionizing the field of neuroimaging.

PET and SPECT imaging are in vivo molecular imaging methods used in mapping the distribution of trace amounts (nano- to picomoles) of radioactive compounds injected into the body. Radiotracers are radioactive isotopes attached to targeted analogs of biologically active molecules found within the body such as a sugars, proteins, enzymes, or hormones. Using highly sensitive scintillation detectors, the minute amount of radioactive atoms bound to the radiotracers within the body are detected each time an atom disintegrates (decays), from an unstable radioactive atom to its stable chemical form. For instance, fluorine-18 (^{18}F), the most common PET tracer, is a radioactive fluorine isotope that decays after a short period of time to a stable ^{18}oxygen (^{18}O) molecule. Depending on the atomic composition of the radioactive isotope, each radioactive decay results in release of either gamma photons, beta particles, or alpha

particles. The amount of time it takes for a radioisotope to decay is measured by the length of time it takes a quantity of the radioisotope to decrease by half, known as the half-life. A quantity of radiation emitted by a radioisotope measured in SI unit is the becquerel (Bq), or non-SI metric unit is the curie (Ci), named after the 1903 Nobel Prize in Physics winners, Henri Becquerel, Pierre Curie, and Marie Curie. 1 Ci = 3.7×10^{10} Bq and 1 Bq = 1 disintegration per second.

When a radiotracer is injected, inhaled, or ingested into the body, the tracer interacts physiologically with the targeted body tissue, decays, and emits gamma photons detected by scintillation detectors. The location of distributed radiotracers in the body can be tracked by the path the photon traveled after exiting the body to strike the detector crystals, known as the line of response (LOR). In SPECT, a single gamma photon is released after tissue absorption and each radiation decay. The LORs are shaped by collimators mounted over the large flat scintillation detectors to allow or block photons, depending on the LOR angle. Photons are counted if they pass between septal walls of the collimator and fall within a set energy window, typically around the radioisotope's peak energy. The sensitivity (the amount of photons detected) and spatial resolution (the full-width-half-maximum (FWHM) of the line spread function) are largely influenced by the shape, width, and length of the collimator. For brain imaging, fan-beam or cone-beam collimators are preferred to parallel-hole collimators due to their ability to converge and magnify objects at a distance away from the detector [52]. Parallel hole is more readily available and can be used if placed in close proximity to the head. SPECT cameras with more than two detectors (dual-head systems) are necessary for brain imaging, to improve sensitivity and minimize motion from long scan times.

In contrast to SPECT, PET tracer LORs are defined by the coincidence detection of two photons arriving at the same time in almost opposite directions, close to 180^0 apart. In PET imaging, a positively charged beta particle, called a positron, is initially emitted following radioactive decay, exists briefly, and is quickly annihilated to two gamma photons. The gamma photons exit the body at opposite directions and are counted if they interact with the detector crystals at the same time. As such, PET systems are rings of detector blocks mounted on a gantry similar to CT systems, but unlike CT, they are stationary. Because of the coincidence detection nature of PET, physical collimation is not required, giving PET a much higher sensitivity profile compared to SPECT (see Fig. 3.2). However, electronic collimation is used in PET to improve signal-to-noise ratio, limited by noncollinearity of annihilated photons and detection of random coincidences. Other contrasting features of PET and SPECT are listed in Table 3.6.

Because of the added costs for production of SPECT tracers and more so for PET, anatomical imaging using CT and MRI techniques is more prevalent in clinical neuroimaging and often used as the first line of investigation before functional imaging. The introduction of hybrid PET/CT and recently PET/MRI has seen a resurgence in demand for PET

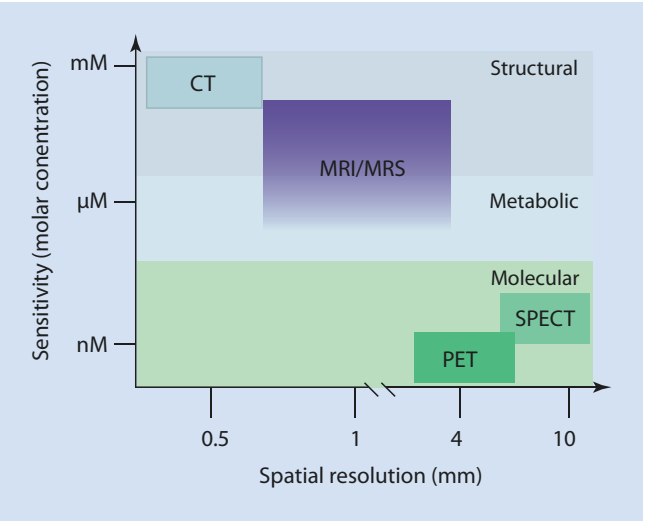


Fig. 3.2 Comparison of sensitivity and spatial resolution limits across neuroimaging modalities

Table 3.6 Key differences between PET and SPECT

Characteristics	PET	SPECT
Radiation decay	Two positrons	Single gamma photon
Half-life	Short (minutes to hours)	Longer (hours to days)
Energy (kiloelectron volts, kev)	~511	93–364, 99mTC = 140
Production	Cyclotron-produced	Generator-produced

imaging. Ten years ago, ^{18}F-2-fluoro-2-deoxy-D-glucose (^{18}F-FDG) was the sole PET tracer approved for clinical diagnostic brain imaging in the United States and Europe. Recently, the US Food and Drug Administration (FDA) approved the use of three PET ß-amyloid tracers for dementia imaging [53] and one new SPECT dopamine transporter (DaT) tracer for parkinsonism syndromes [54]. In addition, a number of promising brain radiotracers with high clinical application have been approved for use in clinical trials or human research studies in the United States, Canada, and Europe (see Table 3.7).

Nonetheless, ^{18}F-FDG still remains the most widely used tracer for PET imaging since it was first synthesized as an analog to Louis Sokoloff and colleagues' ^{14}C-2-deoxyglucose [55]. The normal regional distribution of ^{18}F-FDG in the brain is well established. ^{18}F-FDG is an analog of glucose where one of the normal hydroxyl groups in position 2 of the glucose carbon cycle has been replaced with ^{18}F. When injected into the bloodstream, ^{18}F-FDG initially behaves similar to glucose and is transported into brain cells and phosphorylated, but then cannot undergo further glycolysis. This

Table 3.7 PET and SPECT tracers for clinical neuroimaging

Tracer	Modality	Use
In routine clinical use (approved by FDA[a], EMA,[b] and Health Canada[c,d])		
F18-2-fluoro-2-deoxy-D-glucose (FDG)[a,d,b]	PET	Glucose metabolism
O15-water (long-standing use in research studies only)	PET	Brain blood flow
99mTC-ethyl cysteinate dimer (ECD)[a,c,b]	SPECT	Brain morphology
99mTC-hexamethylpropyleneamineoxime (HMPAO)[a,c,b]	SPECT	Brain blood flow
F18-Florbetapir[a,d,b]/F18-flutemetamol[a,b]/F18-florbetaben[a,b]	PET	β-Amyloid plaque burden
I123-Ioflupane[a,b]	SPECT	Dopamine transporter (DaT)
Selected emerging tracers		
Avid F18-AV1451	PET	Tau distribution
C11-PK11195/F18-FEPPA	PET	Neuroinflammation
C11-raclopride/C11-DTBZ/F18-fluoro-L-DOPA	PET	Dopamine receptor
123I-Iodobenzamide/123I-iodobenzofuran	SPECT	Dopamine (D_2) receptor
[123I/125I]6-Iodo-2-(4′-dimethylamino-)phenylimidazo[1,2-a]pyridine (123I/125I IMPY))	SPECT	β-Amyloid plaque imaging
GA67-EDTA	SPECT	Blood-brain barrier

[a]Food and Drug Administration (USA)
[b]Approved for clinical use within the European Union by European Medicines Agency (EMA)
[c]Health Canada approved for routine clinical evaluation in selected clinical indications
[d]Health Canada approved for selected clinical trials or human clinical research studies

traps and accumulates ^{18}F-FDG in the brain in proportion to the local cerebral glucose consumption, providing a means of quantifying regional brain glucose metabolism. An increase in neuronal activity in response to a task will evoke a concomitant increase in CMRglc (see below explanations on the meaning of regional glucose use in the brain). Lesions, brain atrophy, or other underlying physiological impairments, such as decreased cognitive status, will show decreased CMRglc in areas associated with lesions or neuronal deficits. Because the brain continuously seeks glucose from the blood, patient preparation for ^{18}F-FDG brain imaging is critical to obtaining high-quality diagnostic images. Patients should be injected after fasting for up to 4–6 hours, in a darkened room, eyes open and awake with minimal sensory stimulation [56]. Imaging using a PET or PET/CT scanner can be performed after a minimum of 20 minutes of rest, ideally after 30–40 minutes. Eyes closed can cause artificial decrease in CMGglu in occipital lobes confounding findings for patients with Lewy body neurocognitive disorder, in whom appearance of decreased occipital CMRglc can often serve as a means of differentiating Lewy body from Alzheimer disease [57].

Attenuation of PET/SPECT photons stopped by the skull encasing the brain must be corrected using transmission scanning methods or CT-based attenuation correction methods [58]. A majority of clinical PET and SPECT scanners are hybrid PET/CT or SPECT/CT scanners, equipped with standard vendor-provided CT attenuation correction options. Failure to correct photon attenuation leads to gross underestimation of radiotracer distribution. For PET/MRI, attenuation correction is a major limiting factor for clinical adoption of the novel technology. PET/MRI is a 3 T MRI scanner with fully integrated PET detectors embedded between the body coil and main magnet gradient coil. Correction of PET signal attenuation in hybrid PET/MRI systems using MR images can be challenging because MR signals are proton-based and not directly translated to electron density. Recent evidence using MRI techniques that model bone signal [59] or include inferred bone anatomy from a CT atlas [60] or subject-specific MRI scan produces similar corrected PET images to CT [61]. However, more work is needed to evaluate the clinical potential of PET/MRI for simultaneous brain imaging.

Currently, clinical evaluation of PET and SPECT brain images is largely limited to visual inspection of known tracer distribution pattern by nuclear medicine physicians. Abnormal findings are reported in regions where spatial patterns differ from normal distribution or abnormal uptake is present in key regions associated with the disease. Quantitative evaluation of brain PET/SPECT, widely used in research settings, is slowly being adopted for clinical use. The magnitude and extent of spatial abnormalities can be quantified as adjuncts to visual inspection by comparing individual patient scans to a group of normal well-matched controls and, similarly, to polar maps generated for clinical interpretation

of myocardial perfusion SPECT imaging. Recent quantitative software developments by scanner vendors, approved by the FDA for use in ß-amyloid imaging (syngo(R).via MI Neurology, Siemens Healthcare, Erlangen, Germany), may in the near future lead to increased clinical use.

Teaching Point
Trace amounts of radioactive compounds interact with brain physiology and result in the emission of gamma photons detected by scintillation detectors as lines of response (LORs), which are reconstructed to produce a 3D image of the brain by the computer. In the case of SPECT, it is a single gamma photon, while with PET it is a positron that splits into two gamma photons emitted in opposite directions and strikes the detector at the same time. PET has better special resolution than SPECT and PET tracers decay faster, which requires having the tracer made locally.

Neuroimaging in the Clinic

Structural Brain Imaging in the Clinic: CT and MRI Scan

When working up a patient presenting with new-onset psychiatric (especially neurocognitive) disorders in old age, practitioners are faced with the question whether ordering diagnostic tests is necessary and whether they add value to the clinical process. A diagnostic test is usually evaluated using metrics such as sensitivity, specificity, and predictive value. When it comes to structural brain imaging, it is accepted that when there is suspicion of brain pathology that can change management plan, it is appropriate to order brain imaging. The question remains: what test is more appropriate to order, a CT scan or an MRI scan? As detailed above there are differences in the type of information learned, ease to access, exposure to radiation, cost and speed, and ease of acquisition.

Indications for which a structural CT scan may be ordered include:

- Need for quick scanning (e.g., in cases like trauma and/or acute-onset headache that could be hemorrhagic stroke).
- Cost; availability is more likely for CT scan and, as such, waiting time is usually much shorter.
- Heavy and/or claustrophobic patient that cannot be comfortable in MRI tube.
- Presence of devices that can malfunction, heat, or get displaced with magnetic field (e.g., pacemaker, ferrogenic clips).
- When looking for calcification or bone-related lesions or when looking for metals (e.g., shrapnel injury).
- In patients that are likely to move in the scanner (e.g., CT scan is brief and as such less vulnerable to motion artifact).

Indications for which a structural MRI scan may be ordered include:

- When more details of the anatomy are needed (e.g., evaluation of regional atrophy), because you can acquire different views without having to move the patient.
- When looking for small lesions like microbleeds, hemosiderin deposits, and lacunae in strategic locations (e.g., thalamic lacunae).
- When repeated imaging is required especially in vulnerable patients, this is mainly because of concern regarding ionizing radiation with CT scan.
- When evaluating areas adjacent to the bones (CT scan is more vulnerable to bone artifacts, e.g., in posterior fossa structures).

Please see Christopher Hess (▶ https://radiology.ucsf.edu/blog/neuroradiology/exploring-the-brain-is-ct-or-mri-better-for-brain-imaging).

Teaching Point
When ordering brain imaging in patients, it is essential to describe the clinical question and what is the indication for imaging so that the right imaging technique is used. An informed practitioner will write better informed referral question to the radiologist. For example, the patient is showing evidence of rapid deterioration in cognition, suspicion of microbleeds; please consider appropriate technique to rule in/out microbleed such as susceptibility weighted image (SWI).

Functional Brain Imaging in the Clinic: PET and SPECT Scans

PET imaging is still limited in its availability, with significant variations to access based on geography. Currently, the most widely used agent for clinical application in neuropsychiatry remains ^{18}F-FDG. This agent is a glucose analog, which accumulates in cells throughout the body in amounts proportional to glucose uptake by those cells. In the brain, the distribution of glucose utilization, and therefore of ^{18}F-FDG, is mostly driven by the activity of glutamatergic synapses (exceptions being, e.g., local inflammation, or the presence of neoplastic tissue). Therefore, a PET-produced 3D map of ^{18}F-FDG regional distribution in the brain is basically a 3D map of regional glutamatergic transmission.

SPECT is mostly applied to brain imaging to establish the 3D distribution of regional cerebral blood flow (rCBF). This technique is nowadays available in nuclear medicine departments. Different agents can be used to depict rCBF distribution, the two most frequently used ones being ^{99m}Tc-ethylene-dicysteine-dimer (ECD) and ^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO). Under most conditions (there are a few exceptions, without clear impact in the field of neurodegenerative diseases), rCBF is also a proxy for glutamatergic transmission, and therefore both

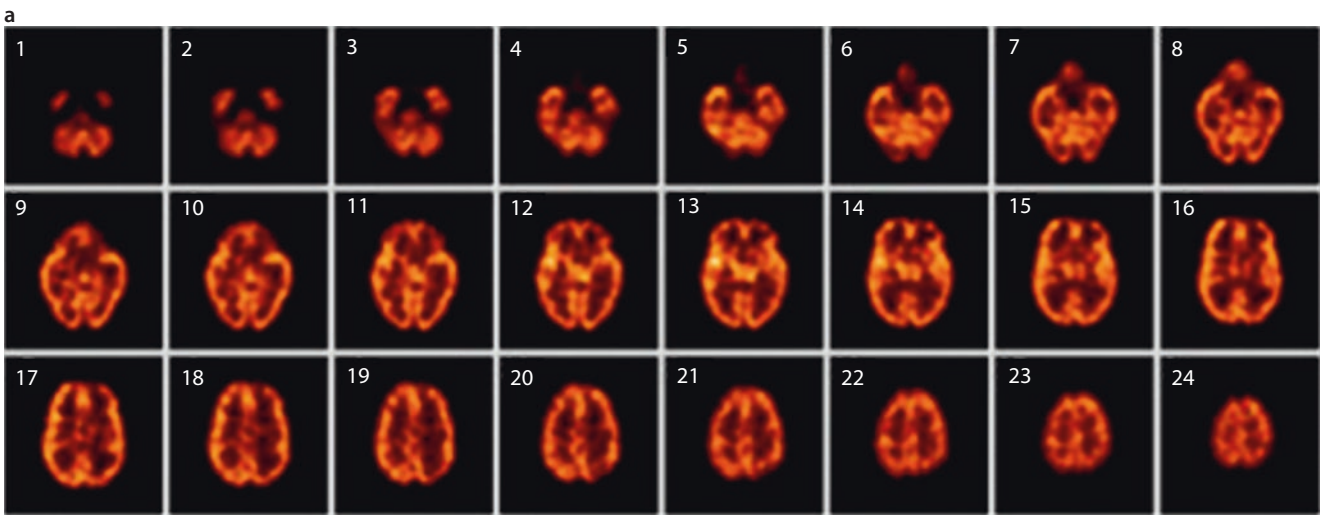
PET ^{18}F-FDG and SPECT rCBF studies generally depict the same process.

Although those studies are therefore largely equivalent from a biological perspective, PET and SPECT studies as mentioned above are quite different from a variety of perspectives. First, as already mentioned, their availability is different (advantage: SPECT), and in many areas, their cost is also not the same, SPECT being in general less costly, although there are exceptions. However, a very significant difference rests in their clinical performance for assessing neurodegenerative conditions, because PET has a clearly higher spatial resolution, which means that its ability to depict glutamatergic activity on a regional basis is better than that of SPECT, and PET offers significantly better diagnostic accuracy than SPECT (see ◘ Fig. 3.3). This has translated in recommendations by several guidelines [62–65] that recommend that PET be used as a first line when molecular imaging is required, reserving SPECT for cases that have no access to PET or do not even mention SPECT as an adjunct to diagnosis.

The use of ^{18}F-FDG PET imaging in the assessment of neurodegenerative conditions is based on the fact that, at least initially, those diseases affect synapses/neurons and therefore glutamatergic transmission (as most synapses in the central nervous system are of that nature) in a regionally defined fashion, which translates in imaging patterns that can be identified to establish the presence of a neurodegenerative disease as well as to differentiate them one from another.

Not unexpectedly, most of the data gathered over the past 35–40 years (cases were studied very early on after the development of the first clinically usable PET scanners, in the late 1970s) have been related to Alzheimer disease. Significant numbers of cases of other types of neurodegenerative diseases have also been evaluated since then, but both the understanding of the pathological process underlying them as compared to that of Alzheimer disease, which would help us understand why the ^{18}F-FDG PET patterns observed are of the type reported, and the clinical certainty associated with those patterns have not reached those of Alzheimer disease. Nevertheless, the following general remarks can be made with confidence:

- In Alzheimer disease, and in most other diseases seen with some regularity in a neuro-PET practice, the pathologic processes involved affect polymodal associative cortical areas (prefrontal, temporal, parietal) early on and spare primary cortices, with the notable exceptions of Lewy body disease (affecting primary visual cortices) and upper motor neuron diseases (affecting the primary motor cortex regions).
- The degree to which some of the polymodal areas are affected more than others allows us in many cases to actually propose a pathological diagnosis.
- There are significant variations however, even for the "same" pathological classifications, associated with known clinical variations (for instance, Alzheimer clinical variants such as logopenic aphasia or posterior cortical atrophy, among others, have typical presentations on ^{18}F-FDG PET imaging).
- ^{18}F-FDG PET imaging is a technique that allows us to actually evaluate cellular losses/dysfunction in the central nervous system. Although scintigraphic patterns of anomalies usually correlate with the clinical presentation of a subject, their significance in terms of disease stage is often not very reliable, because the link between pathology of the brain and clinical status is modulated by parameters such as cognitive reserve of, and environmental demands on, patients. Therefore, questions such as "Is this patient demented?" cannot be addressed; however, ^{18}F-FDG PET can help determine whether or not a neurodegenerative process is present, whatever the clinical state of a subject might be.



◘ **Fig. 3.3** **a** Standard SPECT rCBF study, as acquired in a general nuclear medicine center

b

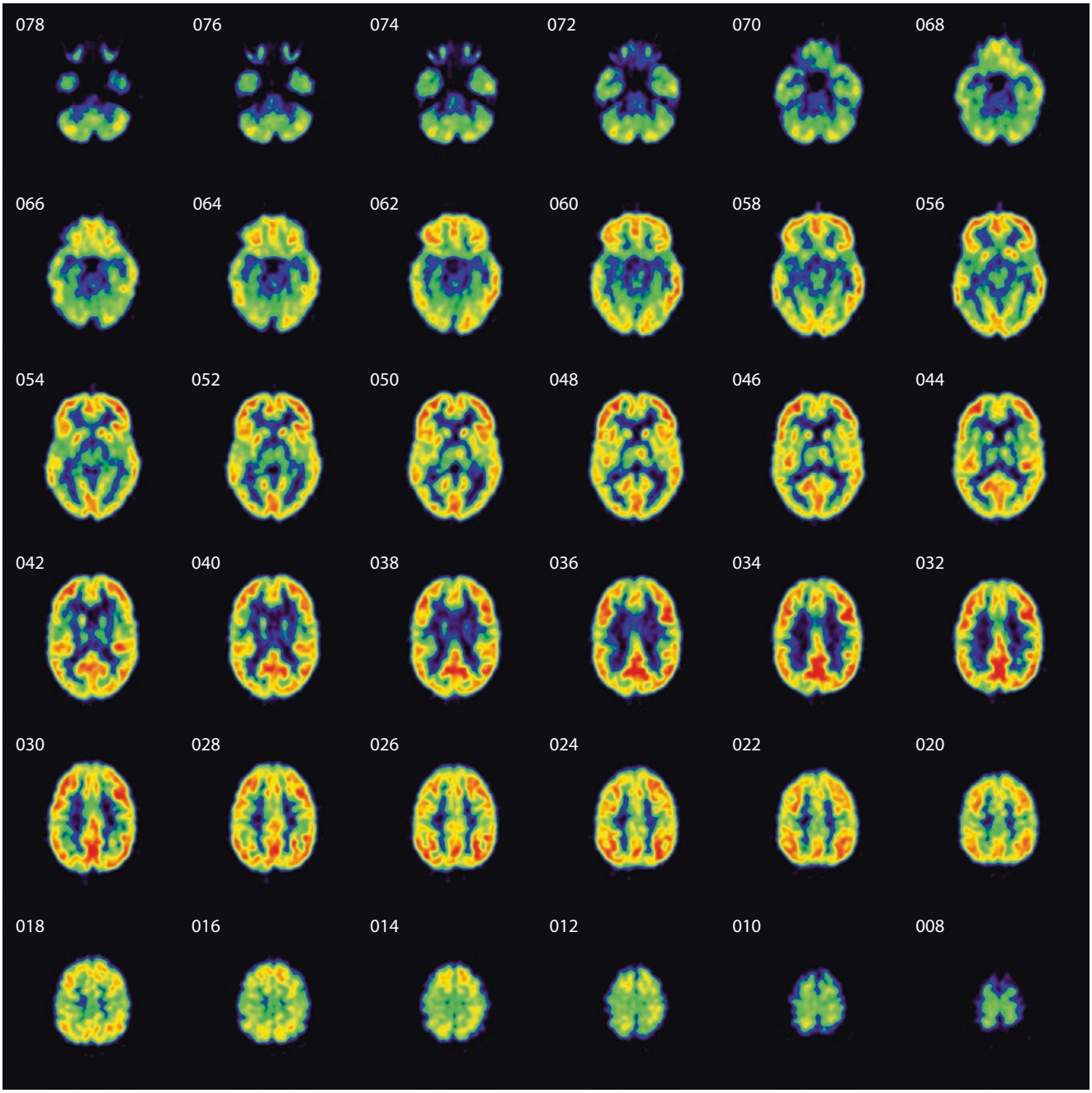


Fig. 3.3 (continued) **b** High-resolution SPECT rCBF study, showing possible improvements to SPECT imaging; however, such results are only available using brain-dedicated imaging systems, which are mostly found in research environments

c

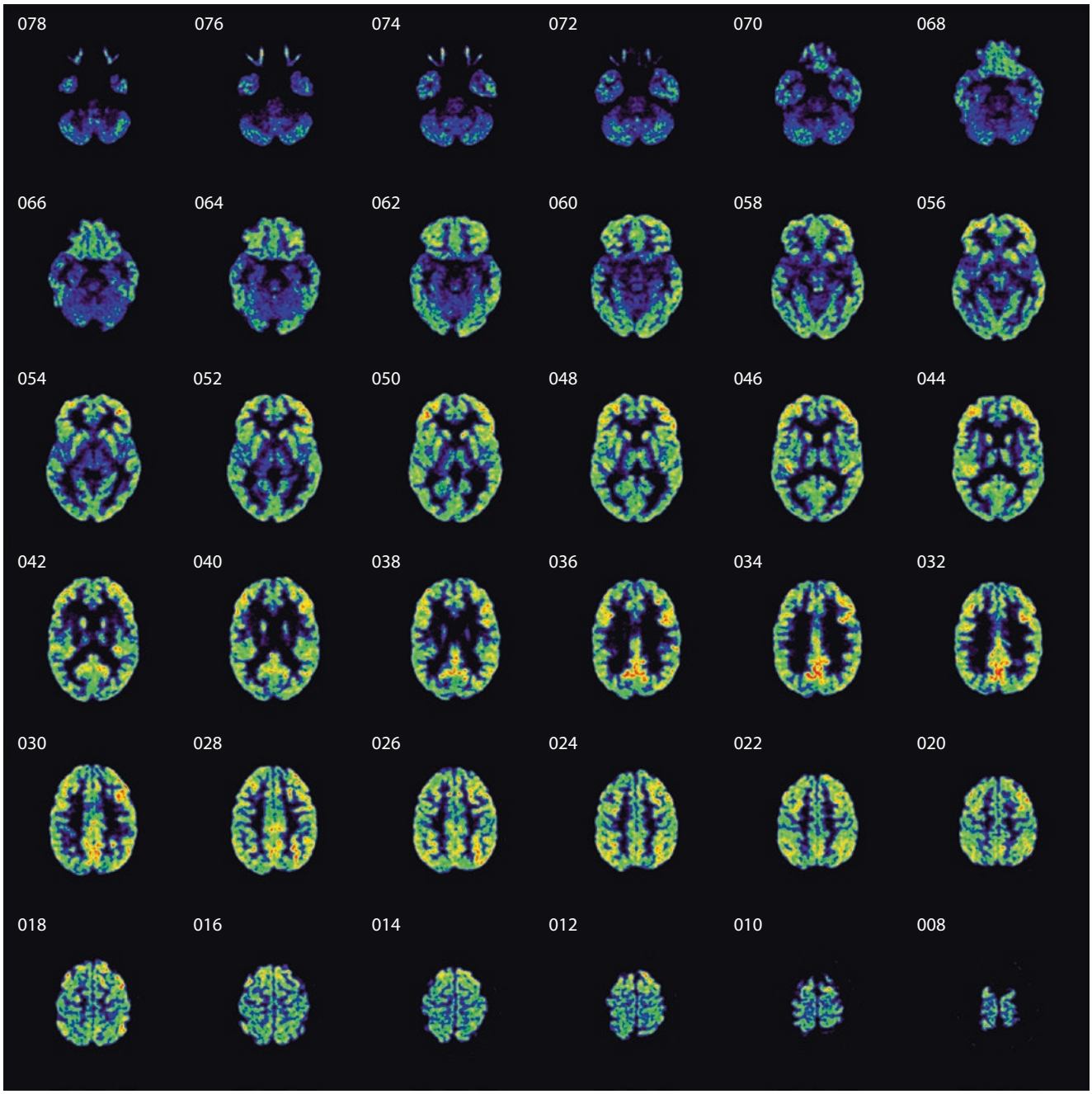


Fig. 3.3 (continued) **c** Standard PET 18F-FDG cerebral study

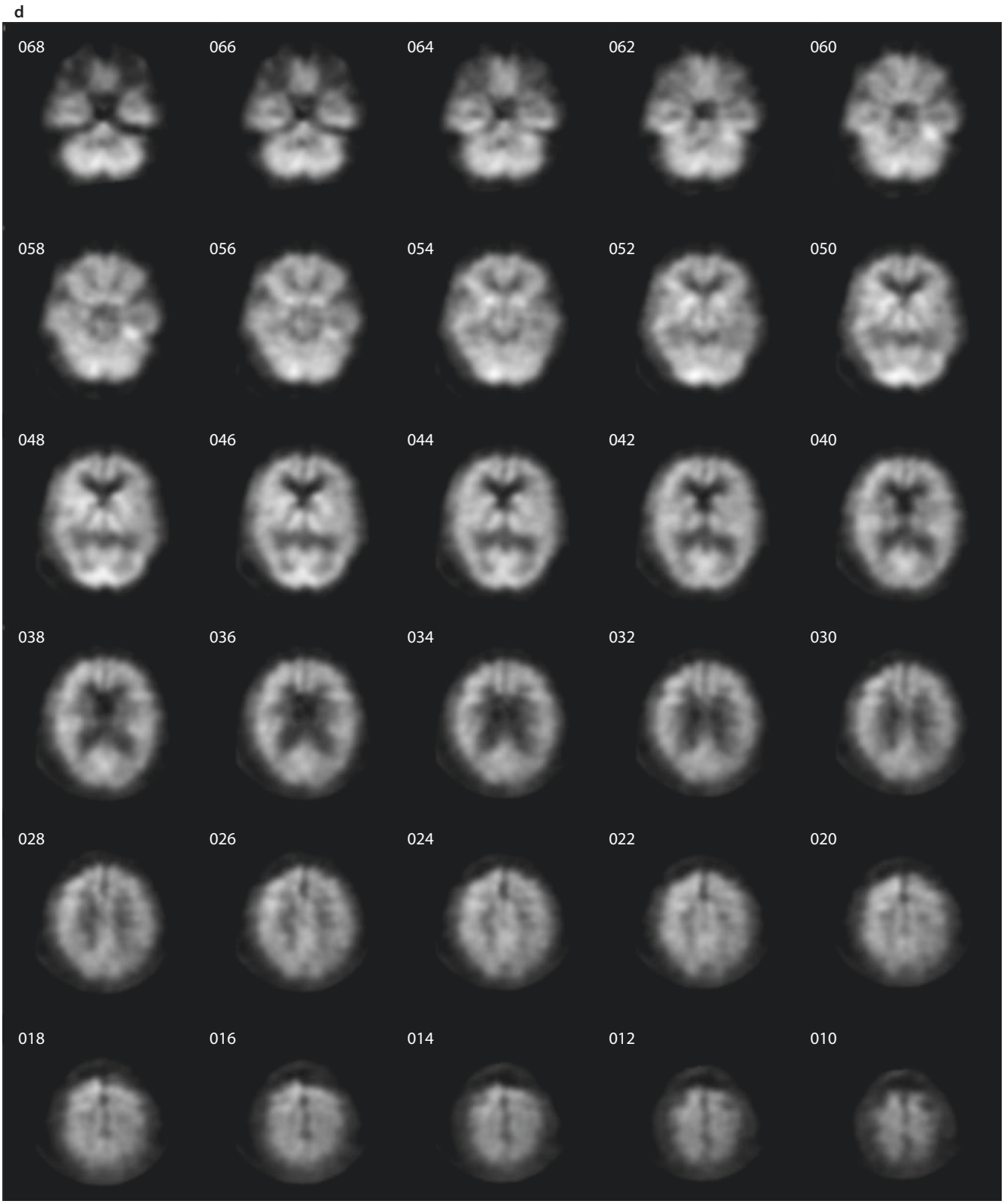


Fig. 3.3 (continued) **d** High-resolution PET 18F-FDG study, which is rapidly becoming a clinical standard (same subject and injection as in **c**)

The case-based discussion that will follow uses the standard acquisition and processing protocol of PET technique employed at McGill University (Montreal, Quebec Canada), with the following specifications:

^{18}F-FDG injection (4 megabecquerel[1] (MBq)/kg, with a lower limit of 180 MBq and a maximum of 550 MBq) took place after a fasting period of 4 hours; the patient's glycemia at that time was below 12 mmol/L (216 mg/dL), the upper limit we accept in order to avoid competition between glucose and ^{18}F-FDG which could result in a poor-quality study. Acquisition was launched 45 minutes post IV, using four successive frames of 5 minutes and 3D acquisition. This was followed by a low-dose CT study for attenuation correction.

Images were co-registered to two standard templates from the Montreal Neurological Institute (MNI_305, with alignment of transaxial slices to a horizontal plane containing the anterior and posterior commissures and the icbm_avg_152_t1_tal_nlin_symmetric_VI_temporal, which allows for full visualization of the temporal lobes in the reoriented transaxial plane). In addition, the patient's study was statistically compared to a normal database of age- and sex-matched subjects. Interpretation of those results was performed visually.

This constitutes our standard acquisition and processing protocol; all other cases presented here will have been managed in this fashion. A similar approach is recommended for all centers performing neuro-PET imaging to ensure reproducibility and accuracy of interpretation.

Teaching Point

SPECT and PET imaging offer opportunity to identify patterns of cerebral blood flow that help define areas of the brain that are functioning below normal. PET has the advantage of having higher special resolution and adds information regarding metabolic state (glucose metabolism) that reflects synaptic functioning. This allowed PET to provide evidence of neurodegeneration in illnesses like Alzheimer disease, Lewy body disease, frontotemporal lobar degeneration, and so on. These tools need to be added to the overall diagnostic process to be useful given that sensitivity and specificity are still not optimum.

3.2 Case Studies

In this section we present case examples that demonstrate the role of neuroimaging in diagnostic work-up of patients in geriatric psychiatry. Because this chapter is about neuroimaging and not particular diagnostic entity, we will present one case with more clinical details, while the rest of the cases are more of a summary of clinical description and imaging findings that help highlight the value of structural and functional neuroimaging in the diagnostic process. The questions arising from the case will focus on neuroimaging mainly.

1 Megabecquerel (MBq) is a measure of radioactive material.

3.2.1 Case 1

Case 1 History

A 70-year-old right-handed retired male police officer with 14 years of education was referred to geriatric psychiatry by cognitive neurology service with a question of behavioral change in the form of "abulia" and whether this might be stemming from depression. He had relatively uneventful coronary bypass surgery about 5 years previously, with only subtle diplopia on left gaze since. A year before current presentation, he had pulmonary embolism and "pulmonary arrest" during a surgery to remove a benign abdominal wall tumor. Since then he has had changes in his behavior in the form of lack of interest in doing things, less talkativeness, mild disinhibition (e.g., when needing to urinate, he would do it in public places, though behind a barrier). He did have few episodes of urinary incontinence from not finding a place to urinate fast enough, which had embarrassed him somewhat, but embarrassed his family much more. His family described these changes as significant departure from his usual character; he was outgoing and conversant before the abdominal surgery a year ago. The patient had partial insight into the changes but could not explain them and did not feel bothered as much as the family by them. More recently, he slept a lot and did very little during the day, which was again very different from his usual pattern. There was no change in language, navigation, or driving skills. There were no headaches, seizures, focal weakness, or weight loss. He tended to complete tasks that his wife left for him but would not do them spontaneously. Gait was slower with mild shuffling over the last year. Medical history was significant for diabetes mellitus, hypertension, and sleep apnea (on CPAP machine that he used regularly), history of coronary artery bypass 5 years ago for ischemic heart disease, left eye motility limitation with diplopia on left gaze, abdominal leiomyoma, which was resected 1 year previously, and the surgery was complicated by pulmonary embolism and pulmonary arrest, as stated previously. He had no history of traumatic brain injury or diagnosed stroke and no previous psychiatric or substance misuse history. He did smoke cigarettes, 1 pack per day for 20 years, but quit about 30 years ago. He was on medications for his vascular risk factors including an angiotensin II inhibitor, a beta-blocker, and oral hypoglycemic in addition to an antidepressant (venlafaxine extended-release 75 mg daily), which was started to help with the "abulia" about 3 months previously, with minor benefit. Family history was significant for ischemic heart disease in his father and half-brother, and there was no family history of neuropsychiatric illnesses (including neurocognitive disorders).

Mental Status Examination

The patient appeared well groomed, cooperative, and alert but with a flat affect. He had sparse spontaneous speech but answered appropriately in full grammatically correct sentences.

Language assessment: Naming, comprehension, and description of picture story (cookie jar theft from Boston Diagnostic Aphasia Test [66]) were normal.

Neurological screening: Cranial nerves were normal, and some increased tone in neck and right arm and mild cogwheel rigidity in right more than left upper limbs were noted. No bradykinesia or tremors and no other abnormal movements were present. Gait was short in strides, posture was stooped forward slightly, and there was some decrease in arm swings. Reflexes were normal and symmetrical. There were no primitive reflexes. Strength was normal; toes were downgoing on plantar reflex.

Cognitive testing: On Mini Mental State Examination (MMSE) [67], he scored 28 out of 30 (1 point lost on the 3-step command and 1 on delayed recall). On Montreal Cognitive Assessment (MoCA) scale [68], he scored 25 out of 30 (2 points lost on delayed recall (but was cued to them), 2 points on digit span, and 1 point on repetition). On paragraph recall, he recalled 17 of 21 facts immediately and 15 of 21 facts after a delay [69]. Clock drawing was normal. Semantic fluency was high (18 animal names generated per minute), while phonetic fluency (letter F) was lower but within the normal range at 12 words per minute. Trail-making Test A was performed at the 50% percentile while Trail-making Test B was at 98th percentile [70].

Mood rating: He expressed mild depressive symptoms (Geriatric Depression Scale-short version was 7 out of 15) [71].

Case 1 Questions and Answers

Case 1 Questions

Question 1. When considering the data presented from this case, what is the main differential diagnosis?

Question 2. What is the indication of brain imaging in this case?

Question 3. What modality of neuroimaging would be appropriate to order in this case, and why?

Case 1 Answers

Case 1 Answer 1 (Question 1—When considering the data presented from this case, what is the main differential diagnosis?)

A. Depression:
   a. Primary: Typically depression would have presented earlier in life. This patient had no past history of depression, and, moreover, his current picture suggested depressive symptoms rather than full-spectrum major depressive disorder.
   b. Secondary to brain disorder: This is more likely, because depressive symptomatology is common with brain disorders due to a variety of pathologies including neurodegeneration or brain insult. (See ► Chaps. 10 and 22 for more details.)

B. Neurocognitive disorder (minor or major) due to neurodegenerative illness such as frontotemporal or Alzheimer-related neurocognitive disorder:
   a. Due to Alzheimer disease: In this case we do not have clear indication of amnestic features and cognitive screening was within normal with only minor impairment in areas of attention and memory retrieval rather than encoding, which would have been more characteristic of Alzheimer disease (see ► Chap. 18 for more details).
   b. Due to frontotemporal neurocognitive disorder: Depressive and apathy symptoms can be seen in frontotemporal neurocognitive disorder, mainly in the behavioral variant (see ► Chap. 19 for details). This is a plausible clinical diagnosis in this case and needs to be explored given the change in the patient's social behavior relatively early in the course (manifested as disinhibition), early apathy/inertia, diminished social interest, and some neuropsychological evidence of impaired attention with relatively preserved episodic memory on cognitive screening tools [72].

C. Neurocognitive disorder due to cerebrovascular disease or other acute brain insult: This is a possible clinical diagnosis given that the onset of his illness was relatively abrupt and had been stable in course over the previous year or so since the abdominal surgery, which was complicated by the respiratory arrest. The profile of cognitive performance on cognitive screening indicates preferential impairment in frontal-executive function (as suggested by impaired digit span and repetition, better semantic compared to phonemic fluency, and by benefit from cueing on recall) and social cognition (impairment in inhibition and limited initiation) [73]. (See ► Chap. 21 for details.)

D. Normal pressure hydrocephalus: Although rare, given the changes in mental status, gait, and bladder control, one would need to rule out normal pressure hydrocephalus. This is important especially because this syndrome is potentially reversible with appropriate treatment such as cerebrospinal fluid shunting procedure [74].

E. Neurocognitive disorder due to other medical conditions: There are several possible etiologies to consider under this category:
   a. The patient has a diagnosed obstructive sleep apnea. This syndrome can be associated with significant cognitive deficits in the areas of attention/vigilance, memory, and visuospatial and executive function [75].
   b. There is a host of potentially reversible conditions for neurocognitive and behavioral changes that need to be considered in this case, including brain tumors, autoimmune processes (e.g., paraneoplastic syndrome, antithyroid antibodies, systemic lupus erythematosus), infections (e.g., herpes simplex encephalitis), and traumatic brain injury. Although the list can be extensive, there was no indication from the patient's history to put him at particular risk for these illnesses; however, clinicians still have to keep these conditions in the differential diagnosis when working up patients [76]. For example, illnesses like herpes simplex encephalitis can present with cognitive and behavioral changes similar to the case presented, though relatively more acute in presentation [77].

F. Neurocognitive disorder due to substance use: This includes alcohol, anticholinergics, benzodiazepines, and other medications. Alcohol abuse needed to be explored in this case, although there was nothing in the history from patient or family report to suggest this.

Case 1 Answer 2 (Question 2—What is the indication of brain imaging in this case?)

There was a short duration of neurocognitive disorder (less than 2 years), atypical cognitive presentation (attention and executive function deficits with relatively preserved memory), unexplained neurological symptoms (left gaze diplopia, parkinsonism), gait changes, and urinary incontinence, which represented neurological signs in this patient. The 2nd and 4th Canadian Consensus Conference on Diagnosis and Treatment of Dementia recommend structural imaging when certain elements from the clinical history and exam are present including what we listed above and also cases with early-onset (younger than age 60 years), rapid unexplained cognitive decline, recent head trauma, history of cancer, unexplained neurological symptoms like new-onset severe headache or seizure, use of anticoagulants, history of bleeding disorder, and any localizing neurological signs [78].

Case 1 Answer 3 (Question 3—What modality of neuroimaging would be appropriate to order in this case, and why?)

Given that the patient had several of the criteria that support ordering structural brain imaging, it is reasonable to order structural brain imaging first. The choice between CT scan and MRI scan, and between with and without contrast, is important to discuss. As discussed in the background section, CT scan is relatively easy to access and easier to tolerate and can detect fresh blood and calcification very well, although it involves exposure to ionizing radiation, provides less detailed anatomical information, and has lower resolution than MRI. Also, it is particularly less informative when it comes to posterior fossa lesions and when lesions are close to the bony structures. For the patient in this case, the clinical process was no longer acute, and there were no major neurological signs, but there was a history of respiratory arrest with the possibility of anoxic/hypovolemic injury, which is usually difficult to detect with CT when is not in the acute phase. Also, an MRI can give more anatomical details and can detect smaller lesions in strategic locations. Although there was nothing in the history to suggest this, tumors are to be ruled out and the use of contrast is usually reserved to cases which metastasize.

Case 1 (Continued)

After basic screen with blood work and confirming that there was no other systemic medical, psychiatric, or substance-related disorder that could have contributed to the case, a brain MRI was ordered to rule out normal pressure hydrocephalus, cerebrovascular accident, and any other incidental finding related to traumatic brain injury, inflammation, and tumors and to evaluate regional brain volumes.

Radiology report: A multiplanar, multisequence MRI of the brain was performed without contrast. There was a finding of mild global cerebral atrophy without any regional specificity. Ventricles were within normal limits, although there was a mild right lateral anterior periventricular edematous signal change that could represent transependymal cerebrospinal fluid flow. No mass or midline shift was seen. A finding of symmetric high signal on T2 sequence at the junction of the internal capsules and lentiform nuclei bilaterally could represent lacunar infarctions. Otherwise, there was no evidence of acute stroke or acute or chronic hemorrhage. Few white matter hyperintensities were distributed bilaterally that may indicate microangiopathic lesions. Hippocampi were symmetrical with no particular atrophy or abnormal signal intensity.

Figure 3.4 shows selected images form the clinical T2 MRI obtained without contrast. They show evidence of lesions bilaterally involving the basal ganglia in the proximity of the globus pallidus. This area is part of the default mode network and is strategic in attention and mood regulation. Additionally, this area is considered "watershed" in terms of blood supply and is vulnerable for hypoxic-hypovolemic injury. This patient sustained a respiratory arrest during his surgery a year previously, which likely resulted in these lesions. The lesions are strategic for cognitive and emotional processing and could potentially explain his presentation. The final diagnostic impression was mood and personality changes due to cerebrovascular changes. These lesions could also explain the subtle changes in his gait. Because of an abnormal signal adjacent to the lateral ventricles, suspicion of increased cerebrospinal fluid pressure was reported and a flow study was suggested. A flow study was performed under fluoroscopy with radioactive material injected to the cerebrospinal fluid. The study was reported negative for normal pressure hydrocephalus.

With the addition of the antidepressant bupropion (through enhanced dopaminergic transmission) to the venlafaxine in his medication regimen, his apathy had improved, and his gait became faster, but, unfortunately, he suffered two non-injurious falls mainly due to being faster while still having problem with gait apraxia. His bupropion was tapered and discontinued and he continued with venlafaxine XR 75 mg daily, later increased it to 225 mg daily; however, this increased dose did not improve clinical response and was confounded by worsening of his constipation. The option of adding an acetylcholinesterase inhibitor was considered, given the evidence in gait modulation [79], but this was thought to be still speculative and off-label and not supported by current clinical guidelines for the treatment of vascular neurocognitive impairment [78].

Case 1 Analysis The patient had a mild neurocognitive disorder due to cerebrovascular accident. He had prominent apathy rather than depression, because he was showing limited motivation and initiation from lack of concern rather than negative emotional experience. He suffered mild apraxia of his gait due to frontal-subcortical disconnect.

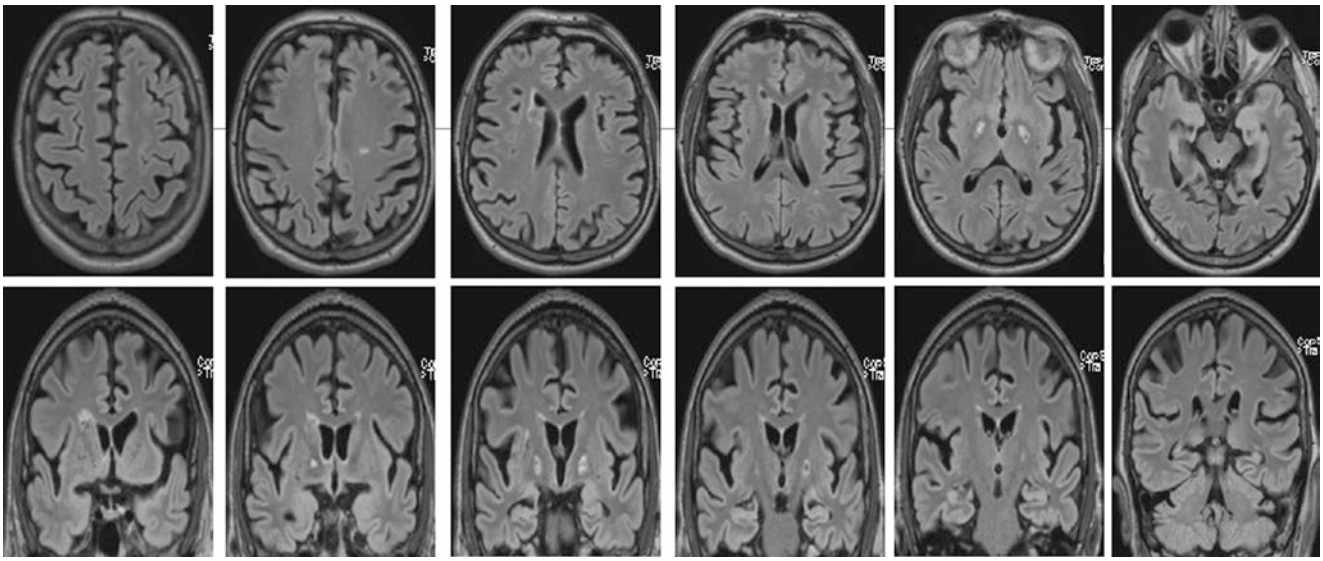


Fig. 3.4 MRI scanning using T2 FLAIR (fluid-attenuated inversion recovery). Upper panel shows transaxial sections while the bottom panel coronal sections. The image shows bilateral "watershed" lesions in the internal capsule adjacent to the globus pallidus. The images are displaced in radiological convention (*left side* of the image is right for the patient). Apart from mild generalized atrophy appropriate for age, there is no evidence of significant hippocampal or any other regional atrophy. Adjacent to the lateral ventricle on the right side (*left* of the image), there is area of possible edema (CSF leakage), which prompted CSF flow study reported normal

3.2.2 Functional Imaging Brief Cases

Case 1

A 47-year-old female with cognitive symptoms, on examination showing decreased encoding and executive function deficits. Her cognitive scores were MMSE 29 and MoCA 28. She reported being diagnosed with fibromyalgia, but otherwise had no other pertinent medical history. Members of her family had been diagnosed with Alzheimer disease (mother and two maternal aunts), all after the age of 70. She had recently undergone an MRI study, which was reported as normal. An ^{18}F-FDG PET scan was performed per protocol described above. Please see Fig. 3.5.

Interpretation: This was a normal study. There was no significant left/right asymmetry, the ratio of activity of the cerebral cortex to that of the cerebellar cortex was clearly above 1 (more about this later in the chapter), and the activity of polymodal associative regions was higher than that of primary motor and somatic (but not visual) cortices. The posterior portions of the cingulate gyri showed uptake higher than that of other cortical areas (more about this later), again with the exception of the primary visual cortex (calcarine cortex). Activity of the mesial temporal structures and of the insular regions was normal. Uptake in the basal ganglia, thalamus, and cerebellum was symmetrical. The brain stem was unremarkable.

Although the goal is not to instruct how to read such studies, the above description merely aims to draw attention to the type of interpretation, which should be performed. In the present clinical context, a normal result had significant prognostic implications, indicating a low (< 10%) risk of ongoing cognitive deterioration linked to a neurodegenerative process over the next 3–5 years [80].

Case 2

A 71-year-old female with amnestic mild cognitive impairment, MMSE 30 and MoCA 26. The physician requesting this study was wondering whether to initiate administration of an acetylcholinesterase inhibitor in a patient who was still quite socially active and functioning reasonably well. The CT scan obtained for attenuation correction during the PET study was considered to be unremarkable. Please refer to Fig. 3.6 for functional images obtained.

Interpretation: This case shows (on slices and statistical maps) clear preferential involvement of polymodal associative cortices, with relative prominence of primary cortices. The anomalies predominate in posterior territories, although there are also mild anomalies in prefrontal regions, and are mildly asymmetric (the typical amnestic Alzheimer disease is generally scintigraphically asymmetric, but rarely massively so; a completely symmetric or a very asymmetric presentation could indicate a variant of Alzheimer disease or another disease process). The posterior portions of the cingulate gyri are clearly less active than some cortical regions (again, not including the visual cortices, which remained normal in this case). On coronal slices, superior parietal lobules are clearly seen as hyperactive as compared to the inferior parietal lobules, which is a reversal of the normal pattern (go back to Fig. 3.5 for comparison). Other structures, including mesial temporal ones, are essentially unremarkable.

That pattern of anomalies described above is "typical for the typical" form of Alzheimer disease, namely, the one presenting mostly with amnestic impairment. Its characteristics have been known for well over 20 years and repeatedly confirmed to have both high specificity and sensitivity for that disease (around 90% for both in most studies). Although a full discussion of the origins of such a distribution of

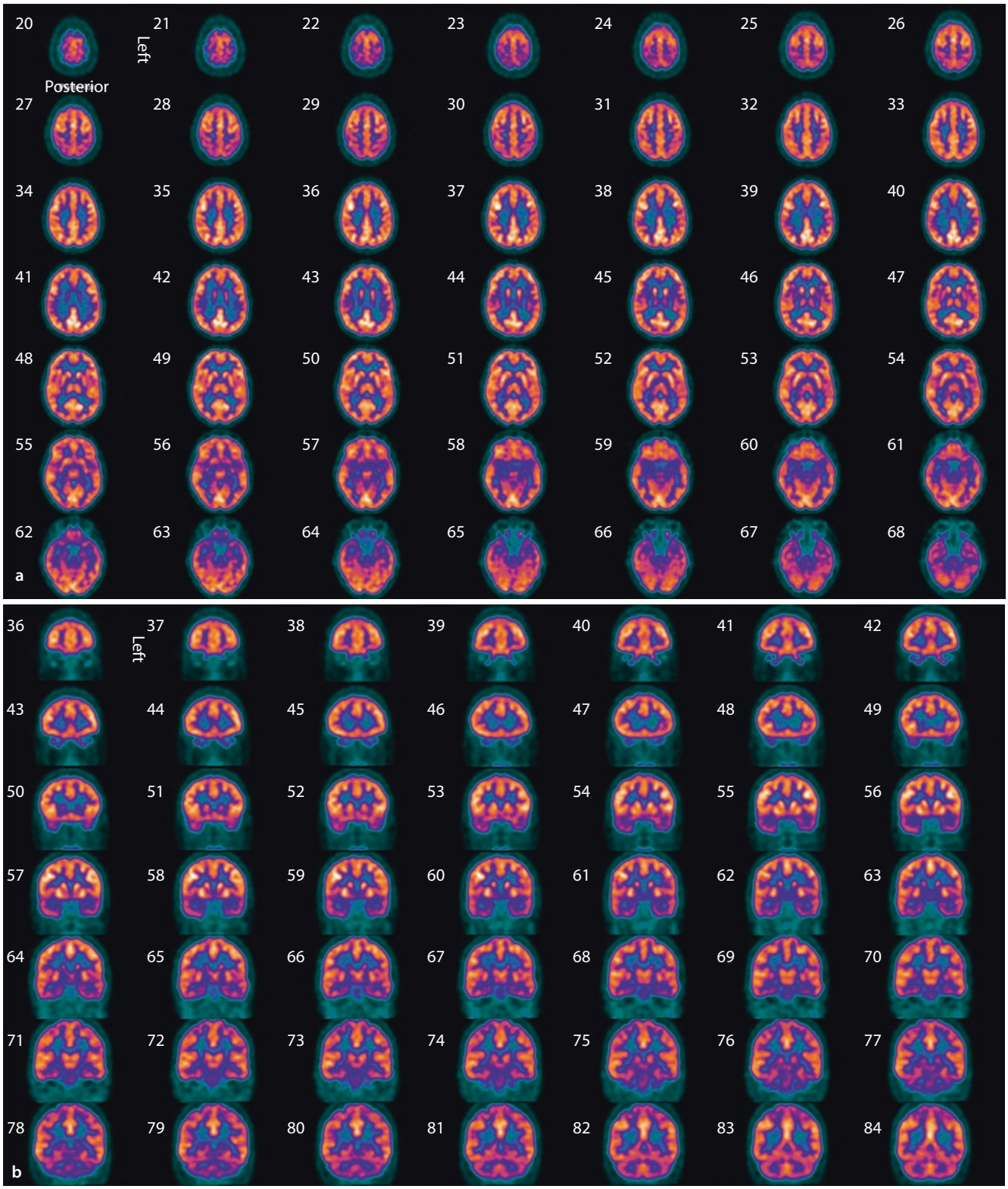


Fig. 3.5 Normal scan in a patient with cognitive concern and family history of Alzheimer disease

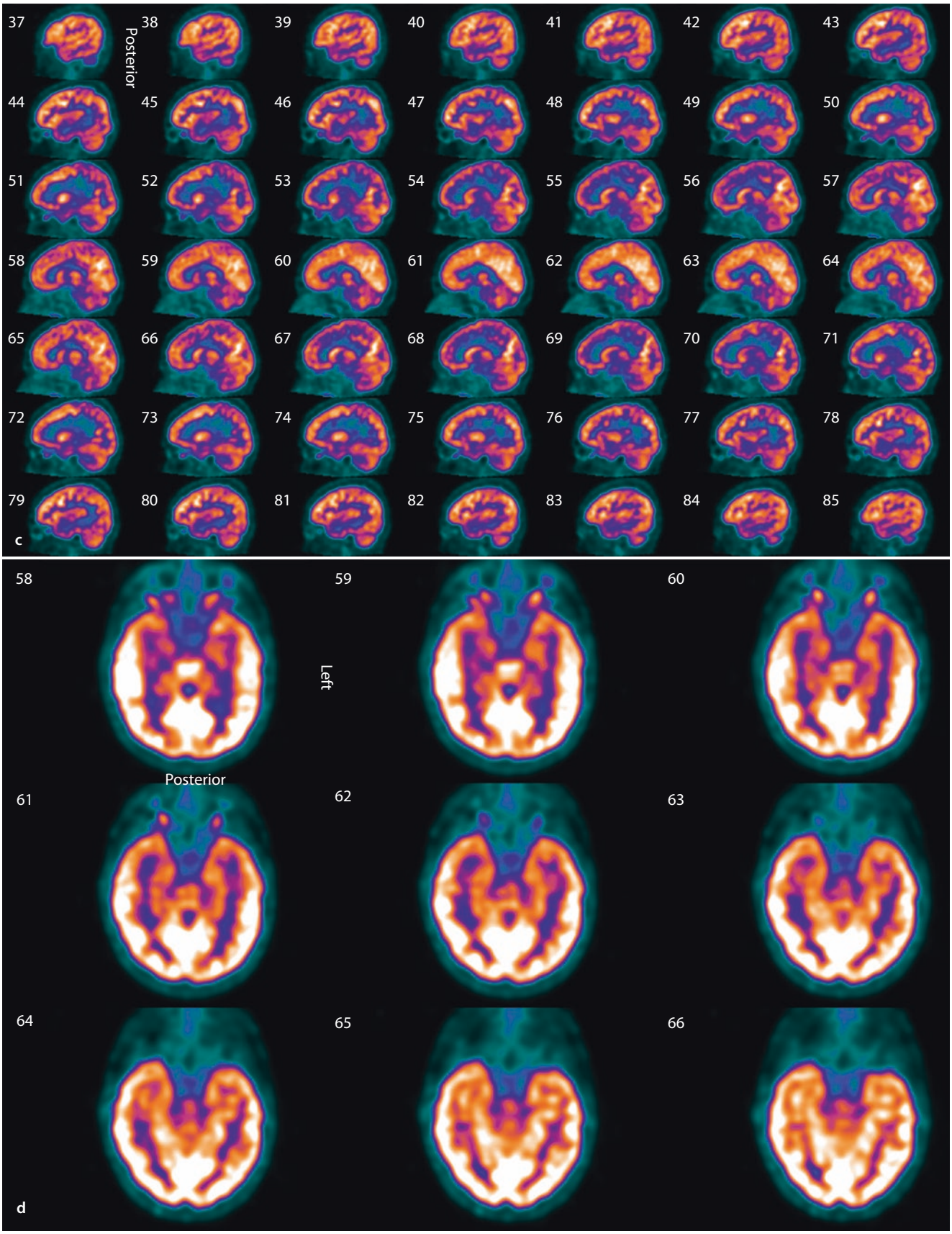


Fig. 3.5 (continued) **a**–**c** Transaxial, coronal, and sagittal slices after registration to the MNI_305 template. **d** Registration along the axis of the temporal lobes

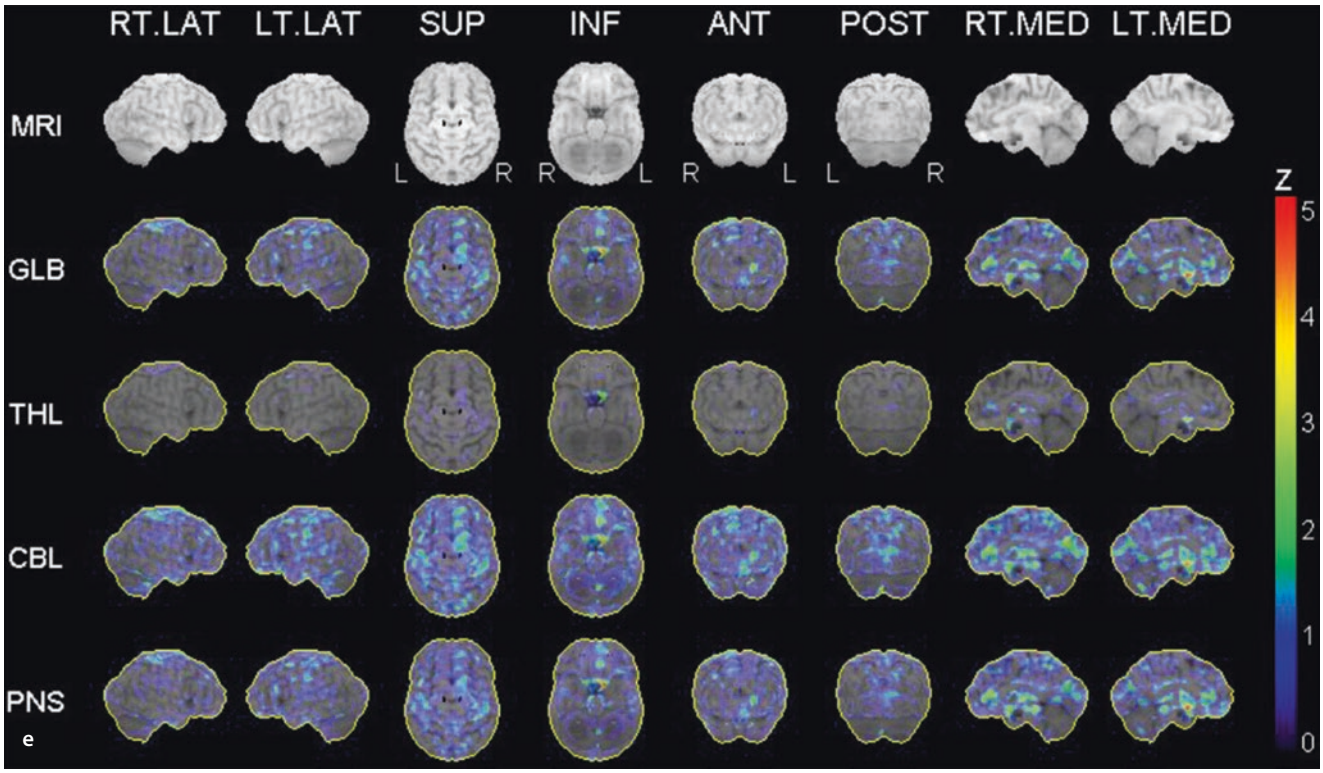


Fig. 3.5 (continued) **e** 3D-SSP decrease map (normalized to pons). Please refer to the text for interpretation

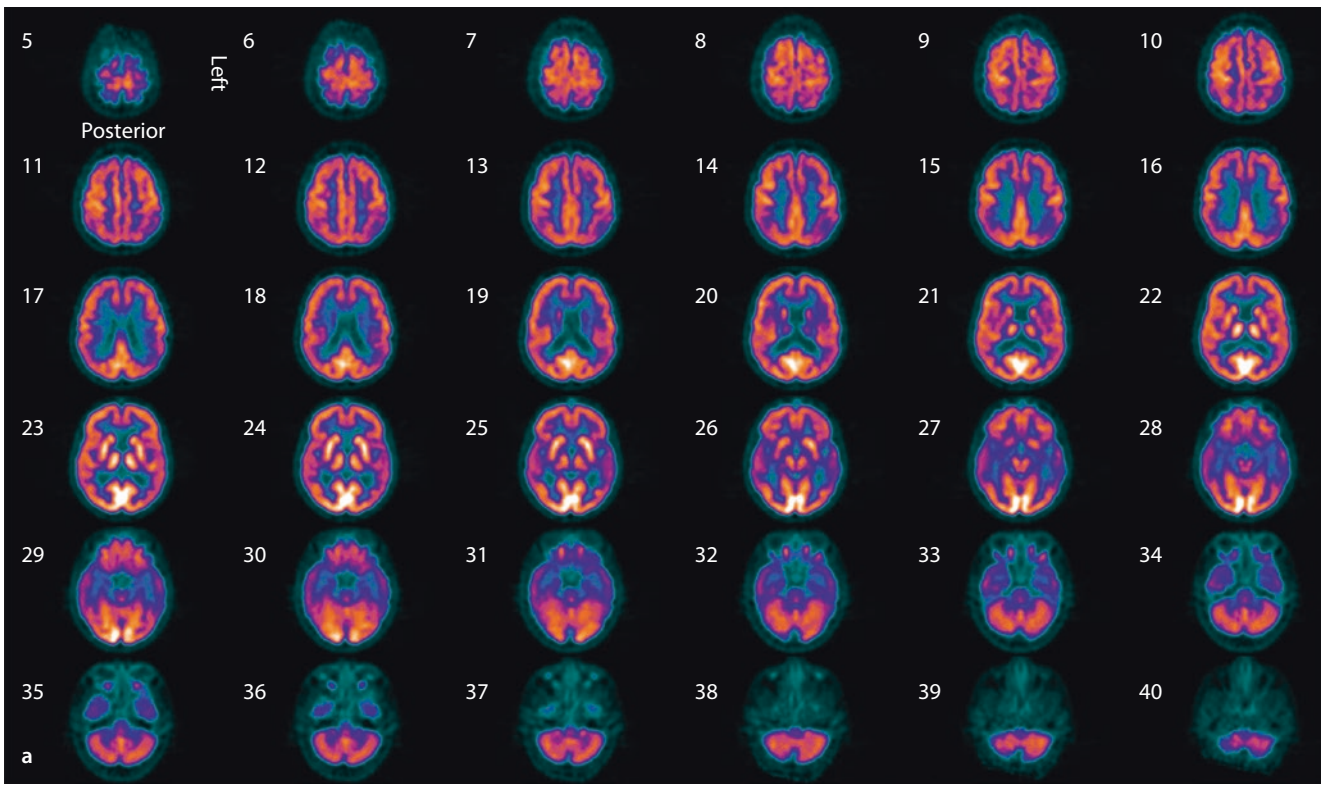


Fig. 3.6 "Typical" Alzheimer disease

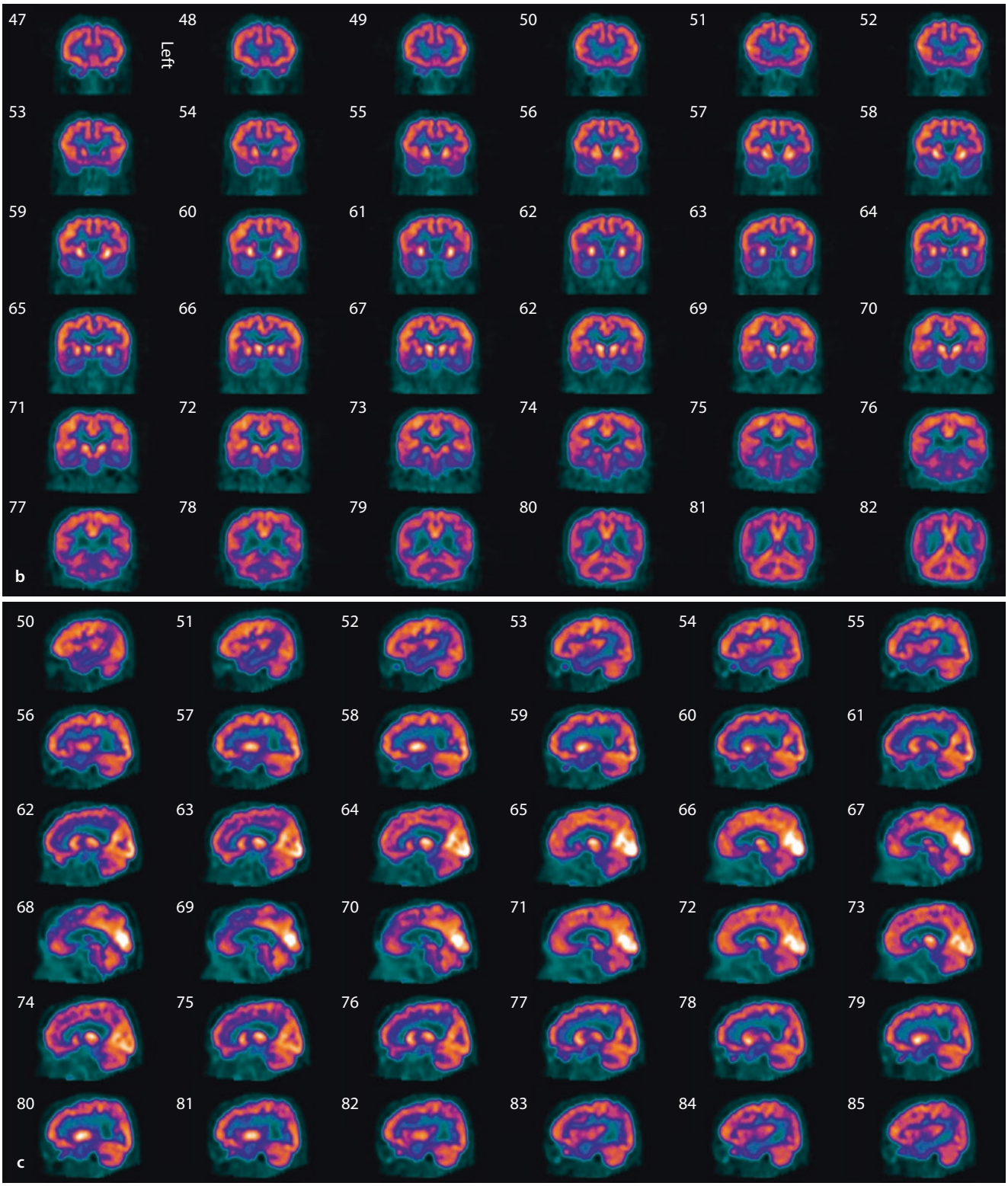


Fig. 3.6 (continued) **a–c** Transaxial, coronal, and sagittal slices after registration to the MNI_305 template

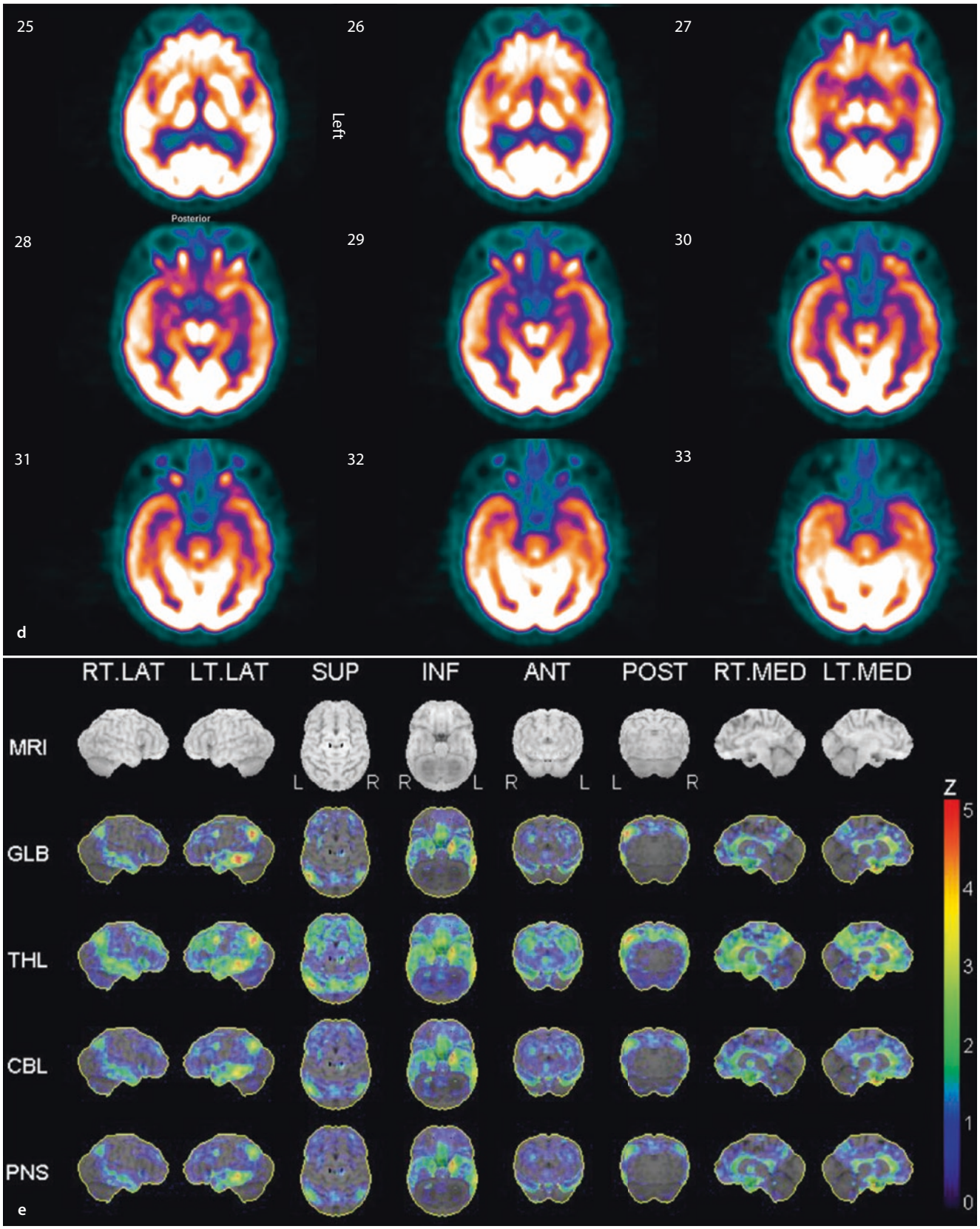


Fig. 3.6 (continued) **d** Registration along the axis of the temporal lobes. **e** 3D-SSP decrease map. Please refer to the text for interpretation

synaptic/cellular anomalies is well beyond the scope of the present text, there are strong indications that it represents selective involvement early on of the so-called default mode network (DMN) of the brain (see Background section), and there are proposed molecular theories for specific involvement of that network in early phases of Alzheimer disease. A portion of the DMN, which is often not clearly seen as abnormal in Alzheimer disease, is the hippocampal formation. In fact, it should be noted that this area is difficult to quantitatively image with PET, unless analysis of the MRI-defined region of interest is performed, and that most studies should perhaps only comment on activity in "mesial temporal structures." Moreover, there are indications (from fMRI and ASL measurements) that the hippocampal formation actually is subject to upregulation of its activity in Alzheimer disease, further explaining why ^{18}F-FDG signal can appear normal.

This pattern is considered to generally precede the appearance of clinical symptoms by many years, approximately 10 years in most cases, but proving this will entail obtaining longitudinal data in initially normal subjects for prolonged periods of time, which remains a challenge. Nevertheless, data from studies in patients with rare, predominantly inherited forms of Alzheimer disease, as well as from sporadic cases, agree on a significant delay between the initial observation of a typical PET ^{18}F-FDG pattern and onset of symptoms. This is of interest, because it implies that subjects with cognitive impairment but no recognizable PET Alzheimer disease (and this likely applies to other neurodegenerative conditions) pattern are likely to show progression of their deficits *because of a neurodegenerative condition* over many years after their study; in fact, this has been experimentally verified in follow-up studies of such subjects.

Case 3

An 83-year-old male referred by a general neurologist with observations of a "pervasive language deficit, not sure if apraxia of speech is involved." This had been slowly evolving over at least 4 years. No other relevant cognitive impairment was reported. No other medical condition was known. A brain MRI scan from approximately 3 years earlier showed some degree of cerebellar atrophy, but was otherwise considered normal for the patient's age, specifying that there was no significant vascular disease. Please see Fig. 3.6 for functional images obtained.

Interpretation: Fig. 3.7 shows a clear neurodegenerative pattern, as described above, as well as a marked asymmetry of the hemispheres, the left one being much more affected than the right. In addition, the most severe anomalies are in the temporal lobe on the left, mostly posteriorly. Also, the posterior portions of the cingulate gyri are mildly to moderately hypoactive (compare to adjacent upper parietal lobules cortex), consistent with Alzheimer disease. However, there is a discrepancy between the severity of the hypometabolism

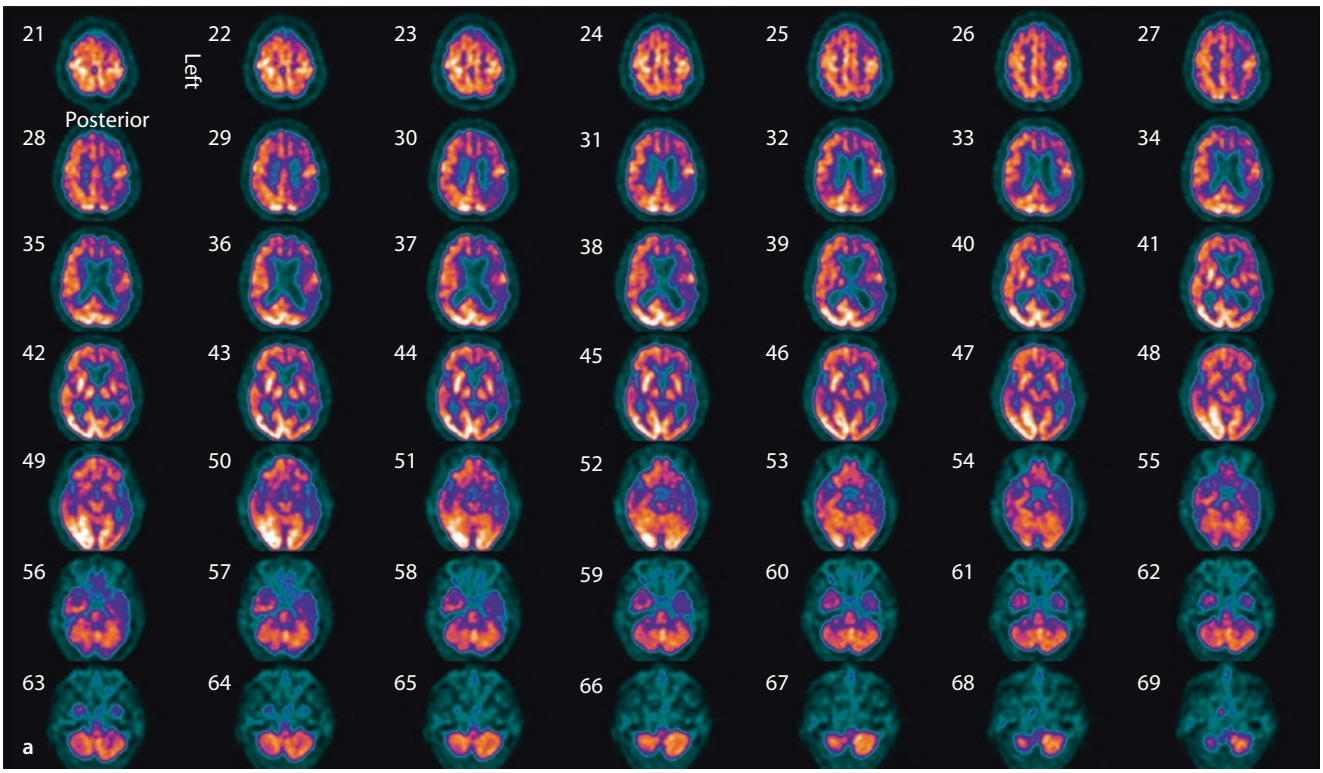


Fig. 3.7 Logopenic variant of Alzheimer disease

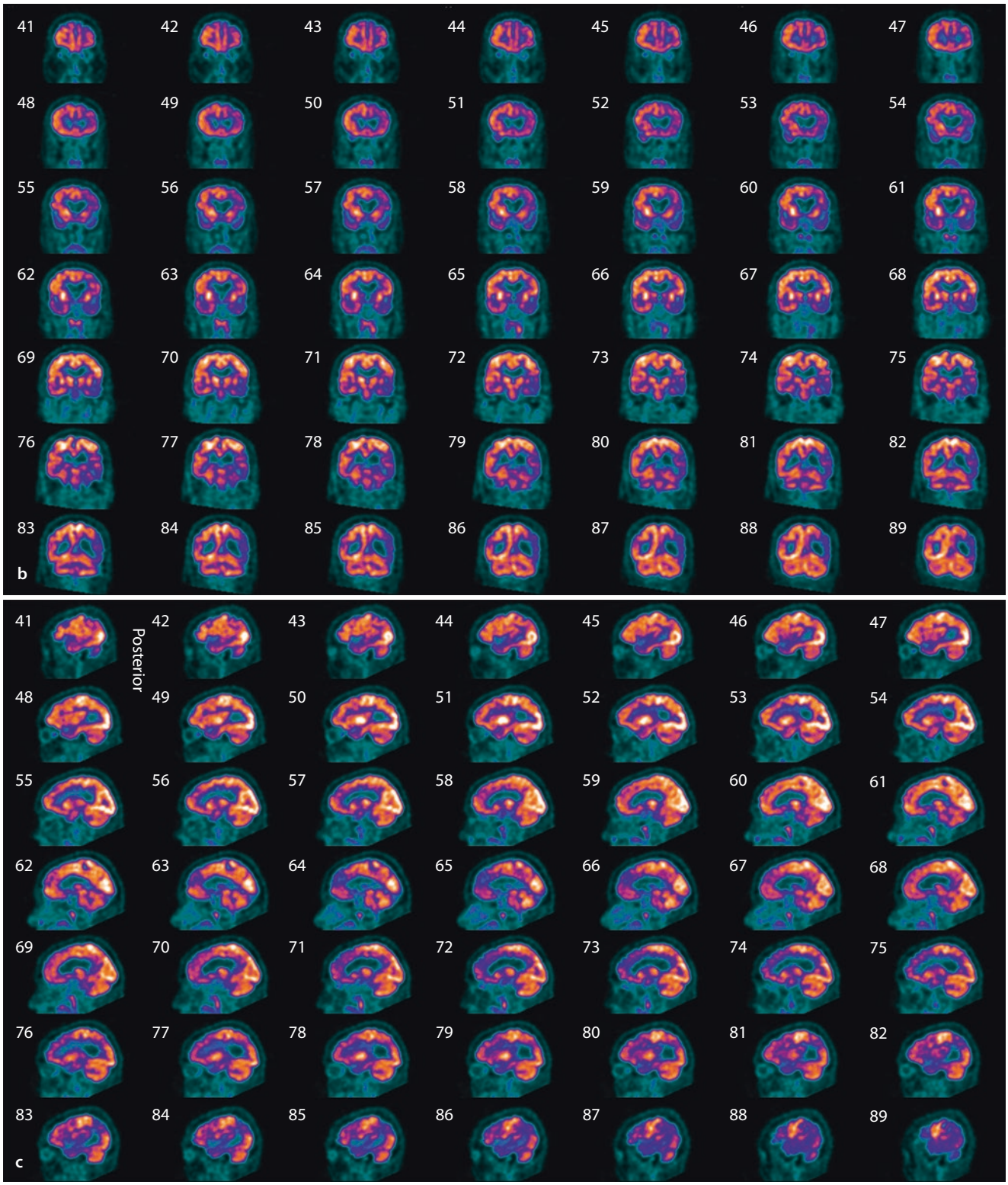


Fig. 3.7 (continued) **a–c** Transaxial, coronal, and sagittal slices after registration to the MNI_305 template

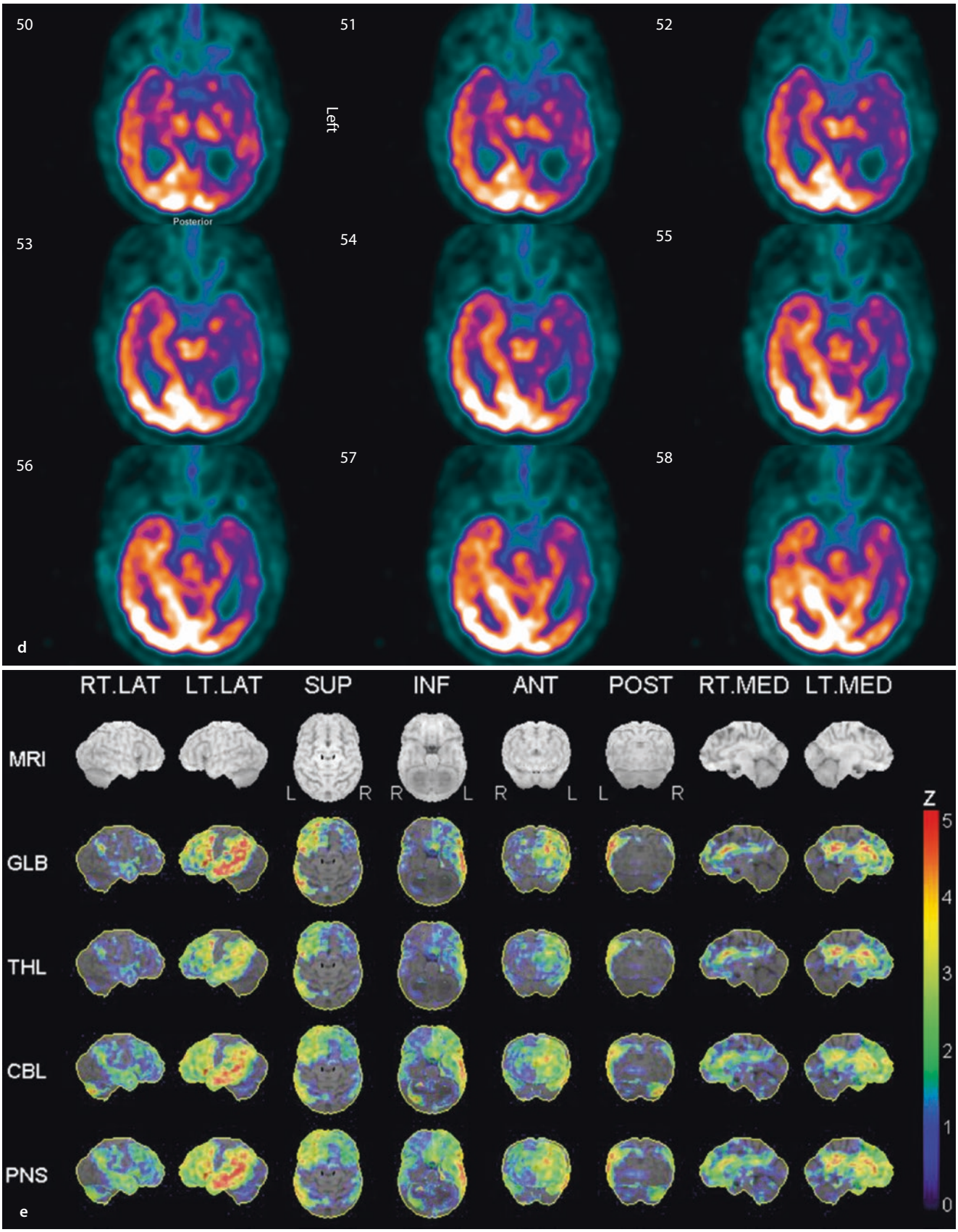


Fig. 3.7 (continued) **d** Registration along the axis of the temporal lobes. **e** 3D-SSP decrease map. Please refer to the text for interpretation

in the left temporal lobe and that in the posterior aspect of the cingulate gyri. As stated above, Alzheimer PET ^{18}F-FDG studies are usually not massively asymmetrical. Given those observations, and the clinical status of the patient, this study is highly subjective of a logopenic variant of Alzheimer disease, one of its not infrequent clinical variants. Approximately 60% of cases of logopenic primary progressive aphasia are related to Alzheimer pathology. (See ▶ Chap. 19.)

Case 4

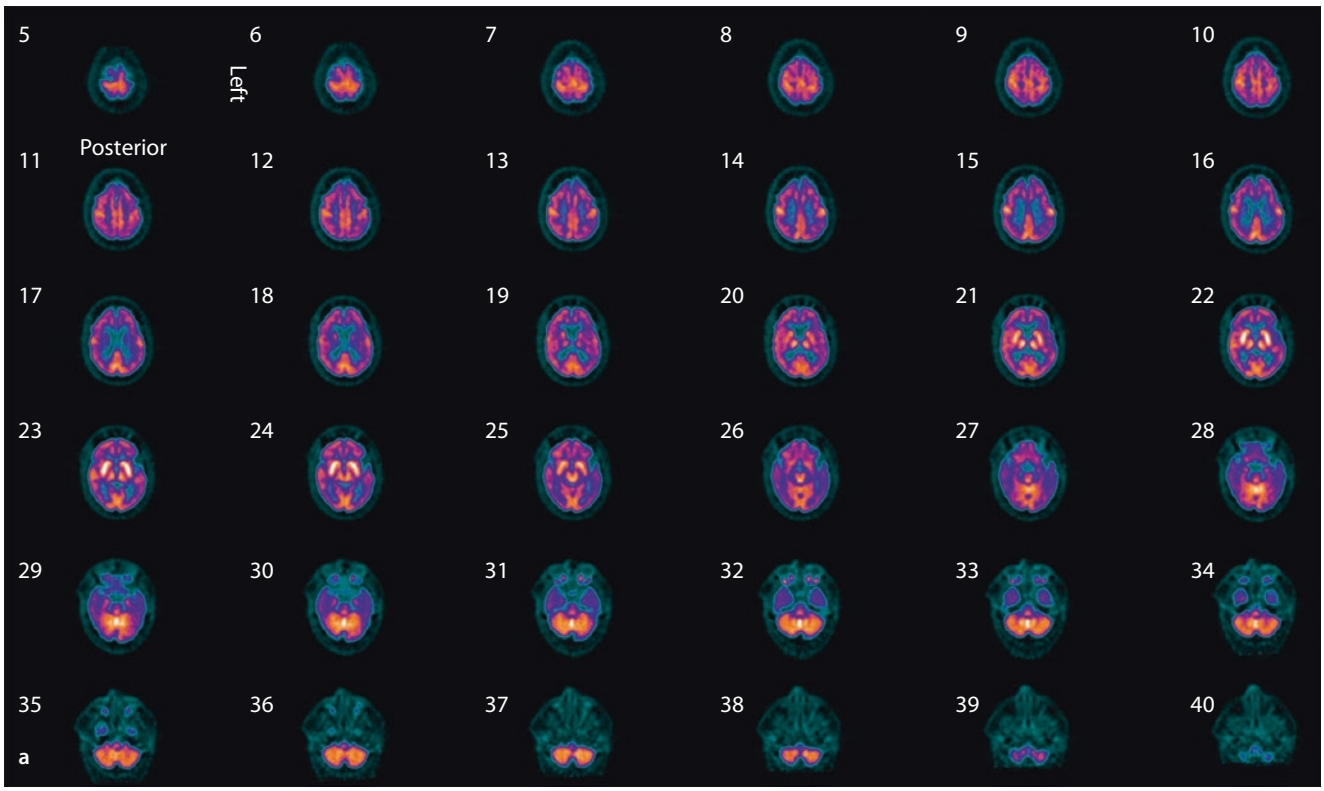
A 72-year-old male with a dysexecutive syndrome progressively increasing in severity over the past 3 years. He had limited memory impairment. There were no other medical condition reported and no known family history of neurodegenerative disease. The attenuation correction brain CT scan showed limited, age-compatible diffuse atrophy, without significant regional dominance, and there was no evidence of significant vascular anomalies. Please see ◘ Fig. 3.7 for functional images acquired.

Interpretation: ◘ Fig. 3.8 shows a typical neurodegenerative pattern. Because there is clearly decreased activity in the posterior aspects of the cingulate gyri, this suggests the presence of Alzheimer disease pathology. However, as compared to the previous examples of typical Alzheimer disease, the current case shows much more pronounced frontal involvement, which is mostly diffuse, but not particularly marked in the frontal polar regions. In addition, mesial temporal structures remain normal, and uptake in the insular areas, although mildly asymmetric (left < right), shows that they are not significantly involved. Those last observations will be commented on later, but decrease the odds of this study being linked to frontal temporal lobar degeneration. Therefore, although no histopathological information was available in this patient (a frequent occurrence, obviously, in such cases), the most likely diagnosis from a scintigraphic perspective is that of a frontal variant of Alzheimer disease.

Case 5

A 79-year-old male was sent for evaluation of a progressive aphasia having started 3 years earlier. He had had a lung cancer 4 years before the current study, with no evidence of recurrence at the time of the PET scan. A brain CT scan showed normal findings for his age, with mild diffuse atrophy. Please see ◘ Fig. 3.9 for functional images acquired.

Interpretation: The patient's study (◘ Fig. 3.9) shows evidence of a neurodegenerative process, with limited prominence of primary motor and somatic cortices signaling involvement of polymodal associative cortices. The anomalies are clearly dominant on the left side and more severe in the prefrontal cortex and temporal lobe than in the parietal regions. The posterior portions of the cingulate gyri are entirely normal. There is insular hypometabolism on the left



◘ **Fig. 3.8** Frontal variant of Alzheimer disease

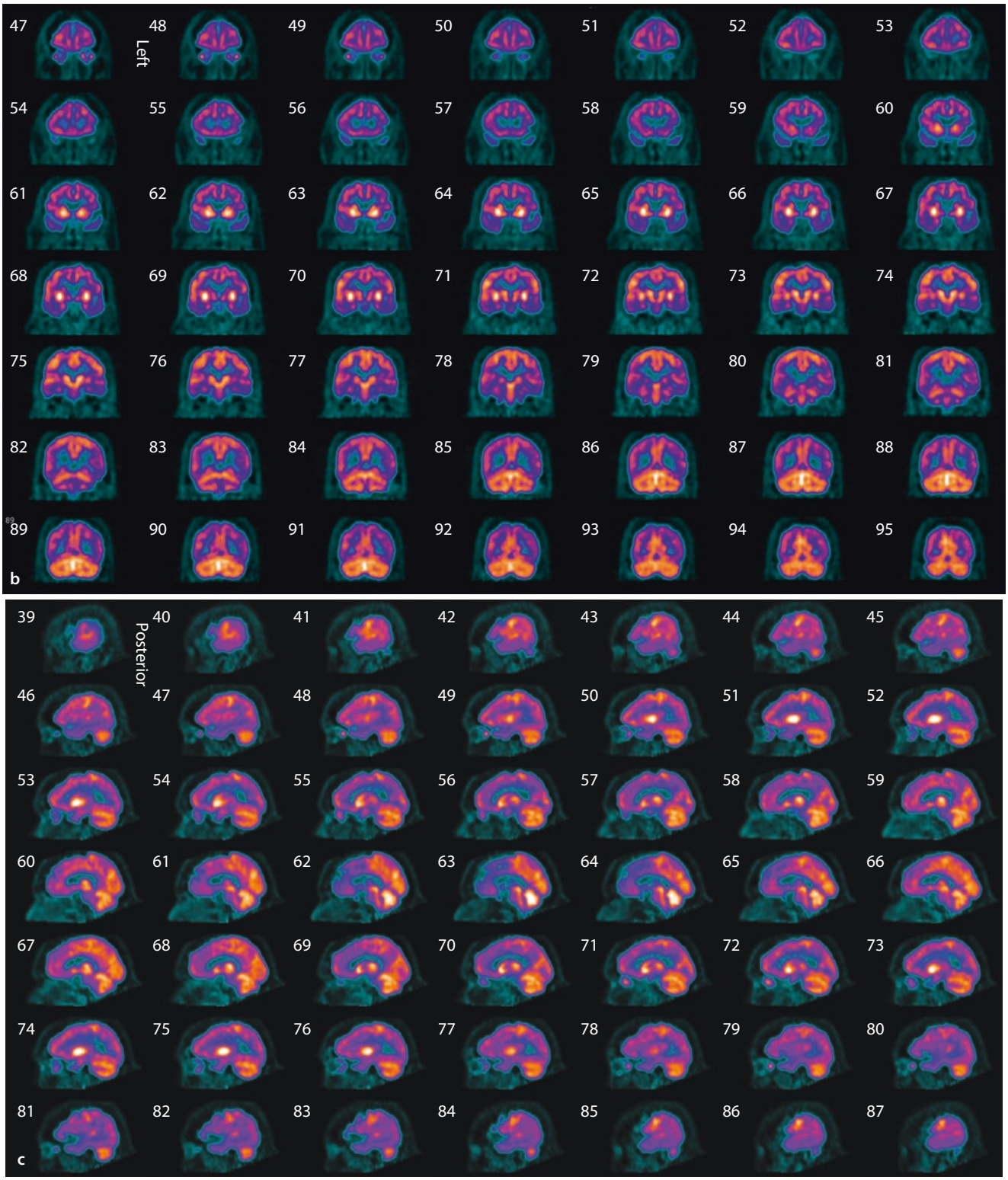


Fig. 3.8 (continued) **a–c** Transaxial, coronal, and sagittal slices after registration to the MNI_305 template

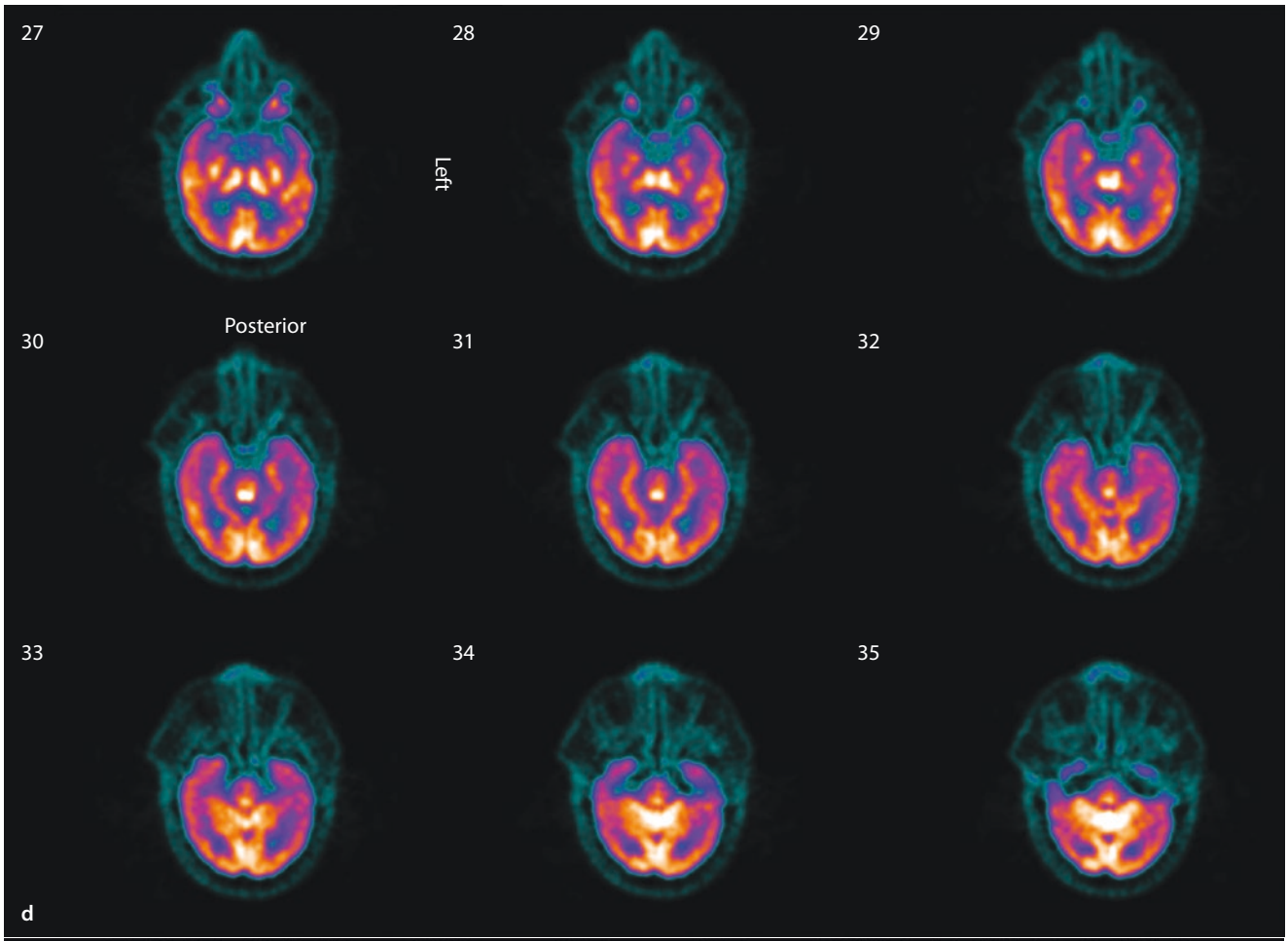


Fig. 3.8 (continued) **d** Registration along the axis of the temporal lobes. **e** 3D-SSP decrease map. Please refer to the text for interpretation

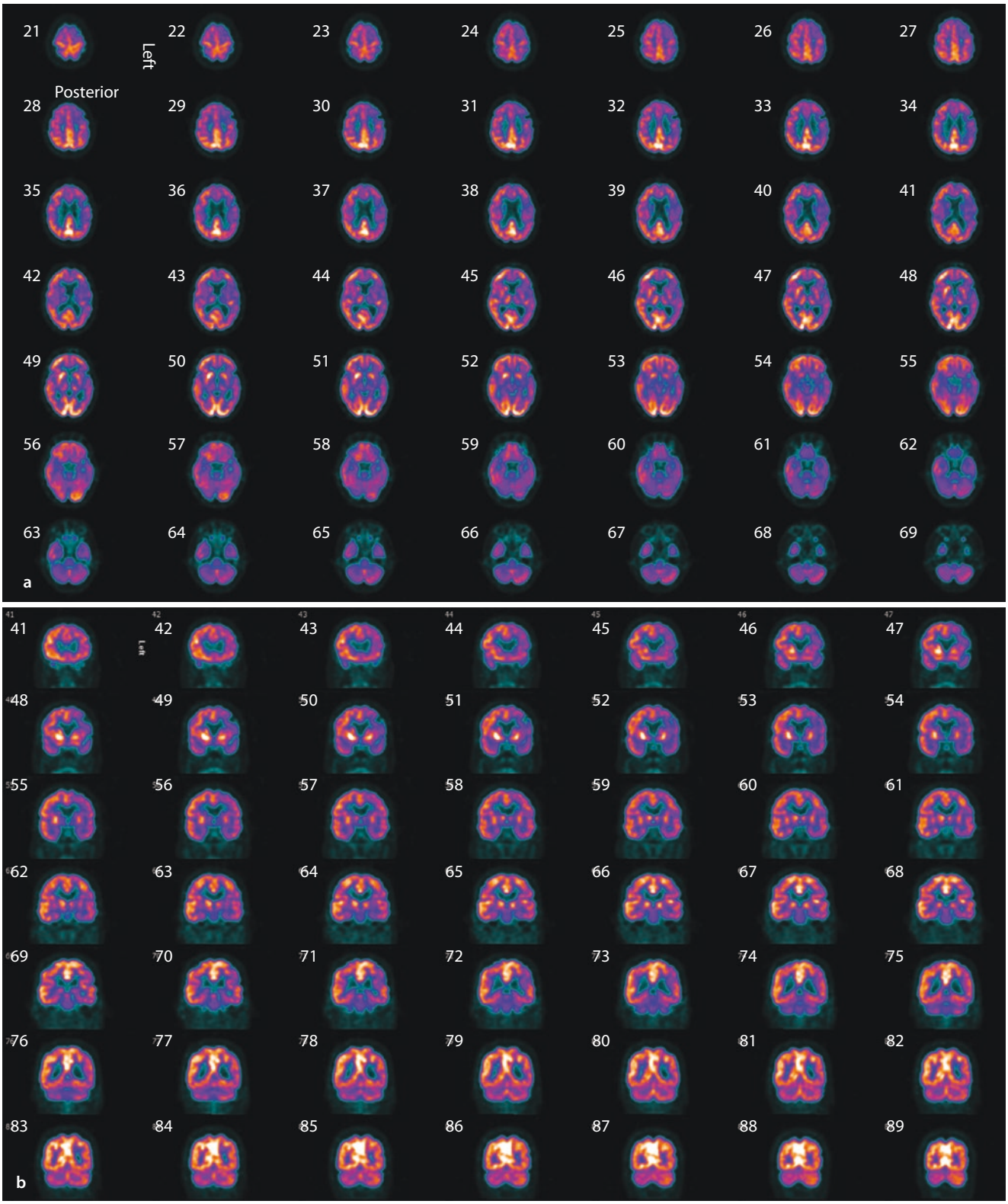


Fig. 3.9 Primary progressive aphasia, nonfluent/agrammatical variant

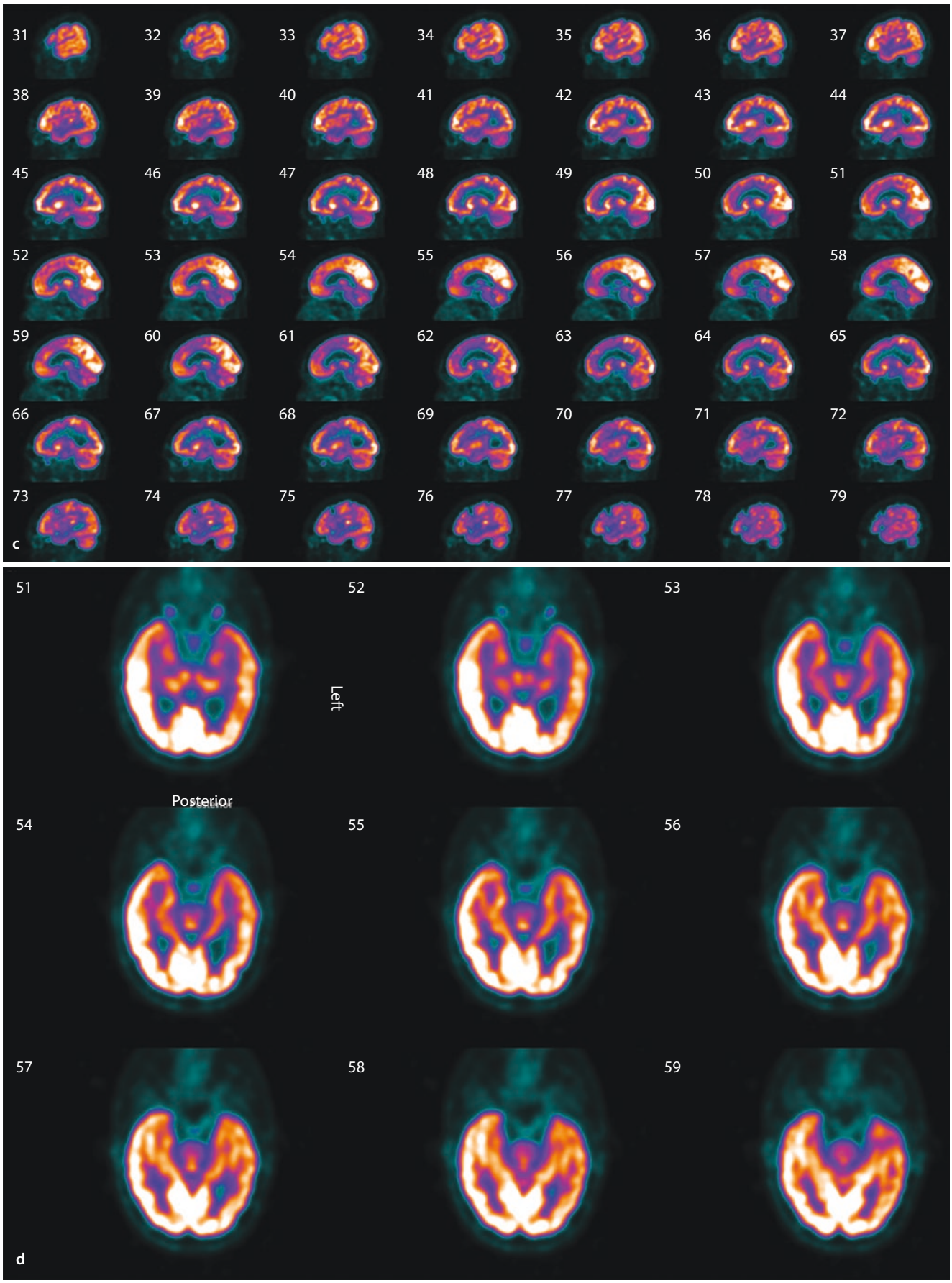


Fig. 3.9 (continued) **a–c** Transaxial, coronal, and sagittal slices after registration to the MNI_305 template. **d** Registration along the axis of the temporal lobes

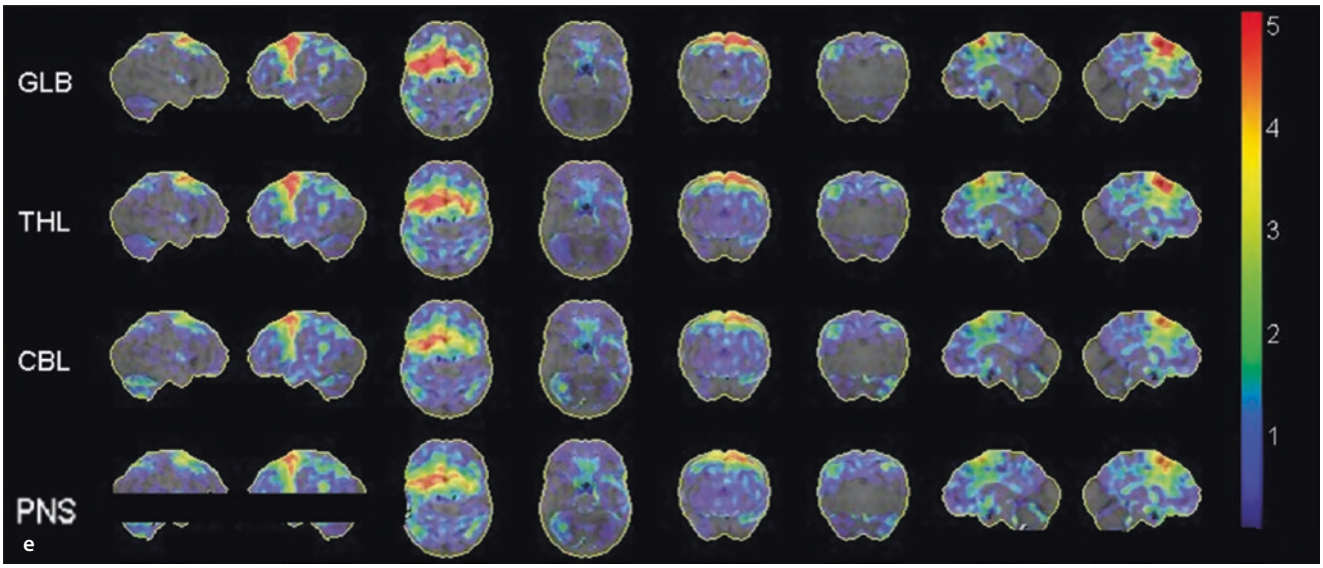


Fig. 3.9 (continued) **e** 3D-SSP decrease map. Please refer to the text for interpretation

side. The basal ganglia and thalamus are hypoactive on the left, while the right cerebellar hemisphere shows clear hypometabolism.

This aspect is characteristic of cases of the nonfluent/agrammatical variant of primary progressive aphasia. Most cases (again, not all, since predicting pathology in such cases remains notoriously difficult, although their neurodegenerative nature is obvious) are associated with frontotemporal neurodegenerative type pathology, as this case is likely to be given the absence of anomalies in the posterior parts of the cingulate gyri. Although it has been presented above that variant Alzheimer disease cases can initially present with normal uptake of ^{18}FDG in those regions, here in Case 5, the picture can be entirely explained by frontotemporal lobar degeneration.

This case shows that there is in general a good correlation between clinical primary progressive aphasia cases and their PET pattern although it is not unusual to see PET patterns which do not match the more typical ones for primary progressive aphasia despite typical clinical picture.

Case 6

A 74-year-old male presenting with limited but clear parkinsonian motor symptoms, slightly greater on the left side of the body, visual hallucinations, and "cognitive decline" (not specified). Please see Fig. 3.10 for functional images acquired.

Interpretation: On Fig. 3.10 there is a definite pattern of neurodegeneration, similar to what was seen in many cases presented above at the level of the convexities. Deficits clearly dominate in the parietal lobes, with some extension in the occipital ones, but with significant temporal and, to a lesser extent, prefrontal anomalies. Interestingly, the posterior portions of the cingulate gyri stand out in this patient, as they do not simply merge with the usually high activity of the primary visual cortex. Such an appearance has been called a "cingulate island" sign, for obvious reasons on those pictures, and is rather specific, although not highly sensitive, for Lewy body diseases. Another interesting aspect of this case is that the activity of the basal ganglia is quite striking, this being slightly more pronounced on the right side. This is indicative of loss of dopaminergic inputs to the striatum because of loss of nigral neurons, which impacts transmission through D_2 receptors slightly more than through the D_1 type, leading to facilitated glutamatergic transmission in the cortical striatal pathways and, therefore, increased glucose consumption; as expected, the right basal ganglia are slightly more active than the left ones, indicating a worse dopamine deficit on the right, which translates to parkinsonian symptoms which dominate on the left side of the body.

Lewy body disease-linked cognitive anomalies are typically classified as idiopathic Parkinson disease-related neurocognitive disorder and Lewy body neurocognitive disorder. The clinical timeline is what differentiates these two diagnoses, with motor symptoms antedating cognitive ones in Parkinson disease type, while the reverse is observed with Lewy body type. It should be remarked that at autopsy, differences between these two conditions are very limited, if at all present. Therefore, non-surprisingly, PET studies in general cannot reliably differentiate the two illnesses.

3.2.3 Sampler CT Scan Cases

In this section we present brief case description and images to demonstrate when CT scan can be useful in facilitating diagnosis.

A 79-year-old single man with history of depression, anxiety, and alcohol dependence (reportedly sober for many years) presenting with cognitive changes after a fall. CT scan in the emergency room is shown in Fig. 3.11a. Please review the image and identify the abnormality. Consider

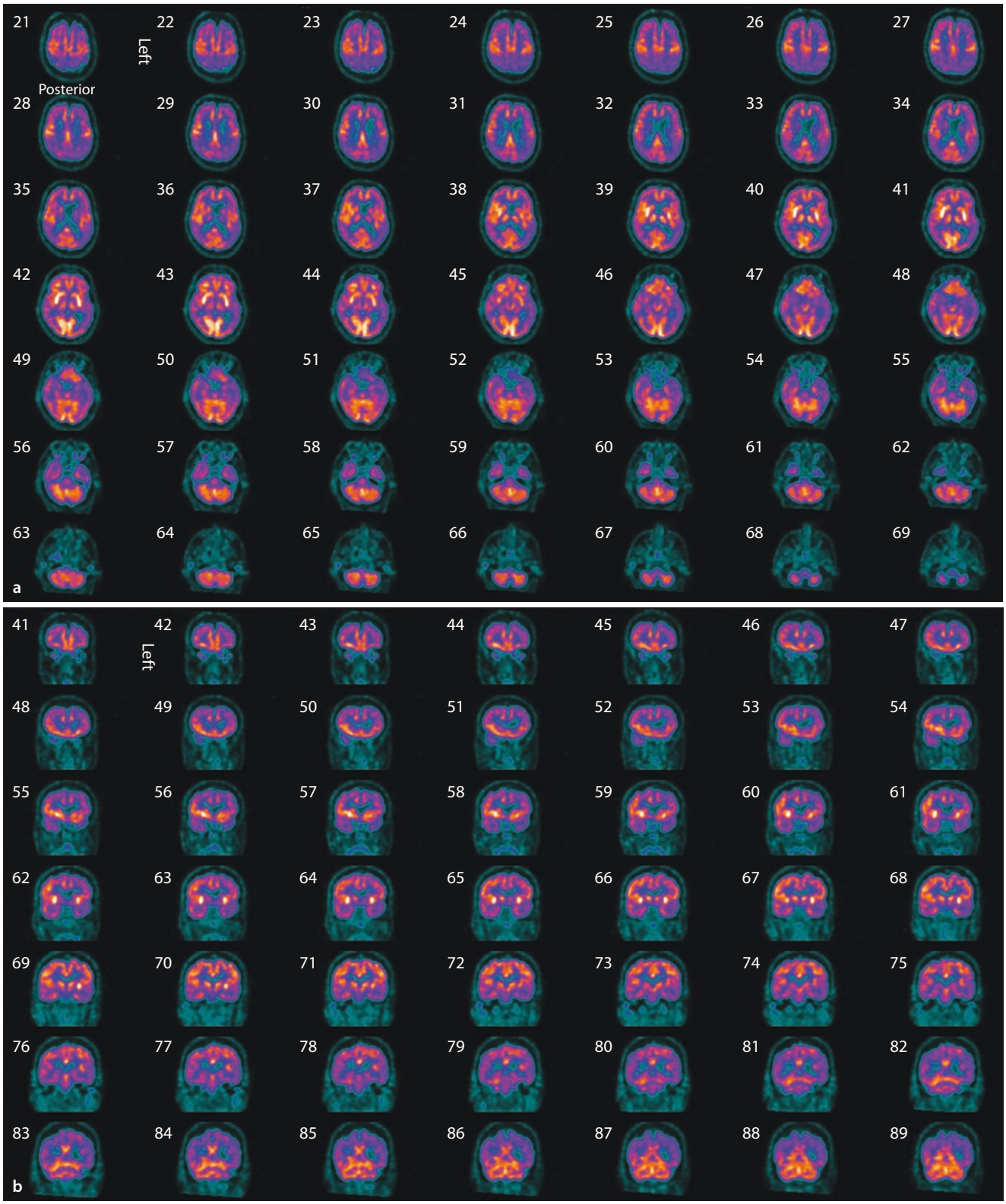


Fig. 3.10 Typical case of Lewy body disease with cingulate island sign and hyperactivity of the basal ganglia

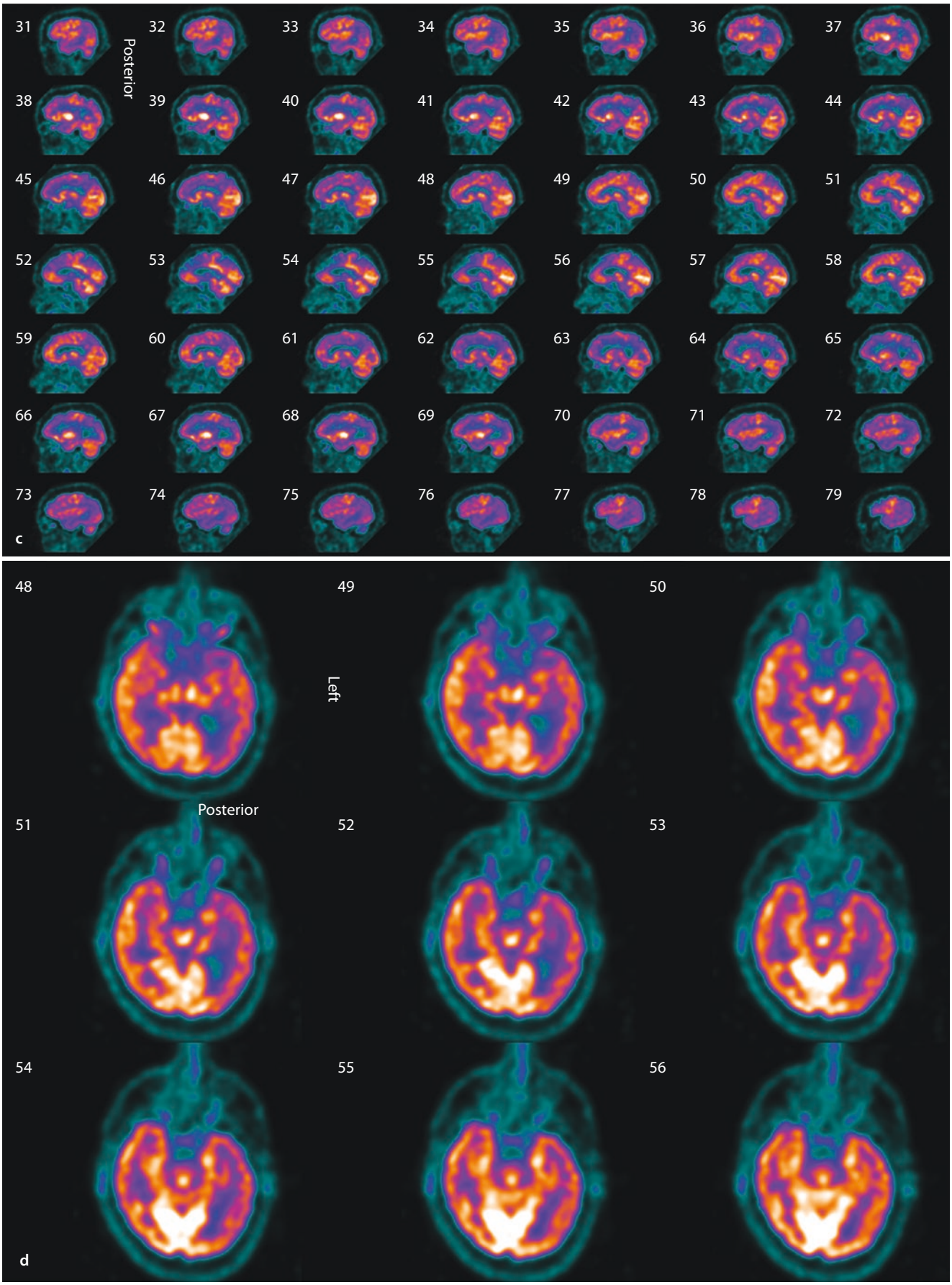


Fig. 3.10 (continued) **a**–**c** Transaxial, coronal, and sagittal slices after registration to the MNI_305 template. **d** Registration along the axis of the temporal lobes

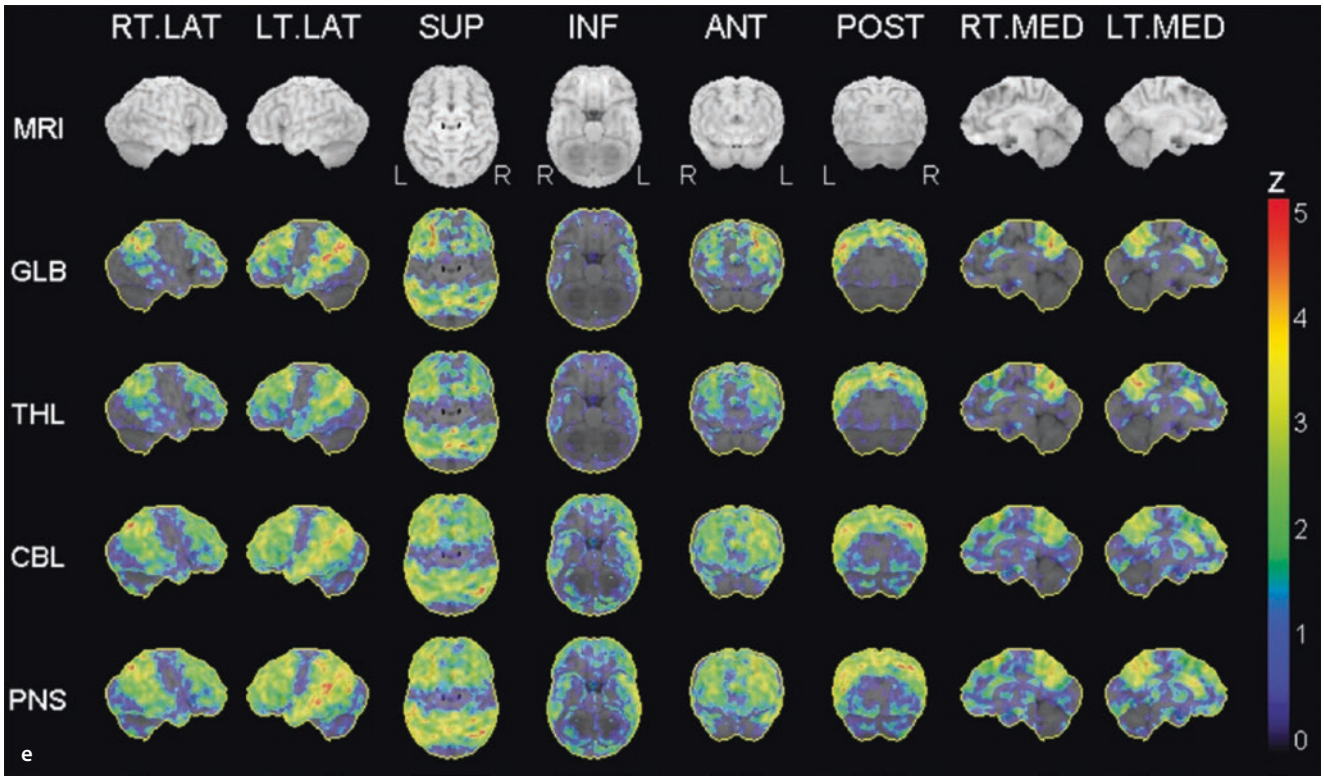


Fig. 3.10 (continued) **e** 3D-SSP decrease map. Please refer to the text for interpretation

possible mechanism by which the pathology has occurred in this patient.

Interpretation: There is evidence of fresh bleeding on the left side in prefrontal area in the form of subdural and intraparenchymal hemorrhage. Also there is evidence of subarachnoid bleeding. This is almost certainly traumatic. The fact that the patient has fallen before with evidence of previous injury to the brain on the right frontal area, and because of the history of alcohol dependence, this factor (alcohol use disorder) needs to be considered as a possible contributing factor as well.

An 87-year-old female with anxiety, depression, and a recent onset seizure. CT scan in emergency room is shown in Fig. 3.11b. Please review the image and identify the abnormality.

Interpretation: A case of chronic subdural hematoma on the left frontal area is seen on brain CT scan transverse section. There is a change in the appearance of the blood as it forms clot to less opacity. Some midline shift is noted. This is an example where a T2 MRI would be more helpful because CT scan beyond certain window of time may miss a smaller subdural hematoma that has organized to similar opacity as brain tissue. Patients in this age group are vulnerable to falls and at times can develop subdural hematoma, which may manifest itself in the form of mental status changes and, like in this case, a seizure.

A 47-year-old female with fatigue, sleepiness, cognitive difficulties, and mood lability/irritability. This evolved over a couple of years. She still works but finds it extremely difficult to maintain her tasks as a single mother who runs home-based advertisement business. She had parkinsonism in the form of slow gait but also had dysarthria and mild ataxia. A CT scan was ordered and is shown in Fig. 3.11c. Please review the image and identify the abnormality.

Interpretation: A case of idiopathic calcification (Fahr disease) is seen on CT scan transverse section; notice the bone-like opacity in the basal ganglia and white matter including cerebellar white matter. This is a rare illness. The fact that the patient had movement changes and cerebellar signs is a good indication for brain imaging, in addition to early age of onset of her cognitive changes.

A 78-year-old man presenting with slowly progressive cognitive decline with amnesia at onset. CT scan was obtained by the primary care physician to rule out "reversible cause" for the cognitive change and is shown in Fig. 3.11d. Please review the image and identify the abnormality.

Interpretation: The history and demographic data suggested Alzheimer disease. Brain imaging is useful mainly to rule out other causes but is not recommended by all guidelines. When a recent image is available, the clinician can review to identify pattern of atrophy that may add certainty to the clinical suspicion of Alzheimer disease. This CT scan transverse image shows widening of the sulci including the Sylvian fissure and calcarine sulcus, in addition to widening of the inferior horn due to hippocampal atrophy suggesting Alzheimer disease.

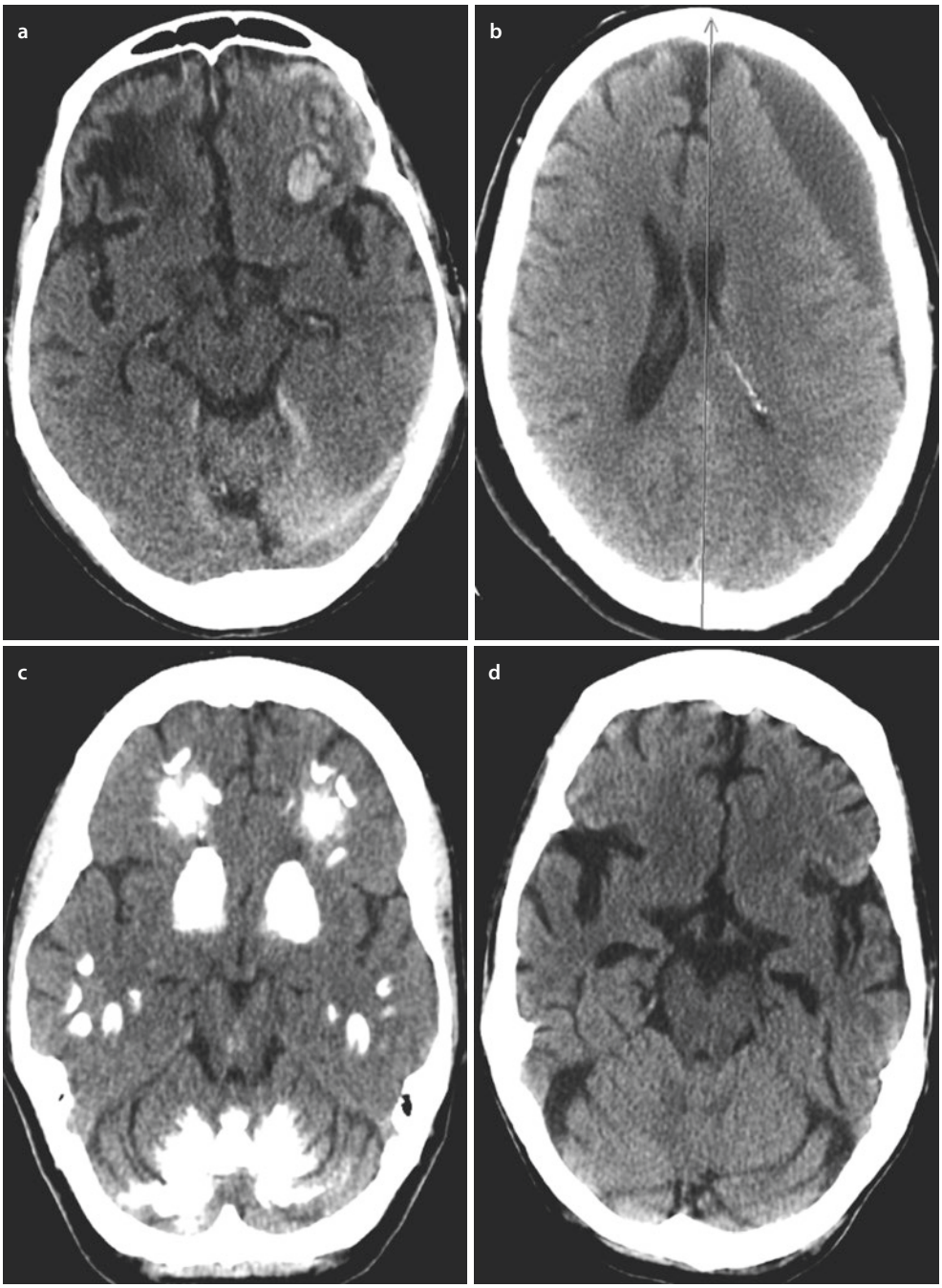


Fig. 3.11 A sampler of clinical cases where structural CT scan can be helpful. **a** A case of acute bleeding in subdural, subarachnoid, and intraparenchymal space evident on this transaxial CT scan (blood and bone appear white on the image). The image shows blood in left frontal area in addition to subarachnoid space in the calcarine sulcus in addition to an area of encephalomalacia (brain tissue loss) from previous injury. **b** A case of chronic subdural hematoma on the left frontal area seen on head CT scan transverse section; notice the change in the appearance of the blood as it forms clot to less opacity. Some midline shift is noted. This is an example where a T2 MRI would be more helpful because CT scan beyond certain window of time may miss a smaller subdural hematoma that has organized to similar opacity as brain tissue. **c** A case of idiopathic calcification (Fahr disease) as seen on CT scan transverse section; notice the bone-like opacity in the basal ganglia and white matter. **d** A CT scan transverse image showing widening of the sulci including the Sylvian fissure and calcarine sulcus in addition to widening of the inferior horn due to hippocampal atrophy as a result of Alzheimer disease

3.3 Key Points: Neuroimaging in Clinical Geriatric Psychiatry

- In this chapter we provided an overview of brain anatomy, functional networks, changes expected for age, available and emerging neuroimaging modalities, and clinical cases to demonstrate how structural and functional brain imaging can facilitate diagnosis of different neuropsychiatric disorders that affect geriatric patients.
- Currently, some of neuroimaging modalities are used clinically to investigate atypical cognitive and psychiatric presentations in old age, while other modalities are being standardized for common illnesses such as major neurocognitive disorders in order to provide confirmation of diagnosis, clarify differential diagnoses, identify treatment targets, and monitor treatment outcomes.
- The progress made in the field of neuroimaging of neurocognitive disorders like Alzheimer disease came from a

large investment of several stakeholders in North American and international initiatives. Having standardized template to acquire clinical, cognitive, and imaging data and making the data available to academic researchers has resulted in significant literature that is bringing us closer to the goal of establishing neuroimaging as a reliable biomarker for neuropsychiatric illnesses.

- When facing an atypical neuropsychiatric presentation, clinicians would normally create a list of possible syndromes that can explain the presentation. After careful clinical inquiry and formulating list of possible diagnoses, brain imaging might be pursued if it will add diagnostic value.
- Brain imaging is an important diagnostic tool, but it needs to be used wisely with a clear question to allow appropriate integration to the diagnostic formulation. Issues such as cost, predictive value, risks involved, type of imaging technique likely to answer the specific question asked, access, and convenience are all important questions.
- When ordering neuroimaging, it is essential for the clinician to provide concise question with a summary of the most salient information relevant to the diagnostic question to be addressed by neuroimaging tools. This will allow radiology and nuclear medicine to choose the right diagnostic imaging tool to answer the specific question and provide accurate reading of the images.
- It is not expected that clinicians become experts themselves in neuroimaging but be informed enough to pose the right question with the right level of details. This will allow more precise and cost-effective use of neuroimaging.
- Patients and their families are asking for clarity in diagnosis and they deserve clear answer but they are vulnerable to false hopes and harm by being exposed to a diagnostic test that may expose them to distress and sometimes radiation without providing significant value.
- Expert consensus guidelines aim to set evidence-informed standards for the use of neuroimaging in illnesses like neurocognitive disorders. The threshold to order brain imaging varies among published guidelines; for example, while US and European guidelines recommend a set of structural brain image, preferably MRI, for any person being worked up for neurocognitive disorders, Canadian guidelines list certain conditions before neuroimaging would be appropriate, for example, early age of onset, atypical presentation, rapidly progressive course, evidence of focal neurological signs, or suspicion of vascular component [78].
- With the rapid flux of research in the field, clinicians are advised to stay up to date with changing guidelines to make sure they maintain appropriate use of neuroimaging in serving their patients.

3.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which one of the following neuroimaging modalities is considered molecular?

A. Diffusion tensor imaging (DTI)
B. Functional MRI (fMRI)
C. PET amyloid
D. SPECT scan
E. Susceptibility weighted image (SWI) MRI

Answer: C

PET amyloid is a way of imaging the brain at the molecular level. It involves using radioactive ligands that attach to the amyloid molecule and give an idea on the density and distribution of amyloid molecule in the brain. This is becoming one of the standard tools in amyloid removal trials.

MCQ 2. When investigating a patient for evidence of previous brain injury and to confirm previous bleeding, which of the following is considered the most appropriate neuroimaging tool?

A. CT scan of the head without contrast
B. CT scan of the head with contrast
C. T2 MRI of the brain
D. Susceptibility weighted image (SWI) MRI
E. PET scanning

Answer: D

SWI MRI is the most appropriate neuroimaging tool to identify previous bleeding mainly microbleeding that usually leaves behind hemosiderin deposits. This is especially helpful in cases of amyloid or hypertensive angiopathy and head injury that resulted in shearing of the white matter tracks.

MCQ 3. When evaluating a patient for possible vascular cognitive impairment due to white matter changes, which of the following is considered the best neuroimaging tool?

A. MRI, T1 with contrast
B. Magnetic resonance spectroscopy (MRS)
C. Diffusion tensor imaging (DTI)
D. MRI, T2, fluid-attenuated inversion recovery (FLAIR)
E. Arterial spin labeling

Answer: D

MRI, T2, FLAIR is the best to visualize white matter hyperintensities; this sequence removes CSF signal, which will allow better visualization of periventricular white matter abnormalities.

MCQ 4. When evaluating a patient with gait changes, urine incontinence, and cognitive changes, you learned that head CT scan showed disproportionally dilated ventricles, which of the following would be the best test to help you confirm the diagnosis?

A. Head MRI with contrast
B. Diffusion tensor imaging (DTI)
C. CSF flow study
D. Opening pressure on lumber puncture
E. MRI angiography

Answer: C

Although there are some radiological features that suggest normal pressure hydrocephalus such as disproportionate ventricular dilation (compared to sulci dilation), CSF flow study is the most specific test for normal pressure hydrocephalus. It is usually done through nuclear medicine [81, 82].

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Neuropsychology in Late Life

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4.1 Background

4.1.1 Rationale

Neuropsychological assessment is indicated to aid in the discrimination of normal age-related versus pathological cognitive changes due to mild or major neurocognitive disorder (NCD) or to another preexisting neuropsychiatric disorder. When NCD is identified or suspected, neuropsychological assessment can assist in determining specific etiology based on the cognitive profile. Neuropsychological assessment is often critically important with respect to diagnosis and treatment planning and can assist clinicians in adapting their communication, psychoeducation, and psychotherapy based on the identified cognitive strengths and weaknesses. Standardized neuropsychological assessment can distinguish normal versus non-normal aging because such tests include normative data that allow the clinician to correct for the impact of normal aging and in some cases other factors that impact test performance, such as level of education. Thus, one can compare the older adult patient with subjective memory complaints objectively against the performance of his or her peers in the general population to determine if the concerns are normative or due to neuropsychiatric disorders, including NCDs.

In addition to identifying if the patient's cognitive ability departs from normative age-related changes, it is also important to consider changes from the patient's own baseline. This is particularly relevant with patients who premorbidly fell in the upper or lower ends of the normal distribution. Cognitive screening may be sufficient to determine if there has been a likely change from an "average" patient's normative baseline; however, more extensive neuropsychological assessment may be required to provide input into changes when the patient is likely to have been "nonnormative" premorbidly which can then more accurately inform medical, psychiatric, or neurodegenerative etiological considerations. While neuropsychological assessment is important in geriatric settings for the reasons outlined, special considerations specific to aging individuals include modifications to the standard clinical interview, obtaining a collateral interview, as well as thorough review of the medical history, cardiovascular risk factors, and current medication profile.

4.1.2 Neuropsychology of Normal Aging

Brain volumes decrease with normal aging beginning with pruning in late adolescence that progresses across the lifespan and accelerates after the fifth decade of life. While there is some degree of global atrophy, the frontal and superior parietal regions appear most impacted in healthy older adults [1]. Volume loss is due to a lesser extent from brain cell or gray matter loss but is more strongly related to loss of white matter integrity. As white matter integrity is essential for neural signaling between and within brain regions, information processing efficiency declines as a result of these changes. Changes in intercellular connectivity and neuronal integrity translate into declines in processing speed, immediate and delayed memory, and executive functions in older individuals [2].

Attention and Executive Cognitive Changes

While normal aging does not impact focused attention or attention span (e.g., as measured by the forward digit span), other aspects of attention are impacted. Healthy older adults are impaired on measures of cognitive inhibition/inhibitory control, whereby effortful mental control is needed to suppress attention to task-irrelevant material. A classic example of inhibitory control is the Stroop color-word task [3]. Patients are instructed to ignore the meaning of typed color words (e.g., red, blue) and say aloud the ink color the words are printed in. Older adults have more difficulty inhibiting their attention to the font color when it is incongruent from the meaning of the word [4]. Another aspect of executive attention impacted in normal aging is working memory, the ability to hold information in mind over a relatively brief period of time while using that information to perform a mental operation, e.g., mental arithmetic. Working memory is typically assessed using the digit span backward task; patients are read aloud strings of single digit numerals and asked to mentally reverse the number sequence before repeating back the numerals in reverse order. Providing older patients with written handouts of important instructions can assist a patient with working memory impairment.

Memory-Related Changes

While forgetfulness is often considered part of normal aging, "memory loss" is not. Rather, as described in ▶ Chap. 18, rapid forgetting is a pathognomonic indication of the most common presentation of NCD due to Alzheimer disease that can easily be distinguished from normal aging and from memory impairment secondary to depression using standardized neuropsychological measures. In assessing memory, it is important to note that memory is not a unitary construct, and normal aging impacts some aspects of memory but not others [5]. Memory is composed of three primary processes: (i) encoding (learning, getting information in), (ii) consolidation (storage, keeping information in), and (iii) retrieval (recall, getting information out). Normal aging effects are most notable at encoding and retrieval.

A word list learning task is useful in distinguishing normal age-related memory declines from those associated with Alzheimer disease. Using the Hopkins Verbal Learning Task-Revised (HVLT-R) [6] or California Verbal Learning Test-2 (CVLT-2) [7], the examiner reads aloud a list of words which the patient repeats back immediately (encoding/

learning phase) over several practice trials. A healthy older adult will encode fewer words than a healthy younger adult secondary to slowed processing speed and decreased working memory. After a delay of 20–30 minutes, the patient is asked to recall all the words they can (free recall). Decreased mental efficiency also impacts free recall, whereby the strategic search of memory stores may become less efficient and fewer words are spontaneously recalled. However, provision of retrieval cues will assist healthy older adults greatly; most older adults will be able to correctly recognize and discriminate all list words from a similar number of non-list words. Preserved delayed recognition memory is an indication that the words acquired during encoding have not been forgotten even if free recall was less than optimal, as is often the case in depression.

In contrast, the older adult with NCD due to Alzheimer disease will not benefit from the provision of recognition cues and may not even recall having ever been read a list, a classic indication of the "rapid forgetting" or loss of consolidation characteristic of the amnestic presentation of NCD due to Alzheimer disease. The free recall vs recognition difference can also be helpful in discriminating depression from NCD, as depressed older adults will also benefit from recognition cues during word list memory testing.

4.1.3 Neurocognitive Disorder

According to the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5) [8], major or mild NCD is evidenced by cognitive decline from the patient's previous level of performance in one or more cognitive domains. Mild NCD is characterized by mild and often isolated cognitive changes in the absence of significant functional declines, whereas major NCD is characterized by more severe and often multi-domain cognitive changes and is accompanied by a global decline from premorbid levels of functioning in activities of daily living. These cognitive difficulties are not better accounted for by delirium or another neuropsychiatric disorder (e.g., depressive disorder, anxiety disorder, schizophrenia). These changes may be based on concerns of the patient, a family member, or a clinician, but according to the DSM-5, "substantial impairment in cognitive performance [is] preferably documented by standardized neuropsychological testing" [9]. As outlined in the DSM-5 and in ► Chaps. 18, 19, and 21, there are numerous possible etiological subtypes of both major and mild NCD with variations in the patterns of cognitive impairments, nature of onset, and course of decline. As illustrated later in Case 1, formal neuropsychological assessment is often more important in the context of a suspected mild NCD, where impairment may be quite subtle and difficult to discriminate from normal aging or cognitive effects of common neuropsychiatric disorders.

Teaching Point

When an older adult presents with subjective memory or cognitive concerns within a geriatric psychiatry context, objective neuropsychological assessment may be particularly helpful. Older adults with various neuropsychiatric disorders, such as depressive or anxiety disorders, may be vulnerable to over-interpreting normal age-related cognitive changes. While depressive and anxiety disorders can lead to cognitive difficulties in their own right, the negative cognitive biases characteristic of these conditions frequently lead patients to be hypersensitive to perceived faults and imperfections, including cognitive ones. As such, minor cognitive slips that other older adults may dismiss are often interpreted as significant by those with negative cognitive bias and rumination. Formal cognitive assessment among these individuals, even in younger adulthood, often reveals that many aspects of cognition are within normal limits compared to peers.

4.1.4 Neuropsychological Assessment Procedures

Interview

The neuropsychological interview allows the clinician to obtain pertinent background information that is often not in medical charts. Data gathered includes demographics, important developmental, educational and psychosocial history, as well as information pertaining to current concerns or complaints [10]. Establishing rapport and engaging the patient in the assessment process at the start of the interview is essential to ensure that valid and reliable assessment data is gathered. Older adults may be worried about the implications of the testing as it relates to their independence. They are also more likely to be anxious due to unfamiliarity with standardized or computerized testing. Taking time to orient the patient to the assessment process, use of technology (if any), reviewing the purpose and goals of the assessment, and allowing sufficient time for the patient to ask questions is imperative with respect to reducing uncertainty and anxiety to ensure more valid test results.

Teaching Point

Begin the interview by explaining the assessment procedure and the cognitive skills to be assessed using lay terms. Review limits to confidentiality. Ask the patient to describe their understanding of why they have been asked to participate in such an assessment. This will provide information as to the patient's level of insight into any cognitive or functional changes. Other qualitative information obtained during the interview that might not be observed in a more structured testing

Teaching Point (Continued)

session includes observations of the patient's behaviors, mannerisms, and spontaneous speech. For example, is the patient socially inappropriate, making sexually charged comments, or relating to the examiner in a much more familiar way than expected? All of these are suggestive of frontal lobe behavioral dysfunction. Attending to qualities of speech and language may identify word-finding problems or paraphasias.

Establishing Premorbid Level of Functioning

The interview should elicit information that is relevant for establishing an individualized premorbid baseline ability, as it will be against this baseline that the patient's performance on age-normative neuropsychological test data will be compared. Premorbid general intellectual ability may be estimated using history of educational and occupational attainment. Establishing educational history should include probing for learning or academic difficulties as most older adults would not have been formally diagnosed with learning disability or intellectual impairment in childhood. As such, the clinician may need to ask probing questions about educational attainment or barriers to education (see Table 4.1). In the absence of a history of familial upheaval or childhood trauma, a patient who describes a history of delayed acquisition of basic academic skills, grade repetitions, and failure to complete high school is likely to have had an undiagnosed intellectual or learning disability. This is important to identify because, in such a case, cognitive difficulties on standardized testing may not actually reflect a decline. It is equally important to consider baseline functioning among those patients who excelled in their youth and younger adulthood. For example, it would be expected that patients who described themselves as "top of the class," who had completed university education, and/or held a successful professional career to have been above average premorbidly. Within this context, the patient may perform within normal limits on standardized age-matched testing, but this in fact may represent a decline from their higher than average baseline.

Table 4.1 Examples of interview questions

Domain	Examples of questions
Premorbid ability	What was your childhood like? Did you struggle to learn to read or write? Was math more difficult for you? How far did you go in school? Were you ever held back a year? What kind of a student were you? Did you fail any classes/courses? What did you do for work? What was your longest held job?
Cognitive difficulties	Do you have any difficulty remembering appointments? Conversations? To relay messages? Items when shopping? Any difficulty coming up with people's names? Names of everyday items? Do you find yourself unable to think of the word you want to use? Do the wrong words ever come out when you are speaking? Any difficulty following other people in conversation? Any difficulty finding your way around? Getting lost? Any difficulty making decisions or choices? Any difficulty doing things with your hands, such as small buttons?
Course	When did you first notice your (cognitive) problem? Did it start all of a sudden? Did it creep up gradually? What was happening in your life when you first noticed your problem? Has it gotten worse over time or stayed the same?
Functioning	Have you noticed any difficulties getting things done around the house? Any trouble paying bills on time? Difficulty preparing meals? Have you accidentally left the stove on? Have there been any mix-ups with your medication? Do you need help with any activities? Have you stopped or modified your work as a result of these difficulties?

Subjective Cognitive and Physical Changes

Asking the patient to explain their understanding of why they have been referred for neuropsychological assessment may reveal specific subjective cognitive concerns, particularly in the case of patients who do not have NCD or who have mild NCD and retain insight. The most common cognitive concern among older adults is memory [11]. Regardless of whether patients spontaneously report concerns or not, it is important to ask probing questions (see Table 4.1) about common memory and other cognitive changes associated with the major classes of NCDs, as many patients may not be aware of or able to spontaneously generate a full description of changes. Moreover, memory complaints may actually be due to other cognitive difficulties, most frequently, poor attention or concentration. Physical problems such as balance or motor problems, sensory loss (visual, auditory, tactile), and pain should also be queried as should medication use and adherence and sleep quality and daytime fatigue. Emotional functioning, including mood, anxiety, and frustration, should also be queried as symptoms of depression are often difficult to distinguish from a dementing process in the absence of formal testing and anxiety can lead to inattention and associated memory difficulties. When patients endorse difficulties, it is important to verify whether this is a change from their baseline or a worsening or reemergence of a long-standing difficulty.

Establishing Nature and Course of Decline

When cognitive, motor, sensory, or emotional changes or concerns are endorsed, it is critical to determine the nature of onset and progression of these changes over time. Sudden or insidious? Progressive or static? Changes associated with certain forms of NCDs such as Alzheimer disease are more likely to begin insidiously and worsen gradually over a number of years. In contrast, cognitive difficulties associated with medical conditions such as myocardial infarction or stroke would have a more abrupt onset and static course. A sudden onset and stepwise course may also be associated with NCD due to vascular disease secondary to accumulation of cerebral damage associated with numerous small vessel and/or transient ischemic events. Cognitive difficulties associated with depressive or anxiety disorders may wax and wane over time in accordance with the mood or anxiety state but may also persist during periods of euthymia and worsen with age.

Teaching Point

Determining the nature of onset and course of changes will allow the examiner to generate hypotheses regarding differential diagnosis and guide in the selection of specific neuropsychological assessment tools to aid in this differential process.

Daily Functioning

It is important to characterize changes to daily functioning including basic activities of daily living and instrumental activities of daily living. Basic activities of daily living include self-care tasks, while instrumental activities of daily living involve more complex tasks such as managing finances and preparing meals. In order for a patient with documented cognitive changes to meet criteria for a diagnosis of major NCD, a substantial change or decline in daily functioning is required. This can often only be obtained from a collateral interview, as patients with most forms of major NCD will often lack insight into functional changes. For example, when Mr. S. is asked about his typical daily activities, he reports that he reads the paper from front to back each morning, plays bridge several times a week, and participates in volunteering at the YMCA. However, Mrs. S. reports that Mr. S. has not been able to do any of those activities for several years.

Collateral Interview

Speaking with a collateral informant very familiar with the patient prior to the onset of any suspected changes is crucial either because the patient lacks insight into changes or they may deliberately minimize or conceal difficulties due to concerns of how this might impact their independence. For older adults with a history of neuropsychiatric illness that impacts cognition, such as depressive disorder, the collateral informant might clarify whether the current presentation is consistent with previous episodes of depression or represents a change. For example, in the case of a moderate to advanced NCD due to Alzheimer disease pathology, the patient may be disoriented to time and describe their abilities and daily activities according to a younger version of themselves. As well, with certain types of NCD, such as the behavioral variant of frontotemporal NCD, subtle personality and/or behavioral changes are the first signs of the disorder and are often accompanied by a loss of insight due to degeneration of frontal brain regions. Thus, patient self-report regarding the type and time-course of any cognitive or functional changes should be validated with the collateral informant. Additionally, the collateral informant might be able to provide further information to help determine premorbid baseline level.

Teaching Point

Speaking with a collateral informant separately, with the patient's consent, is preferred, especially in situations where the patient may lack insight into cognitive difficulties, so that the informant can speak more openly about their concerns. Most patients will readily agree to have their collateral informant interviewed separately. Occasionally, some patients will not authorize a separate collateral interview, and in such cases where objective cognitive deficits are absent or minimal, the lack of collateral can make it impossible to determine if the patient meets criteria for minor NCD. In such cases, repeat neuropsychological assessment would be recommended to monitor for further declines over time.

Cognitive Screening

Cognitive screening with tools such as the Mini Mental State Exam (MMSE) [12] or the Montreal Cognitive Assessment (MoCA) [13] is the recommended first step when older adults present with subjective cognitive complaints in both acute and tertiary care settings because they are brief and can inform the need for lengthier cognitive testing. The MoCA is recommended, as it is copyrighted but freely available for use by most healthcare professionals and has been translated into 56 different languages, and there are three alternate versions of the English MoCA for use in serial assessment. When using a screening tool, it is important to review administration instructions prior to beginning in order to ensure the data gathered is valid. An administration manual for the MoCA is available online (► www.mocatest.org). Other considerations when using screening measures include completing the testing in a quiet, distraction-free setting, when the patient is alert, comfortable, and wearing corrective lenses or hearing aids (if required), and completing the testing in the patient's native language or most commonly used current language. The MoCA screens most aspects of cognition, including attention/concentration, executive functions, memory, language, visual spatial skills, and orientation. This can be useful for screening normal age-related concerns,

concerns of the "worried well," or identifying individuals whose performance is suggestive of a decline. Cognitive screening measures are also useful for monitoring cognition over time in patients at risk for decline.

A score above the cutoff on cognitive screening may belie cognitive changes. This is often the case early in the course of NCD where cognitive changes may be too subtle to be detected by a screening measure. In such cases, more extensive neuropsychological assessment will be required.

Teaching Point

While cognitive screens can be useful for identifying suspected NCD and monitoring patients over time, it is important to refer patients for comprehensive neuropsychological assessment before the total score on the screen drops much below the cutoff. Once a sufficient level of cognitive impairment is reached, differential diagnosis becomes more complicated and is often not possible with neuropsychological testing. It is preferable to err on the side of caution at the earlier signs of cognitive change rather than wait until NCD is strongly indicated before seeking full neuropsychological assessment.

Comprehensive Neuropsychological Assessment

There are three main goals to completing a comprehensive neuropsychological assessment with older adults: first, to aid in differential diagnosis of cognitive changes due to normal aging from major or mild NCD or a primary psychiatric disorder; second, to characterize the cognitive profile of spared and impaired functions to provide input into differential diagnosis of a specific etiology of the identified deficits; and, third, to use the cognitive profile to generate individualized recommendations regarding treatments and supports.

Format of Assessment

Information gathered from the clinical interview, collateral informant, referral source, and medical history/chart review together guide test selection for a full assessment. Most neuropsychologists follow a "flexible battery" approach whereby routine test batteries are informed by patient groups, while supplemental measures and procedures may be integrated to evaluate specific concerns. A basic neuropsychological test battery with older adults will include measures to assess the major domains of cognition: intellectual ability, attention/concentration, memory, language, visual spatial and constructional skills, social-emotional function, and praxis. Within the usual tests allocated to assess these domains, additional measures may be added to further assess particular concerns. For example, to query behavior-variant frontotemporal NCD, the clinician may administer the Frontal Behavior Inventory [14] to obtain an objective measure of behavioral disturbance in addition to standard cognitive executive function performance.

Intellectual Ability

Assessment of intellectual ability includes both estimation of premorbid general ability and current objective ability. Premorbid intellectual ability is measured most often using a single word reading test, such as the Test of Premorbid Function (TOPF) [15] or the North American Adult Reading Test (NAART) [16]. Scores are transformed using an algorithm into estimated premorbid IQ. Current general intellectual ability is most often assessed using a version of the Wechsler Adult Intelligence Scale (WAIS). The full WAIS is currently in its fourth revision (WAIS-IV) [17], and the commercially available short form, the Wechsler Adult Scale of Intelligence, is in its second revision (WASI-II) [18]. The advantage of using the full WAIS-IV is that in addition to the traditional Full-Scale Intellectual Quotient (FSIQ), the results generate four index scores: a verbal intellectual ability index (VIQ), a performance-based or nonverbal intellectual index (PIQ), a working memory index (WMI), and a measure of information processing speed (PSI), as well as the General Ability Index (GAI)—a new addition to the WAIS-IV which represents a full-scale IQ factoring out the negative impact of slowed processing speed and working memory difficulties. The GAI is important to consider with psychiatric populations who often present with slowed processing speed and working memory impairments secondary to mood or anxiety issues which may "pull down" the FSIQ. The WMI and PSI scores can be helpful in interpreting results of memory and executive functioning tests, especially with younger patients (see ► Sect. 4.2.1). However, the full WAIS-IV can take two or more hours to administer in its entirety, and so it is often onerous for use with very old individuals and with those patients who are strongly suspected of having a NCD. The WASI-II is a good alternative, with both a four-subtest and a two-subtest option, generating an estimated FSIQ, VIQ, and PIQ in a fraction of the time. Comparison of estimated premorbid and current FSIQ will reveal if there has been a generalized decline. A difference of 1.5 or more standard deviations between scores is considered reflective of a significant decline.

Teaching Point

Given that the majority, if not all, objective measures of premorbid intelligence are based on measures of single word reading, it is important to note that the score may not be valid for an individual with a history of a reading or verbal learning disability or for someone whose first language is other than that being assessed. In such a case, broader level of educational and occupational attainment may be better qualitative estimates of premorbid ability.

Attention/Executive Function

Attention and concentration are typically assessed using both auditory verbal and visual stimuli. Simple auditory attention span is most frequently assessed using the digit span test,

whereby strings of single digit numerals of increasing length are read aloud and the patient repeats them back. The simple auditory attention span is resistant to most forms of NCD and remains relatively intact until later in the illness progression. Normal span is seven plus or minus two digits. More complex auditory attention, involving working memory, is assessed with the backward version of the digit span test, whereby strings of digits are read aloud and the patient is asked to repeat them in a backward sequence. Standardized forms of the digit span test, along with age-corrected normative data, are included within the WAIS-IV as well as the Wechsler Memory Scales. Visual attention is often assessed with the Trail Making Test, which is also comprised of a simple version (Trails A) whereby the patient is instructed to connect a series of numerals scattered across a page using a single pencil line as quickly as possible. The more complex version (Trails B) is considered by many a measure of executive function as it involves holding in mind and alternating between two sets of material. Patients are shown a paper with numbers and letters scattered across and are asked to alternately sequence the numbers and letters, in numerical and alphabetical orders, as quickly as possible. There is evidence for the use of Trails B as a screening measure for driving ability [19]. Trails B time of over 3 minutes, and/or three or more errors, is useful for screening of cognitive impairment that might negatively impact driving. Other measures of executive function involve simple problem-solving and set shifting measures such as the reasoning and conceptual shifting subtest of the Kaplan-Baycrest Neurocognitive Assessment (KBNA) [20], while subtle difficulties in higher functioning patients may be detected using complex measures of abstract reasoning or problem-solving such as the Category Test [21] or Wisconsin Card Sorting Test [22]. Verbal fluency may also be considered a measure of executive function, as frontal lobe integrity is required to perform the strategic semantic memory search needed to generate words that match the given cue. The Controlled Oral Word Association Test (COWA) [23] is a measure of phonemic fluency that involves quickly generating words to match a given letter cue. Semantic verbal fluency involves asking the patient to name as many items belonging to a given category in 1 minute. Commonly used semantic categories include animal names or fruits and vegetables.

Teaching Point

When completing verbal fluency testing, it is again important to consider the native language of the patient, as this may negatively impact performance even if the conversational speech is very fluent. In addition, the impact of slowing due to normal aging and the effects of formal education must be taken into account. Therefore, the raw verbal fluency score is not as relevant as a norm corrected score. Various normative data sets are available that correct scores for age and education [24].

Memory

Assessment of memory utilizes both verbal and visually based content and measures of immediate and delayed recall and recognition. Memory difficulties represent the most common subjective cognitive complaint among older adults. However, memory is not a unitary construct. It is composed of a learning or encoding phase, a consolidation phase, and a retrieval phase. Thus, it is very important that formal memory assessment involves assessment of all three stages of the memory process, and that it is completed with measures that correct for normal aging. Verbal learning and memory is assessed using list learning tasks, such as the California Verbal Learning Task-2 (CVLT-2) [7], the Rey Auditory Verbal Learning Task (RAVLT) [25], or the Hopkins Verbal Learning Task-Revised (HVLT-R) [6]. List learning tasks are composed of a list of words that is read aloud to the patient over several learning trials. Immediate recall of the list is provided by the patient after each trial, and a learning curve is generated that indicates whether the patient is able to acquire more information and benefit from repetition. After a delay, the patient is asked to spontaneously recall all the words from the list, assessing free recall. Poor free recall does not necessarily mean that all the words learned during acquisition were not consolidated or have been forgotten. In this regard, providing recognition cues after free recall typically assists with memory retrieval for both healthy older adults and those with depression indicating that difficulties during free recall are retrieval based rather than reflective of rapid forgetting or reduced retention.

Teaching Point

Intact recognition in the face of poor recall indicates that memory storage is intact but that frontally mediated strategic memory retrieval is impaired. If the patient also demonstrates impairment on executive measures, this pattern will suggest that executive impairment is likely contributing to poor memory in daily life.

Verbal memory is also assessed using story memory tasks, such as the logical memory subtest of the Wechsler Memory Scale-IV (WMS-IV) [26] or the story subtest of the Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) [27]. Story memory tasks involve the presentation of a larger volume of auditory verbal information in a more meaningful context compared to list-learning tasks. This allows the examiner to determine whether a patient's memory can benefit from the provision of greater context and meaningfulness. Qualitatively, the clinician might also assess if the patient is able to recall the "gist" of the story, but forgets the details, suggestive of left frontal impairment. Poor story recall compared to better list memory performance also provides useful clinical information to help with treatment planning. This type of memory profile indicates that the patient will have better retention and recall if new information is provided in small

chunks and repeated several times rather than providing all the new information at once, even if within a more meaningful context.

Visual memory is often assessed using tasks that involve viewing or copying geometric designs, drawing them again immediately, and then again after a delay. After free recall, elements of the design are presented in a recognition format. Similar to verbal list learning memory tasks, there are visually mediated analogues. In particular, in the Brief Visuospatial Memory Test-Revised (BVMT-R) [28], patients are shown a set of simple geometric designs on a page and then draw them immediately from memory. There are three learning trials, followed by delayed recall and recognition. In contrast, in figure memory tasks such as the Rey-Osterrieth Complex Figure (Rey-O) [29], patients copy a larger more complex geometric design while viewing the stimulus. A few minutes later, they are asked to draw the figure from memory (immediate recall) and again after a longer delay (delayed recall), followed by a recognition trial. Using both tasks allows the neuropsychologist to assess the impact of attention and organizational skills on memory. If inattention is a factor, first trial performance on the BVMT-R will be much lower than the last learning trial. Using both types of visual memory tasks is also helpful to elucidate the impact of performance anxiety. Patients who are very anxious about memory testing may do poorly on the BVMT-R as it is clearly presented as a memory task, whereas the encoding phase of the complex figure task appears to be a simple visual copying task and is much less threatening for patients with memory concerns and anxiety.

Teaching Point

Poor visual recall may occur in the absence of impaired retention for two primary reasons. If organization and attention to detail during the copy trial are poor, the figure will not be encoded in a systematic and organized way. Poor organization will make the material much more difficult to retrieve from memory in a holistic fashion and impede free recall. Individuals with poor encoding often produce a very fragmented figure at free recall but correctly recognize all the elements on the delayed recognition trial. If attention to detail is poor during encoding, the patient may produce a reasonable gestalt with the correct overall outline of the shape but fail to include many details.

Language

The assessment of language begins during the interview with careful observation of spontaneous speech. Does the patient mispronounce common words, "talk around" a subject, use incorrect words, or use non-words/neologisms? Does the patient endorse word-finding problems or experience the "tip-of-the-tongue" phenomenon? In addition to these qualitative assessments, formal language assessment is crucial in the older adult population as many healthy older adults will begin to experience some word-finding difficulties, but this can also be one of the first symptoms of either a language-variant frontotemporal NCD or NCD due to Alzheimer disease. In this regard, using standardized tests to differentiate between normative and pathological changes is important and, especially so, during early stages of neurodegenerative disease. Confrontational naming tasks, such as the Boston Naming Test (BNT) [30], are most common. Line drawings of common to less common items are presented to the patient, and they are asked to name aloud the item within a time limit. Total scores can be compared against age- and education-matched normative data [24] to indicate if a clinically significant naming disturbance is present. Qualitative evaluations of naming are also important. Does the patient provide an incorrect but semantically similar name, e.g., saying "dice" when shown a picture of dominoes, or does he/she mispronounce the word, e.g., "elescator (sic)" for "escalator" without spontaneous self-correction, or persistently mispronounce the word when prompted? These are signs of aphasic language disturbance (semantic and phonemic paraphasias, respectively). Aphasic errors may be present in the context of a normal total score, in which case they may be subtle indicators of a language disturbance that warrants further monitoring. Verbal fluency is often considered an executive task; however, evaluating the fluency with which language is produced is also an important aspect of the language assessment. As illustrated later in Case 1, Mr. X. endorsed subjective word-finding problems on interview. His BNT score was in the high average range, but his fluency was low average. This profile suggests that his subjective experience is secondary to slowed processing speed and/or a decline in frontally mediated semantic search but is not due to an aphasic disturbance.

Visual Spatial and Constructional Skills

Difficulties with visual spatial and constructional skills are often early symptoms of some forms of NCD showing predominant subcortical features, such as NCD due to Lewy body disease or to vascular disease, and these difficulties often emerge later in the disease process in other forms of NCD such as Alzheimer disease. Difficulties with these aspects of cognition are less likely to be spontaneously reported on interview. Asking probing questions about changes to way-finding ability, ability to perform hobbies such as putting puzzles together, knitting, or doing handiwork may provide some indications if there has been a decline. Formal testing with tasks such as the copy trial of a complex figure, clock drawing, and the block design subtest from the WASI-II or WAIS-IV all provide objective evidence of visual spatial and constructional performance. The total score compared to age-matched controls is informative, as is qualitative information about how the patient approached the task. Examining differences between the rendering of the gestalt and the details provides information whether more right hemisphere (gestalt) or left hemisphere (details) processes are impacting this area of cognition.

Teaching Point
Examination of constructional skills in older adults should take into consideration the presence of physical limitations which may negatively impact results. For example, the presence of arthritis or tremor in the hands or significant psychomotor slowing (e.g., as in depressive disorder) would negatively impact total scores on constructional tasks. In order to ascertain the contribution of such factors to poor performance in this domain, these tasks should be compared to visual tasks that do not have a significant motor or speed component, such as the Judgement of Line Orientation Task (JLO) [31].

Praxis

Given that apraxia is a symptom of one of the most common forms of major NCD (NCD due to Alzheimer disease), the assessment of older adults should always include at minimum a praxis screen such as the one included in the KBNA [20]. Subtle apraxia will often not generate subjective concerns on interview. Probing questions about changes to the patients' ability to do things with their hands (e.g., buttoning, typing, using hand tools) may elicit some information. Many clinicians will also commonly use nonstandardized, qualitative assessment of transitive and intransitive gestures to screen for apraxia. For example, the clinician may instruct the patient to "show me how you would brush your teeth." Signs of concern include the patient using a "body part as object" such as sticking out their finger and motioning with it, rather than positioning the hand as if holding a toothbrush. Formal praxis assessments include a number of these types of prompts and include both spontaneous movement trials and trials whereby the patient is asked to imitate gestures produced by the examiner.

Importance of Qualitative Observations

It is imperative that neuropsychological assessment is conducted by a trained psychologist or psychometrist who is able to make good behavioral observations of the patient's test-taking behavior. Qualitative observations of test-taking behavior are often as important as the test scores. Moreover, these observations together with the test scores should be interpreted by a psychologist with training and experience working with older adult populations, as there can be multiple reasons why a final total score is below expectation. As illustrated in the following case studies, careful examination of subscores and cognitive profiles are often necessary to accurately determine the source of subjective and objective difficulties.

4.2 Case Studies

In this section, case-based discussion will be used to emphasize the previous points and to illustrate the importance of attending to behavioral observations and integrating numerous sources of biopsychosocial and medical information when conducting cognitive assessments with older adults. The cases will consolidate learning for trainees and those expanding their skills and practice in this area.

4.2.1 Case 1

Case 1 History

Mr. X. is a 55-year-old married police officer with three teenaged children. He suffered a myocardial infarction at age 49, after which he experienced a subjective memory decline. He and his wife reported a number of changes, including difficulties with word finding and following conversations, misplacing commonly used items, and forgetting personal events. Mr. X. underwent screening with the MoCA and performed entirely within normal limits. Given his young age, he was referred for a neuropsychological assessment to further evaluate his subjective concerns.

Interview Mr. X. stated that his memory difficulties started suddenly following myocardial infarction. Initially they were not prominent but have gradually worsened. He denied experiencing difficulties with way finding, though on occasion he may forget where he was going. On a daily basis, he will enter a room and forget why he went there. He stated that he is usually good at remembering to take his prescribed medications. He has always enjoyed cooking and will still prepare meals for his family, but when alone he may just have a sandwich. Bill payments are a big problem, as he will discover a bill is overdue when he thinks he just paid it. He relies on his wife to keep track of his appointments. He writes things down but often then loses the notes.

Collateral Interview Mrs. X. corroborated the changes to her husband's cognitive abilities and stated that he will tell her the same message numerous times without being aware of his repetition. She noted that he is not as mentally sharp as he used to be. He was previously very high functioning and able to multitask effortlessly; now he will become irritable and distracted if someone is talking to him while he is attempting to perform a task. He used to be active in a bowling league and coaching his son's hockey team but has withdrawn from activities given his concerns about difficulty keeping up in conversations.

Medical History In addition to coronary artery disease, medical conditions include moderate obesity, hypertension, type 2 diabetes mellitus, and sleep apnea. A recent magnetic resonance imaging of his brain showed cerebral small vessel disease. The sleep apnea is treated with continuous positive airway pressure (CPAP), but Mr. X. has gained weight and the mask does not fit properly anymore. Mr. X. reported a history of mild depressive disorder, and he has become increasingly irritable and "short fused" over the last 2–3 years.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What is the unique aspect of Mr. X.'s neuropsychology profile that is most important to take into consideration when interpreting the results?

Question 2. What differential diagnoses would be relevant in Mr. X.'s case?

Question 3. What is the etiology of Mr. X.'s subjective concerns and objective impairments?

Question 4. What are the main neuropsychology-informed treatment recommendations in this case?

Case 1 Answers

Case 1 Answer 1 (Question 1—What is the unique aspect of Mr. X.'s neuropsychology profile that is most important to take into consideration when interpreting the results?)

The neuropsychological assessment results are summarized in Table 4.2. Testing revealed Mr. X.'s current general intellectual abilities to fall in the superior range. There is no evidence of a generalized decline in intellectual ability compared to his premorbid ability. Most other aspects of neurocognitive functioning fall within normal limits compared to age-matched normative data; however, his performance varied from the mildly impaired to superior range across tests, with lowest performance obtained in the areas of information processing speed, working memory, and mental set shifting. Mental health screening using the Depression

Table 4.2 Profile of neuropsychological test results for Mr. X.

Domain	Functional area	Test	Performance level
Intellectual functioning	Global intellectual functioning	Wechsler Adult Intelligence Scale (WAIS-IV) full-scale IQ	Superior
	Estimated premorbid IQ	Test of premorbid functioning	High average
Attention	Simple attention	Digit span forward	Average
	Working memory	WAIS-IV working memory index	Low average
		Digit span backward	Low average
		Digit span sequencing	Low average
	Visuomotor attention	Trails A	High average
	Processing speed	WAIS-IV processing speed index	Low average
		Stroop word reading	Mildly impaired
Executive functioning	Alternation	Trails B	Low average
	Concept formation	Wisconsin Card Sorting # categories, % conceptualization, total errors, failure to maintain set	High average
	Perseveration	WCST perseverative errors	High average
	Response inhibition	Stroop color-word naming	High average
Memory	Verbal acquisition Verbal learning Verbal delayed recall Verbal delayed recognition	Wechsler Memory Scale logical memory (stories) immediate recall	Average
		Logical memory stories delayed recall	High average
		Logical memory % retention	Superior
		California Verbal Learning Test (CVLT-II) total words learned	Superior
		CVLT-II list delayed recall	High average
		CVLT-II recognition discrimination	High average
	Visual acquisition Visual learning Visual delayed recall Visual delayed recognition discrimination	Brief Visual Memory Test-Revised (BVMT-R) total	Superior
		BVMT-R delayed recall	Average
		BVMT-R delayed recognition discrimination	High average

Table 4.2 (continued)

Domain	Functional area	Test	Performance level
Language	Overall verbal functioning	WAIS-IV verbal comprehension index	High average
	Vocabulary	WAIS IV vocabulary	High average
	Phonemic fluency	Verbal fluency (FAS)	Low average
	Semantic fluency	Animal fluency	Low average
	Confrontation naming	Boston Naming Test	High average
	Verbal reasoning	WAIS-IV similarities	High average
Visual perception construction	Overall visual perceptual organizational skills	WAIS-IV perceptual reasoning index	Very superior
	Visual abstraction	Matrix reasoning	Very superior
		Visual puzzles	Very superior
	Visual planning/organizing	Rey Complex Figure copy	Intact, well organized
	Visual construction	Block design	High average
Motor functioning	Right-hand speed/dexterity	Finger tapping/grooved pegboard	Low average
	Left-hand speed/dexterity		Low average

Performance level descriptions based on normative data correction for age, gender, and education level (when possible corrected based on all three variables): very superior (≥ 98th percentile); superior (91st to 97th percentile range); high average (68th to 90th percentile range); average (30th to 67th percentile range); low average (16th to 29th percentile range); mildly impaired (6th to 15th percentile range); mildly-to-moderately impaired (2nd to 5th percentile range); moderately impaired (0.6th to 1.9th percentile range); moderately-to-severely impaired (0.1st to 0.5th percentile range); and severely impaired (< 0.1st percentile)

Anxiety and Stress Scale (DASS) [32] revealed mildly elevated symptoms of depression, anxiety, and stress. Therefore, the unique aspect of Mr. X.'s neuropsychology profile that is most important to take into consideration when interpreting these results is his superior IQ.

Case 1 Answer 2 (Question 2—What differential diagnoses would be relevant in Mr. X.'s case?)

Mr. X. and his wife both report concerns regarding declines in his cognition which began following a myocardial infarction at age 49 years but worsened more noticeably in a gradual fashion within the last 2–3 years. His mood has also declined over the same time frame. Given his history of depressive disorder, recent increase in irritability, and endorsement of mild symptoms on self-report, one consideration would be that Mr. X.'s subjective cognitive concerns could be attributable to a depressive disorder. Depressive disorder tends to be associated with attentional impairment, slowed processing speed, and retrieval memory problems.

In examining his profile, relative difficulties are noted in the areas of information processing speed, working memory, and mental set shifting. These areas of cognition are vulnerable to the effects of normal aging and are still within normal limits compared to his age-matched peers; thus, his profile could be interpreted as depressive disorder related. However, when one considers his global IQ, probable declines of as much 2 standard deviations are evident within these cognitive domains, which is in excess of normal age-related changes or changes that would be expected given mildly elevated symptoms of depression and anxiety.

Case 1 Answer 3 (Question 3—What is the etiology of Mr. X.'s subjective concerns and objective impairments?)

Mr. X. has multiple cardiovascular risk factors such as obesity, coronary artery disease, hypertension, type 2 diabetes mellitus, and sleep apnea. He has a history of depression, which also appears to be an independent risk factor for cardiovascular disease [33]. Ultimately, he had a cerebrovascular disease burden that could predispose him to cognitive decline. In fact, a number of studies suggest that cardiovascular risk factors are independently associated with the development of major NCD [34]. For example, coronary artery disease may lead to major NCD through its association with cerebral small vessel disease (as in Mr. X.'s case), which disrupts the cerebral blood flow regulation, perfusion, and blood-brain barrier, with resulting increased susceptibility to neurological insults [34]. Given that there has not been a globalized decline in IQ and Mr. X. is maintaining functional independence with minimal supports from his wife at this time, a diagnosis of mild vascular NCD is warranted.

Case 1 Answer 4 (Question 4—What are the main neuropsychology-informed treatment recommendations in this case?)

Mr. X. will benefit from the following neuropsychology-informed treatment recommendations:

A4.1. Given the presence of numerous cardiovascular risk factors, ongoing optimal management and medical monitoring, including monitoring of cognition, is recommended. Neuropsychology reassessment in approximately 12 months would be advised to monitor for progression to major NCD.

A4.2. Although Mr. X. performed well on memory testing, attention and information processing speed deficits were noted. Given that attention is the gateway to memory, poor attention in daily life is likely to be associated with memory difficulties even when none are noted during the structured assessment session. To compensate for difficulties with attention and information processing speed, it will be helpful for Mr. X. to give himself more time to complete tasks than he is used to requiring in the past. Eliminating distractions when performing complicated tasks or when listening to important information is also recommended. Providing psychoeducation to family members to help minimize distractions and communicate at a slower pace will also be important.

A4.3. The "see-it-and-say-it" strategy is also useful to focus the attention on the task at hand and improve subjective memory. This strategy is useful for circumventing commonly "forgotten" events. For example, when locking the door, one is to look at their hand with the key in the lock and say aloud, "I am locking the door." By using multiple modes of registration of the event, one focuses the attention on the act and increases memory quality of the event.

A4.4. Mr. X. may benefit from using a memory aid such as a large calendar to record all important information in a central location. He should develop a habit of checking the calendar every day to help stay oriented to time. Programming alarms into his phone for medications, checking blood glucose level, time to eat, etc. will help him remember and better manage these tasks.

A4.5. Creating a daily routine that includes physical activity, preparing healthy meals, and taking care of paperwork and bill payments according to a schedule will help Mr. X. stay organized.

A4.6. Re-engaging socially is encouraged as this has also been shown to benefit cognition and mood.

A4.7. Although he adheres to CPAP treatment for his sleep apnea, the machine has not been optimized since he gained weight. Ensuring his CPAP machine is optimized is strongly recommended as insufficient oxygen saturation during sleep may cause cognitive difficulties as well as irritability.

Case 1 Analysis Mr. X. presented with a number of cardiovascular risk factors for the development of cerebrovascular disease and subsequent vascular cognitive impairment. (See ▶ Chap. 21.) Relative difficulties were noted in his neuropsychological profile in the areas of information processing speed, working memory, and mental set shifting. However, these areas of cognition are known to be vulnerable to the effects of normal aging, which were still within normal limits when compared to his age-matched peers. Consequently, his profile could have been associated with a depressive disorder. However, the evident decline of as much as 2 standard deviations within these cognitive domains in the context of his global IQ was considered to be in excess of normal age-related changes or changes that would be expected given his mildly elevated symptoms of depression and anxiety. Important neuropsychology-informed treatment recommendations pertinent to Mr. X.'s situation include medically supervised lifestyle changes, optimal management of cardiovascular risk factors and the use of cognitive strategies, and regular monitoring of his cognitive function.

4.2.2 Case 2

Case 2 History

Mr. Y. is an 80-year-old married, Caucasian male with a grade 12 education. He spent 30 years working for a manufacturing company, and after the company downsized, Mr. Y. took up a job as a school maintenance man until his retirement at age 65. He presented with episodes of dizziness and confusion following cardiac stent procedure. Brain MRI revealed mild to moderate chronic microangiopathic changes. On cognitive screening with the MoCA, he scored 20 out of 30, with points lost on delayed recall, trail making, and clock drawing. He endorsed having experienced hallucinations, "a couple of times." His wife reported that he was becoming more forgetful and irritable and commented on significant sleep disturbance, including night wakening and daytime somnolence. Given his poor performance on the MoCA together with significant medical risk factors and concerns of his wife, a provisional diagnosis of major NCD was made, he was referred for an on-road driver's test, and Mr. Y. was referred for neuropsychological assessment to aid in differential diagnosis.

Interview Mr. Y. was seen for the neuropsychological assessment several months after his initial cognitive screening. He presented as quite nervous about the purpose of the testing. He stated that he has been told that he has a "low IQ." He struggled in school and failed several times and believed that he was pushed through. His best subjects were math and machine shop, while he failed all language-related subjects. Indeed, he struggled to read the assessment consent form. He reported that when he was seen by his doctor, there were many questions he did not comprehend, including the one about hallucinations, but he was too nervous to ask for clarification.

Mr. Y. was encouraged to ask clarifying questions, and his anxiety appeared to diminish over the interview. He stated that he felt much better overall in recent months. He denied any memory concerns. He denied episodes of confusion or forgetting names of people or objects. He had previously been having dizzy spells (consistent with orthostatic hypotension), but these had reportedly resolved. He has had some falls, but there did not appear to be evidence of head injury. He had recently passed the on-road driver's test and had driven to the clinic that day. He denied difficulties with way finding or disorientation. Socially, Mr. Y. reported participating in a variety of activities in his retirement home. He denied any significant mood problems, apart from some stress about the assessment. In relating his work history, Mr. Y. referred to himself as exceptionally dedicated and hardworking, a perfectionist in many ways. Rather than taking holidays, he picked up a part-time job. Work was always highly valued in his family, and he prided himself on his vocational accomplishments. Mr. Y. was quite concerned that the results of this assessment might have negative implications for his independence, particularly his driving.

Collateral Interview Mrs. Y. no longer endorsed the same concerns as she did several months previously. She confirmed her husband has always had difficulties with language and communication. She denied recent episodes of confusion and denied disorientation or incontinence. She denied significant concerns about her husband's cognition or functioning and generally corroborated his statements. She did confirm that he wakes in the night and suffers from restless legs. He is at his best in the morning and tends to nap in the afternoon. He had been referred for a sleep study, but at the time of the assessment, it had not yet taken place.

Medical History Mr. Y.'s medical history is significant for long-standing hypertension, remote stroke, and congestive heart failure. He is a remote smoker and endorses occasional use of alcohol. He is of normal weight. He had undergone a stent procedure a year prior. There were some questions of transient ischemic attacks. He has no documented psychiatric history.

Neuropsychological Assessment Results These results are summarized in Table 4.3. Mr. Y.'s current general intellectual abilities fall in the average range, which does not reflect a decline. Within the intellectual measures, Mr. Y. performed better (high average) on the visual performance subtests. Across most measures, Mr. Y. performed well within expected limits for his age, and there were some areas of significant strength including visual constructional skills (block design, judgment of line orientation, and his copy of a complex figure). His attention was somewhat variable, ranging from mildly impaired to high average. Verbal learning and memory were uniformly intact across both list learning and story memory. Although his delayed recall of a complex figure was average, his recognition of figure elements was impaired.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What factors could account for the difference in presentation between Mr. Y.'s cognitive screening and full neuropsychological assessment?

Question 2. What psychological and/or personality factors might be contributing to Mr. Y.'s presentation?

Question 3. Why was it important to ask for detailed educational history in an 80-year-old man referred for assessment of NCD?

Question 4. What could account for impaired visual recognition in the face of strong free recall?

Question 5. What are the main neuropsychology-informed treatment recommendations in this case?

Case 2 Answers

Case 2 Answer 1 (Question 1—What factors could account for the difference in presentation between Mr. Y.'s cognitive screening and full neuropsychological assessment?)

Possible factors that could account for the difference in presentation between Mr. Y.'s cognitive screening findings and full neuropsychological assessment include a change in medical status over time, decreased incidence of "dizzy spells" since the time of cognitive screening, and comorbid anxiety. During the cognitive screening visit, Mr. Y. was highly anxious and unclear of expectations. Addressing his anxiety and providing extra time for Mr. Y. to air his concerns provide him with clear explanations of purpose of testing, decreased his anxiety, and allowed him to focus better during the full assessment. (For more details, please refer to *Case 2 Analysis*.)

Case 2 Answer 2 (Question 2—What psychological and/or personality factors might be contributing to Mr. Y.'s presentation?)

Based on the history provided, a possible generalized anxiety disorder and probable obsessive-compulsive personality disorder may account for psychological and personality factors that could explain his current presentation.

Case 2 Answer 3 (Question 3—Why was it important to ask for detailed educational history in an 80-year-old man referred for assessment of NCD?)

It is probable that Mr. Y. had a verbal learning disability, which negatively impacted his performance during the cognitive screening session and is important to take into account when interpreting test data as poor performance may be long-standing and not reflective of a decline from baseline.

Table 4.3 Profile of neuropsychological test results for Mr. Y.

Domain	Functional area	Test	Performance level
Intellectual functioning	Global intellectual functioning	Wechsler Adult Intelligence Scale-II (WASI-II) estimated four-subtest full-scale IQ	Average
	Estimated premorbid IQ	Qualitative based on occupational history	Average
Attention	Simple attention	Digit span forward	Average
	Working memory	Digit span backward	High average
		Digit span sequencing	Average
	Processing speed	Trails A	Low average
Executive functioning	Alternation	Trails B	Average
	Concept formation/abstract reasoning	Wisconsin Card Sorting # categories, % conceptualization, total errors, failure to maintain set	Average
	Reasoning/conceptual shifting	Practical reasoning/conceptual shifting (KBNA)	Low average
	Phonemic fluency	Verbal fluency (FAS)	Average
	Semantic fluency	Animal fluency	Low average
	Perseveration	WCST perseverative errors	Low average
Memory	Verbal acquisition Verbal learning Verbal delayed recall Verbal delayed recognition	Wechsler Memory Scale (WMS-IV) logical memory (stories) immediate recall	Average
		Logical memory stories delayed recall	Average
		Logical memory % retention	Average
		Word list 1 total immediate recall (KBNA)	Low average
		Word list 2 delayed recall (KBNA)	Average
		Word list delayed recognition (KBNA)	Average
	Visual acquisition Visual learning Visual delayed recall Visual delayed recognition discrimination	Complex fig. 1 immediate recall (KBNA)	Superior
		Complex fig. 2 delayed recall (KBNA)	High average
		Complex figure delayed recognition	Mildly impaired
Language	Vocabulary	WASI-II vocabulary	Average
	Confrontation naming	Boston Naming Test	High average
	Phonemic fluency	Verbal fluency (FAS)	Average
	Semantic fluency	Animal fluency	Low average
	Verbal reasoning	WASI-II similarities	High average
Visual perception construction	Visual perceptual organizational skills	Hooper Visual Organization Test	Average
	Visual abstraction	Matrix reasoning	High average
	Visual planning/organizing	Complex figure/clock drawing (KBNA)	Superior
	Visual construction	Block design	Average
Motor functioning	Psychomotor speed	Finger tapping (dominant hand)	Mildly impaired
		Finger tapping (non-dominant hand)	Mildly impaired
	Manual dexterity	Grooved pegboard (dominant hand)	Average
		Grooved pegboard (non-dominant hand)	Low average

Table 4.3 (continued)

Domain	Functional area	Test	Performance level
Praxis	Intransitive	Intransitive gestures (KBNA)	Average
	Transitive	Transitive gestures (KBNA)	Average
	Buccofacial	Buccofacial movements (KBNA)	Average

Performance level descriptions based on normative data correction for age, gender, and education level (when possible corrected based on all three variables): very superior (≥ 98th percentile); superior (91st to 97th percentile range); high average (68th to 90th percentile range); average (30th to 67th percentile range); low average (16th to 29th percentile range); mildly impaired (6th to 15th percentile range); mildly-to-moderately impaired (2nd to 5th percentile range); moderately impaired (0.6th to 1.9th percentile range); moderately-to-severely impaired (0.1st to 0.5th percentile range); and severely impaired (< 0.1st percentile)

Case 2 Answer 4 (Question 4—What could account for impaired visual recognition in the face of strong free recall?)

Factors that could account for impaired visual recognition in the face of strong free recall include a response bias related to perfectionism. Patients with perfectionist tendencies may be reluctant to answer yes on recognition unless they are absolutely certain of their response. In such cases, patients may benefit from reassurance that it is "okay to guess." (For more details, please refer to *Case 2 Analysis*.)

Case 2 Answer 5 (Question 5—What are the main neuropsychology-informed treatment recommendations in this case?)

Mr. Y. will benefit from the following neuropsychology-informed treatment recommendations:

A5.1. Given Mr. Y.'s advanced age and history of cardiovascular disease, ongoing medical monitoring, including monitoring of cognition, is recommended.

A5.2. Maintaining a healthy lifestyle, including exercise, abstaining from smoking, and excessive alcohol use, as well as following a heart healthy diet, is recommended to maintain optimal brain health and cognition.

A5.3. Encouraging Mr. Y. to remaining socially active is recommended as this has also been shown to benefit cognition and mitigate cognitive decline.

A5.4. Given the subtle difficulties with "mental stickiness" noted, Mr. Y. will perform at his best in a structured environment where expectations are clear and consistent. Having a regular routine that he follows will also be beneficial. Unexpected or new problems may be anxiety provoking for him, and in such circumstances, he will benefit from being provided very clear instructions. He should be encouraged to enlist support from his wife or other trusted family member in situations that are unclear or unfamiliar to him as his anxiety may interfere with his ability to keep pace.

A5.5. Following through with the referral for the sleep study is recommended. Undiagnosed or untreated sleep disturbance can cause cognitive difficulties as well as daytime fatigue and could lead to cognitive impairment. (See ► Chap. 24.)

Case 2 Analysis Mr. Y. performed below cutoff on the MoCA but performed far better on more detailed neuropsychological assessment. In this case, the examiner being attentive to behavioral cues during the interview suggested that psychological/learning factors may be implicated (e.g., patient appearing nervous at outset, struggling to read consent form). Taking time to build rapport, answer his questions, and ease his concerns about not understanding test instructions given his self-reported "low IQ" allowed Mr. Y.'s anxiety to dissipate and increased the chance of obtaining more valid test data. In addition, based on his self-report of being a "workaholic" and perfectionist, together with his anxious presentation and request for the "rules to be clear," it is probable that Mr. Y. has some obsessive-compulsive personality traits or obsessive-compulsive personality disorder. Individuals with anxiety, obsessive-compulsive personality disorder in particular, benefit tremendously from the opportunity to ask for clarification of expectations/instructions. Even within a standardized testing session, it is often necessary with older adults, especially those with comorbid anxiety disorder, to take extra time and provide reassurance and normalization of their anxiety before or between test administrations. In terms of his learning style, based on his self-reported educational difficulties, it is probable that Mr. Y. had an undiagnosed verbal learning disability, which further underscores the importance of giving clear instructions and checking in with him to ensure he has understood test expectations before proceeding. In Mr. Y.'s case, the TOPF was not used to assess premorbid function, as presenting a reading test would have only increased Mr. Y.'s anxiety and provided an inaccurate estimation of his premorbid general intellect. Rather, his occupational attainment was used as an estimate of premorbid ability.

Other areas where perfectionism and performance anxiety may have exerted an impact on Mr. Y.'s test result profile include his slightly poorer performance on the simpler version of the Trail Making Test (the part A) versus his solidly average performance on the part B version that involves quickly shifting mental set, as anxiety can contribute to inconsistent attention. In addition, perfectionism contributed to test-taking behavior and response biases on recognition trials of memory tests; Mr. Y.'s visual memory was very

strong, yet he performed more poorly on recognition versus free recall. This was secondary to his tendency to not want to "guess," and he was unable to answer yes for recognition items unless he was 100% certain. Similarly, Mr. Y. performed more poorly on the simple finger tapping speed task compared to the more challenging speeded manual dexterity pegboard task; after testing, he explained that he was really concentrating on letting the tapper key come all the way back up to position before tapping again, essentially sacrificing speed for accuracy, a common occurrence in the context of perfectionism. Without taking into account his performance anxiety and perfectionism, one might be left with very different opinions about Mr. Y.'s cognitive abilities.

Overall, although Mr. Y. does have a number of cardiovascular risk factors, after controlling for the impact of his anxiety, perfectionism, and verbal learning disability, his performance on cognitive tests is well within expectations for a man of his age. Relative weaknesses, mainly in the low average range, were noted in the area of executive functions. This may be a reflection of very early changes secondary to cardiovascular disease that do not yet meet criteria for impairment, or they may represent another manifestation of "mental stickiness" often seen in the context of perfectionism. Monitoring over time will reveal whether these relative difficulties are trait or reflective of an emerging decline. Thus, at this point, a diagnosis of major NCD is not warranted, but monitoring would be recommended.

4.3 Key Points: Neuropsychology in Late Life

- A high proportion of older adult patients will present with subjective cognitive concerns, particularly memory concerns.
- Discriminating cognitive changes due to normal aging from pathological cognitive changes can be difficult, particularly in the context of preexisting neuropsychiatric disorders which may render patients vulnerable to both cognitive compromise and to over-interpreting normal age-related declines.
- Assessment starts with thorough clinical interview, soliciting information about the nature, onset, and course of cognitive changes, whether these changes coincided with medical or psychosocial stressors.
- Establishing a good premorbid baseline against which suspected or observed cognitive declines can be measured is essential. This will involve asking about developmental and psychosocial history, including educational and occupational attainment.
- Objective neuropsychological assessment is considered the "gold standard" for documenting substantial impairment in cognitive performance necessary for accurate diagnosis of mild or major neurocognitive disorder.
- Conducting neuropsychological assessments with aging and neuropsychiatric populations requires special considerations, including obtaining reliable collateral information, taking extra time to establish rapport and ease patient concerns about the testing process, and considering individual differences in premorbid baseline.
- Results obtained from a thorough neuropsychological assessment will assist with differential diagnosis of neuropsychiatric disorders including NCD and will also direct the need for reassessment, cognitive rehabilitation, or other therapeutic interventions.

4.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Changes in intercellular connectivity and neuronal integrity associated with the normal aging process translate into declines in the following areas of cognition:

A. Processing speed, encoding, memory retrieval, and executive functions
B. Focused attention, memory consolidation, and memory retrieval
C. Language, visual spatial and constructional skills, and praxis
D. General intellect, mental set shifting, and orientation

Answer: A

Brain changes associated with healthy normal aging lead to inefficiency of intracellular communication within and between brain regions. While normal aging does not impact focused attention or attention span, more complex or executive attentional processes are impacted. In particular, it is well established that healthy older adults are impaired on measures of cognitive inhibition/inhibitory control, whereby effortful mental control is needed to suppress attention to task-irrelevant material [35]. As a result of declines in cognitive inhibition, older adults may be more vulnerable to distractions and have increased difficulty sustaining mental engagement in effortful cognitive tasks. Another aspect of executive attention impacted in normal aging is working memory, the ability to hold information in mind over a relatively brief period of time while using that information to perform a mental operation. Changes in working memory contribute to increased time needed by healthy older adults to learn new tasks or to complete complex projects that involve holding instructions in mind. Older adults may need to refer more frequently to printed instructions compared to healthy younger adults.

Memory concerns represent the most frequent subjective complaint of older adults. While forgetfulness is often considered part of normal aging, "memory loss" is not. Memory is composed of three primary processes: (i) encoding (learning: getting information in), (ii) consolidation (storage: keeping

information in), and (iii) retrieval (recall: getting information out). Normal aging effects are most notable at encoding secondary to declines in processing speed and at retrieval, for the most part secondary to decreased processing speed. Slowed processing speed at encoding results in smaller amounts of information being encoded as compared to younger adults. In addition, at the moment of spontaneous retrieval, executive attention impairments also impacts free recall, whereby the strategic search of memory stores may become less efficient and fewer words are spontaneously recalled. However, provision of retrieval cues will assist healthy older adults greatly; most older adults will be able to correctly recognize and discriminate all list words from a similar number of non-list words. Preserved delayed recognition memory is an indication that the words acquired during encoding have not been forgotten even if free recall was less than optimal, as is often the case in depression. Neuropsychological assessment demonstrates that despite the decrease in the amount of information initially encoded and the amount of information spontaneously recalled, providing recognition cues improves recall indicating that memory retention is intact; that is, the information that was encoded or got into memory stores is retained well over time. Thus, information that is taken in is not forgotten, but less information may be "getting in," and healthy older adults may have greater difficulty getting information out, compared to previous levels of ability. This is an effect of normal age-related changes and is not reflective of a pathological memory decline.

A decline in general intellectual ability over the estimated premorbid baseline is not a normal part of aging and is a sign of a pathological process. For example, NCD due to Alzheimer disease is typically associated with lack of memory consolidation ("rapid forgetting"), as well as language and word-finding problems, visual spatial constructional impairment, apraxia, and disorientation. Thus, answer A is the correct answer.

MCQ 2. Why is it important to determine an older patient's developmental, educational, and occupational attainment as part of a neuropsychological assessment for suspected NCD?

A. It is good clinical practice to complete a thorough history as part of any neuropsychiatric assessment.
B. Patients with higher levels of education would be expected to perform better on cognitive tasks.
C. With patients who fell at either the upper or lower limits of the normal distribution premorbidly, special consideration will be required in interpreting results of standardized neuropsychological tests to determine if there has been a substantial decline.
D. Asking about remote personal history is a good way to establish rapport and put patients at ease before starting standardized testing.

Answer: C

While a thorough interview is important in any clinical setting and can often be helpful in establishing rapport and putting patients at ease, within the context of a neuropsychiatric assessment for suspected NCD, more extensive probing about remote developmental and educational history is particularly pertinent. Obtaining an individualized estimate of premorbid cognitive and intellectual ability is essential, as it will be against this baseline that the patient's performance on age-normative neuropsychological test data will be compared. Premorbid general intellectual ability may be estimated using history of educational and occupational attainment. Establishing educational history should include probing for learning or academic difficulties as most older adults would not have been formally diagnosed with learning disability or intellectual impairment in childhood. The clinician may need to ask probing questions about educational attainment or barriers to education (see Table 4.1). In the absence of a history of familial upheaval or childhood trauma, a patient who describes a history of delayed acquisition of basic academic skills, grade repetitions, and failure to complete high school is likely to have had an undiagnosed intellectual or learning disability. As illustrated in Case 2, this is important to identify because in such a case, premorbid learning or cognitive difficulties may interfere with standardized testing but are not reflective of a decline. A patient who was of low general intellect premorbidly, for example, with a full-scale IQ under 70, would typically perform poorly relative to age-matched peers on other measures of cognition including memory, language, and executive functions. Without factoring in the premorbid low intellect, the obtained profile of impairment could be misinterpreted as indicative of a NCD, when it is better explained as a preexisting intellectual disorder. Relying on functional changes and input from collateral informants is often critical in determining decline in patients with premorbid extremely low IQ. As illustrated in Case 1, it is equally important to consider baseline functioning among those patients who excelled in their youth and younger adulthood. For example, it would be expected that patients who described themselves as "top of the class," who had completed university education, and/or held a successful professional career would have been above-average premorbidly. Within this context, the patient may perform within normal limits on cognitive screening and be dismissed as "worried well." Even on standardized age-matched testing, the premorbidly high functioning patient may perform within average limits, but this in fact may represent a decline from their higher than average baseline. Thus, obtaining very detailed information about remote personal and developmental history is critical for establishing premorbid functioning for comparison in judging whether a substantial decline has occurred. Thus, statement C is the correct answer.

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Pharmacotherapy: Safe Prescribing and Adverse Drug Events

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5.1 Background

5.1.1 General Principles of Pharmacotherapy in Old Age

As a consequence of multimorbidity, older adults carry a high burden of polypharmacy, with increased risk of adverse drug events (ADEs) and potentially avoidable emergency department and hospital admissions. Altered pharmacokinetics and pharmacodynamics result from age-related changes in body composition and organ-system function and frequently necessitate dose modification or avoidance of certain medications. Diet is often unrecognized as an important factor in drug absorption, metabolism, and efficacy. Dietary supplements also can interact with medications, contributing to the risk of adverse drug reactions.

The severity and frequency of adverse side effects, together with altered pharmacokinetics and pharmacodynamics, render many drugs potentially inappropriate for older patients. Tools like the Beers criteria and the STOPP/START criteria have been developed to assist clinicians in recognizing and minimizing the use of these *potentially inappropriate medications (PIMs)*.

Certain types of medications are associated with a high risk of adverse effects in the geriatric population. Anticholinergic medications cross the blood-brain barrier to varying degrees, potentially impairing cognition and precipitating delirium, in addition to adverse peripheral side effects such as constipation, dry mouth, and urinary retention. Many medications from a variety of classes possess anticholinergic properties and when used concurrently can produce a significant anticholinergic burden.

Most psychotropic medications have been associated with an increased fall risk. Many atypical antipsychotics affect glucose metabolism and may cause weight gain, and therefore must be used cautiously or avoided in patients with obesity, diabetes mellitus, and the metabolic syndrome. A number of psychotropic medications, chief among them the selective serotonin reuptake inhibitors (SSRIs) and the selective norepinephrine reuptake inhibitors (SNRIs), may induce the syndrome of inappropriate antidiuretic hormone secretion (SIADH), causing hyponatremia that can become severe enough to cause delirium, coma, and death. Lithium has a low therapeutic index in older patients. Reduced kidney function affects the dosing of lithium, and it can affect renal tubular function, causing impaired water retention and diabetes insipidus. Moreover, the reduced thirst response in older individuals and the common use of diuretics can lead to dehydration and lithium toxicity. Lithium commonly affects thyroid function, most often causing hypothyroidism but rarely causing hyperthyroidism, and also is associated with hyperparathyroidism.

Although rare, neuroleptic malignant syndrome and serotonin syndrome represent potentially life-threatening conditions and have a spectrum of symptoms culminating in rhabdomyolysis, hyperthermia, and brain injury and death. Familiarity with these conditions permits early recognition and management. Typical and atypical antipsychotics, also referred to as first-, second-, and third-generation antipsychotics, as well as some SSRIs may prolong the corrected QT interval (QTc), increasing the risk of potentially fatal ventricular tachycardia. A number of medications, ranging from macrolide antibiotics to amiodarone, can increase the QTc and should be used cautiously in combination with each other and with QTc-prolonging psychotropics. SSRIs reduce serotonin levels in platelets, inhibiting aggregation and increasing bleeding risk. This is of especial concern in older patients because of the prevalence of anticoagulant and platelet-inhibiting drugs used for heart and vascular disease.

5.1.2 Epidemiology of Polypharmacy and Adverse Drug Events

Polypharmacy conventionally is defined as five or more prescription medications, based on epidemiological evidence that the threshold of five or more drugs independently predicts incident falls, disability, frailty, and mortality [1]. Among older adults aged 70 years and older, roughly 60% take seven or more drugs and over 10% take at least ten drugs [2]. Polypharmacy also contributes to potentially serious drug-drug interactions and adverse drug events (ADEs) [3, 4], which account for 6–12% of hospital admissions among older adults [5, 6]. The prevalence of polypharmacy increases with age in parallel with the increased prevalence of multimorbidity, compounded by the indication for multiple medications as standard of care for a variety of chronic conditions, such as heart failure with reduced ejection fraction and diabetes mellitus. In all age groups except the very young, polypharmacy has increased over time, with the largest rise among adults over the age of 69 [7].

Central nervous system (CNS) polypharmacy has been defined as concurrent use of three or more CNS-acting medication classes. A recent study examined 1062 office visits from the US National Ambulatory Medical Care Survey that documented CNS polypharmacy during the years 2004 to 2013. After adjustment for age, sex, race, and ethnicity, the study found a significant 10% reduction in the use of benzodiazepines between 2004 and 2011, as well as a dramatic 55% reduction in the use of tricyclic antidepressants. Although there were no temporal changes in the use of either selective serotonin reuptake inhibitors or non-benzodiazepine, benzodiazepine receptor agonist sleep aids, there was a significant 24% rise in opioid use during this time period [8]. Older adults in their last year of life have experienced a substantial increase in extreme polypharmacy (≥10 medications), and in the final month of life, this polypharmacy not infrequently includes drugs intended to prevent future illness (e.g., statins), whose continuation seems questionable. In the last month of life, psychoactive medications were prescribed to 51% of patients [9].

Table 5.1 Examples of age-related changes in pharmacodynamics

Drug	Pharmacodynamic effect	Age-related change
Furosemide	Peak diuretic response	↓
Morphine	Analgesic effect	↑
Verapamil	Acute antihypertensive effect	↑
Scopolamine	Cognitive function	↓
Temazepam	Postural sway	↑
Diazepam	Sedation, postural sway	↑
Warfarin	Anticoagulant effect	↑

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In the USA, there has been a nearly linear increase over time in the number of specialty physician referrals made by primary care providers [10], resulting in an increase in the number of potential prescribers for an individual patient. Many specialists are unable to keep up with current prescribing standards in other specialties, thus prescribing medications for the illness they are treating that may have significant drug-drug interactions or that pose a threat for ADEs due to age-related changes in pharmacokinetics (i.e., drug metabolism) and pharmacodynamics (i.e., drug action).

Pharmacokinetic alterations of drugs attributed to organ-system aging are reviewed in ▶ Chap. 1, ▶ Sect. 1.10, and in ◘ Table 1.2, Summary of age-related changes that affect the pharmacokinetics of drugs. Pharmacodynamic changes occur as a result of age-related alterations at the organ-system or cellular level that affect the action of the drug, and commonly alter the timing, peak effect, or magnitude of the drug's intended action or side effects. ◘ Table 5.1 provides examples of pharmacodynamic changes with aging [11].

Specialists may also prescribe a drug without having an accurate knowledge of the patient's other medications or medical conditions, a phenomenon known as "silo prescribing." The dosing guidelines developed by pharmaceutical companies and approved by the US Food and Drug Administration, Health Canada, the Therapeutic Goods Administration of Australia, and other national regulatory agencies are largely based on standard adult dosing without factoring in clinically significant differences in the pharmacokinetics and pharmacodynamics of medications in older patients. Unless a medication has specific geriatric dosing guidelines, a good rule of thumb is to select a dose below the standard starting dose for adults. Because the lower starting dose may not be effective in some patients, timely follow-up is required to be able to titrate the dose upward as needed to achieve the desired clinical outcome. ◘ Table 5.2 gives examples of prescribing behavior that can result in adverse drug events.

5.1.3 Prescription Complexity

Polypharmacy contributes to the complexity of medication regimens but is not the only determinant. Older adults commonly must cope with changing medications and doses, when and how to take a medication (e.g., with food, before bedtime), and remembering to take medications with multiple daily doses or infrequent dosing (e.g., once weekly). Evidence is accumulating that the *complexity* of the patient's medication regimen, not just polypharmacy and their multimorbidity, predicts both hospitalization and hospital readmissions (◘ Fig. 5.1) [12].

Teaching Points

Polypharmacy involves the simultaneous prescription of ≥ 5 medications, increases with age and multimorbidity, and has been associated with an increased risk of drug-drug interactions, adverse drug events, hospitalization, and mortality. Pharmacokinetics of medications often changes in old age as a result of declining renal function and alterations in hepatic metabolism, necessitating changes in dosing. For some medications, the action of the drug (pharmacodynamics) changes, causing alterations in the onset, peak effect, or magnitude of action, as well as an increase in severity and frequency of adverse reactions, even after adjusting for changes in pharmacokinetics. The complexity of drug regimens can lead to medication nonadherence and also predicts hospitalization independent of the number of drugs.

5.1.4 Drug-Food/Nutrient Interactions

A food-drug interaction may be a physical or chemical reaction that occurs between a medication being taken for therapeutic effect and components of the patient's diet, including nutritional and dietary supplements. From a chemical standpoint, this interaction can be synergistic, competitive, or antagonistic in nature. The nature of the interaction may alter the effectiveness of the drug and thus impact the systemic medical and/or psychiatric status of the patient. Alternately, the interaction may affect absorption of the nutrients/food being ingested, thereby affecting the nutritional status of the patient. Like most drug-drug interactions, food-drug interactions may be pharmacokinetic or pharmacodynamic in nature.

Absorption

Orally administered drugs are particularly susceptible to a reduction in bioavailability due to the presence of food at either of their primary absorptive sites, the stomach and the lumen of small intestinal tract. For some drugs this decreased absorption is minimal; however, for medications such as alendronate and other bisphosphonate drugs, administration with food may reduce absorption by as much as 85%

Table 5.2 Examples of prescribing behavior that can result in adverse drug events or failure to achieve the desired results

Type	Examples
"Silo prescribing": prescribing by specialists who are not up-to-date in the management of diseases outside their specialty and/or without awareness of potential contraindications and drug-drug interactions (see PIMs below)	Oxybutynin prescribed by gynecologist for urinary urgency in patient with mild cognitive impairment Doxazosin prescribed by urologist for urinary hesitancy in patient with orthostatic lightheadedness Paroxetine prescribed by psychiatrist for depression in patient with glaucoma
Contributing to medication regimens that are overly complex, increasing the risk of nonadherence and ADEs (see text for discussion)	Excessive polypharmacy Multiple daily dosing when a single sustained-release option is available Difficult or confusing dosing schedules (e.g., fasting, once weekly with water only, do not lie down afterward for 30 minutes)
Increasing dose(s) of medication or adding additional medication when not effective, without assessing possibility of and reasons for medication nonadherence	Unrecognized cognitive impairment Neglect by a caregiver charged with dispensing medications Misunderstanding medication regimen and rationale for medications due to medical illiteracy, low educational level, or language barrier Unrecognized cultural beliefs regarding use and purpose of medications
Medication prescribed to treat unrecognized side effect of another medication	Haloperidol for new hallucinations in patient begun on ropinirole for restless leg syndrome Donepezil for "early dementia" in patient routinely taking amitriptyline, lorazepam, and hydrocodone/acetaminophen (paracetamol) Meclizine prescribed for "dizziness" in patient taking high-dose gabapentin
Using standard "adult" doses without accounting for altered drug metabolism and effects due to age-related physiologic changes	A given dose of fluoxetine may have higher serum levels and delayed elimination in older patients, especially women Age-related increase in sedation and postural sway with benzodiazepines, leading to increased risk of falls/fractures Prescription of morphine to geriatric patients due to age-related reduction in renal function (reduced clearance of drug)
Prescribing without awareness of pharmacologically active over-the-counter drugs and supplements	Patient started on warfarin for prevention of thromboembolism in chronic atrial fibrillation who develops excess bleeding despite therapeutic INR because also taking supplemental fish oil capsules, increasing bleeding risk
Use of potentially inappropriate medications (PIMs) (see text for discussion)	Bupropion to treat depression in a patient with history of seizures First-generation antihistamine (e.g., diphenhydramine) in older patient with allergic rhinitis Calcium channel blocker (e.g., amlodipine) for hypertension in older patient with constipation Amitriptyline for depression or neuropathic pain

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[13]. The absorption of iron can also be significantly reduced by the concurrent consumption of coffee or tea [14]. Some medications, on the other hand, require food for optimal absorption, e.g., lurasidone, a newer atypical antipsychotic, which needs at least 350 calories of food for efficient absorption [15]. Apart from absorption, gastric emptying time may also be affected by the administration of food; meals with a high-fat or high-fiber content may cause a reduction in gastric emptying time. Dietary fiber, in particular, is known to affect the absorption of digoxin and amitriptyline, leading to lowered serum levels of these drugs [16]. Laxatives, which are commonly used by older patients, may accelerate gastrointestinal transit time and hence reduce absorption by shortening contact with the small bowel mucosa, affecting, for example, the absorption of antipsychotics.

Chelation reactions are usually mediated by divalent and trivalent cations (e.g., iron, calcium, magnesium, zinc, aluminum [aluminum]), which bind the drug and hinder absorption. Chelation is a major potential source of drug interactions between food/nutritional supplements and susceptible medications (e.g., tetracycline, ciprofloxacin). For example, even the small amount of calcium in the milk added to coffee or tea can markedly reduce the absorption of tetracycline [17]. Alteration of gastric pH due to the use of chronic acid suppression therapy may result in alteration in the levels of drugs, such as ketoconazole, which are most efficiently absorbed in an acidic environment; conversely, there may be an increase in ketoconazole bioavailability in response to drinking an acidic beverage such as a cola [18]. Calcium carbonate, the principal form of dietary calcium, requires dissociation in an acidic environment for absorption in the duodenum and jejunum. Proton pump inhibitors (PPIs) reduce calcium absorption and in as little as 1 year may promote the development of osteoporotic fractures [19, 20]. They also reduce the absorption of vitamin B_{12}, increasing the risk of peripheral neuropathy and cognitive decline.

Fig. 5.1 Factors contributing to the complexity of medication regimens

Data are emerging showing a relationship between PPI use and an increased risk of major neurocognitive disorder due to Alzheimer disease. The plausibility of this association has been demonstrated in rodent models, in which PPIs enhance the production of beta amyloid and alter its degradation by microglia, leading to higher levels of beta amyloid in the brain [19].

Metabolism of Drugs

The metabolism of medications may be also affected by food. Grapefruit has been found to be a potent inhibitor of hepatic CYP3A4, which is necessary for the metabolism of several drugs. The consumption of grapefruit or grapefruit juice can lead to increased levels of carbamazepine, triazolam, buspirone, and lurasidone, all of which rely heavily on CYP3A4 for their metabolism. Grapefruit juice, when consumed at the same time as the ingestion of the statin drugs simvastatin and atorvastatin, increases the levels of those drugs by 260%, compared with water, and by 90% if consumed 12 hours later [21]. This can lead to toxic levels of the statin and to rhabdomyolysis. Drug administration may also be harmful to levels of vitamins. Both phenobarbital and phenytoin may increase the metabolism of vitamin D, vitamin K, and folic acid. Some foods may be harmful especially when ingested in large quantities; for example, foods high in tyramine (e.g., aged cheeses, cured meats, soy sauce), in a person concurrently taking a monoamine oxidase inhibitor (e.g., tranylcypromine) may lead to a hypertensive crisis, characterized by increased heart rate, flushing, and headache.

Distribution of Drugs

Highly protein-bound drugs (e.g., phenytoin, warfarin) may be displaced in a person who has a poor nutritional status and a reduction in serum albumin. Displacement reactions may impact the volume of distribution and the plasma half-lives of these medications.

Altered Effect

Caffeine contained in food or beverages concurrently taken with methylphenidate may further increase the excitatory side effects of this medication. Large amounts of caffeine may also reduce the effects of anxiolytics and mood stabilizers. Ethanol acts as a stomach irritant and may augment gastric mucosal injury from salicylates or nonsteroidal anti-inflammatory drugs. It also adds to the CNS depressant effects of sedating psychotropics like benzodiazepines and sedating antihistamines like diphenhydramine. It is well known that vitamin-K-containing foods, such as spinach, interfere with the action of the anticoagulant warfarin.

Nutritional Status

Medications may affect the nutritional status of patients by reducing food intake due to side effects, including decreases in appetite, constipation, nausea, diarrhea, taste disturbances, and dryness of the mouth. Medications should be carefully assessed for any such negative effects and, where possible, dose reductions, alternate drugs, and nondrug measures offered to treat the target symptoms. Atypical antipsychotics and the antidepressant, mirtazapine, may also lead to significant weight gain, and glucose monitoring is essential, as well as a dietician referral to decrease the risk of obesity and subsequent systemic metabolic derangements, additional medications, and morbidity.

5.1.5 Dietary Supplements and Drug-Supplement Interactions

Dietary supplements are not subject to the regulations imposed by national drug safety organizations like the US Food and Drug Administration, and their contents and potency often are unknown. Based on the 2002 US Food and Drug Administration Health and Diet Survey, over 75% of adults over the age of 54 used a dietary supplement; of these individuals, 84% took a multivitamin or multimineral supplement, 81% took a single-ingredient vitamin or mineral (e.g., calcium), and 34% reported use of herbs, botanicals, or other dietary supplements [22]. The high prevalence of supplement use has been associated with adverse drug reactions. Based on extrapolation from representative surveillance data from 63 US emergency departments from 2004 to 2013, an estimated 23,005 (95% CI 18,611–27,398) emergency department visits annually could be attributed to adverse events related to dietary supplements; approximately 12% of these visits were made by persons age 65 and older [23]. Older patients have a high prevalence of multimorbidity and polypharmacy, leading to the potential for supplement-drug interactions.

Table 5.3 Examples of interactions between dietary supplements and psychoactive medication

Supplement	Drug/drug class	Adverse drug event
St. John's Wort	Tricyclic antidepressants Benzodiazepines SSRIs	Potential decrease in tricyclic levels 25–50% reduction in levels Increased drowsiness, serotonin syndrome
Ginseng	Monoamine oxidase inhibitors	Reported manic-like symptoms, tremulousness, headache
Ginkgo biloba	Trazodone	Report of coma

Data extracted from Gardiner et al. [25]

A number of herbs and herbal supplements may interact with warfarin. For example, St. John's wort (*Hypericum perforatum*) increases warfarin clearance and reduces its plasma concentration. Conversely, chamomile tea, consumed by patients for its purported calming, anxiolytic, and gastric-soothing effects, inhibits the metabolism of warfarin by CYP1A2, CYP3A4, and CYP2C9, potentially increasing the risk of bleeding [24]. Case reports link fish oil and cranberry juice with an elevated international normalized ratio (INR) in patients taking warfarin. St. John's wort potentially decreases digoxin levels and decreases bioavailability of verapamil and may lower plasma blood levels of statins [25]. Table 5.3 summarizes the potential interactions of three common supplements with psychoactive medications [25].

Teaching Points

Diet and individual foods and beverages can affect the absorption, metabolism, distribution, and effectiveness of medications with potential short-term and long-term adverse consequences. Similarly, dietary supplements, consumed by 75% of US adults, can interact with individual drugs and have been associated with emergency department visits for adverse reactions, both from the supplement and because of drug-supplement interactions.

5.1.6 Potentially Inappropriate Medications (PIMs)

Polypharmacy and ADEs may result from the prescription of medications that are inappropriate for older adults by virtue of an unfavorable risk to benefit ratio that results from age-associated alterations in drug metabolism or increased vulnerability to potential side effects, especially if safer alternatives are available. PIMs have been associated with a 43% increased risk of ADEs [26]. Among 518 patients aged 65 and older admitted to an Australian tertiary care center, 55% were taking one or more PIMs, and 27% were taking two or more. Sixty-one percent were discharged on at least one PIM. In 5.6% of cases, a PIM was found to potentially cause or contribute to the reason for admission [27]. Among 400 Brazilian outpatients aged 60 and older, nearly 30% experienced the iatrogenic "trifecta" of polypharmacy *plus* potential drug-drug interactions *plus* ≥ one PIM [9]. Evidence is accumulating that PIMs lead to overall greater use of healthcare services, especially hospitalization, and add to healthcare costs [28].

Identifying PIMs

Researchers have developed tools to recognize PIMs because clinicians cannot possibly know all the harmful side effects and interactions of even commonly prescribed medications. The two most widely used PIM tools are the Beers criteria [29] and the STOPP/START criteria (*S*creening *T*ool of *O*lder Persons *P*otentially Inappropriate *P*rescriptions/*S*creening *T*ool to *A*lert Doctors to the *R*ight *T*reatment) [30]. Updated in 2015 by a thirteen-member expert panel to reflect new drugs and the evolution of knowledge regarding drug-drug interactions and adverse side effects in older adults, the Beers criteria offer the advantage of rating both the quality of supporting evidence and the strength of their recommendations. New for the 2015 update are lists of select drugs which should be avoided or whose dose should be adjusted based on renal function, as well as select drug-drug interactions known potentially to be harmful in older adults.

The Beers criteria are oriented to drugs used in the USA and Canada. The STOPP/START criteria, developed in Ireland, focus on the European pharmacopoeia. Comparisons of the performance of the two PIM tools suggest that STOPP/START is more sensitive than Beers criteria. Among a sample of 1329 Irish primary care patients with a mean age of 75, 346 PIMs were found by the STOPP/START criteria, compared to 243 by the Beers criteria [31]. Although the STOPP/START do not rate the strength of the supporting evidence or make prescribing recommendations, they have been shown to be superior to the Beers criteria in identifying PIMs that lead to ADEs [32, 33]. In a meta-analysis of outcomes associated with application of the STOPP/START criteria, Hill-Taylor et al. found that the criteria can reduce PIM prescriptions in both the hospital and community environments [32]. Individual studies have shown a significant benefit of the STOPP/START criteria in reducing falls, primary care visits, and average drug cost [33]. Some clinicians may disagree with the recommendations in the Beers criteria, such as the categorical recommendation against the use of typical and atypical antipsychotics as treatment for the behavioral problems of major neurocognitive disorders. PIMs ultimately are decision support tools to inform the clinician of potential harm that must be balanced against potential benefit from a medication for an individual patient. Clinicians should integrate at least one PIM decision support tool into their prescribing practice for older patients. The Beers criteria can be downloaded as a pocket card or as part of the iGeriatrics Mobile App for Apple™ or Android™ [34].

Teaching Points

Potentially inappropriate medications (PIMs) are drugs associated with an unacceptably high risk of adverse drug events in older adults, often when safer alternatives exist. The use of these drugs offers a low benefit to side effect ratio and should be avoided or minimized except when a safer alternative is unavailable or contraindicated for a given patient. Tools have been developed using literature searches and expert opinion to identify PIMs, of which the two most commonly used are the Beers criteria and the STOPP/START criteria, developed for the North American and European pharmacopoeias, respectively. The Beers criteria can be found on convenient smartphone applications.

5.1.7 Medications of Special Concern for Older Adults

Anticholinergic Medications

To varying degrees, anticholinergic drugs cross the blood-brain barrier and bind to muscarinic and histamine receptors, causing sedation and, in older adults, impairing cognition and precipitating delirium. First-generation antihistamines such as diphenhydramine have a well-known association with delirium. In addition to adverse side effects in the central nervous system (CNS), anticholinergic drugs contribute to dry eyes, dry mouth, precipitation or exacerbation of narrow-angle glaucoma, constipation, urinary retention, and tachycardia, all in a dose-dependent manner. Some of these side effects have been therapeutic targets. For example, the antimuscarinic drug, oxybutynin, is used to treat urinary urgency and incontinence. Strongly anticholinergic medications are considered PIMs, but many commonly prescribed drugs have mild anticholinergic properties which go unrecognized by clinicians and which, taken together, can produce a substantial anticholinergic burden. A number of scales have been developed that calculate the total anticholinergic burden of a patient's prescriptions. The two most commonly used, the Anticholinergic Cognitive Burden Scale (ACB) and the Anticholinergic Risk Scale (ARS), used a combination of literature review and expert opinion to rank the anticholinergic activity of a drug from 0 (none) to 3 (severe). The results for individual drugs are then summed. In a community-based study of adults aged 65 and older (mean age, 77 years), nearly half were prescribed medications with an ACB score of ≥ 3 and roughly 20% were receiving medications with an ACB score of ≥ 5. Higher ACB scores were associated with the number of prescription and over-the-counter medications, as well as with the number of chronic illnesses [35]. The prevalence of anticholinergic burden in this study may have been skewed because patients were referred for a pharmacy evaluation by a senior services program. In a large population-based French study of adults over the age of 75, 10% received at least one prescription with a high anticholinergic burden. In the nursing home population, the prevalence of high anticholinergic burden rose to 24% [36]. Studies using the ACB have shown a significant association between total anticholinergic burden and cognitive impairment [37].

The long-term, cumulative exposure to anticholinergic drugs has been linked to the development of major neurocognitive disorders, including Alzheimer disease [38, 39]. The cognitive side effects of anticholinergic drugs should raise caution about the growing pharmaceutical interest in antimuscarinic agents as potential treatments for refractory mood disorders [40]. In older adults, anticholinergic drugs also have been associated with an increased risk of community-acquired pneumonia and traumatic fractures [41]. ◘ Table 5.4 lists commonly prescribed medications with moderate to high anticholinergic burden, together with safer alternatives [42–45]. ◘ Table 5.5 shows common medications by class whose mild to moderate anticholinergic activity often goes unrecognized, but which can contribute to significant anticholinergic side effects when simultaneously prescribed with other anticholinergic medication [42–45].

Teaching Points

Anticholinergic drugs cross the blood-brain barrier to varying degrees, causing sedation and potentially impairing cognition in older adults that can result in frank delirium. These medications also cause a variety of peripheral manifestations ranging from dry mouth to constipation in a dose-dependent fashion. Many common medications have mild anticholinergic properties which, when added together, can produce a cumulative anticholinergic burden that can be clinically significant.

Psychotropics and Fall Risk

Approximately one-third of adults 65 and older fall annually, and a substantial proportion of these falls result in traumatic fractures. Psychotropic medications play a significant role in adding to fall risk in the older population. Bloch et al. conducted a meta-analysis of 71 studies with data on psychotropic drug use and falls in adults aged 60 years and older. The authors defined a psychotropic drug as any drug that affected the CNS, but focused their review on antidepressants, benzodiazepines, sedative-hypnotics, narcotics, and antipsychotics. ◘ Table 5.6 summarizes their key findings, showing that psychotropic medication increases the risk of any fall between 29% and 44%, while increasing the risk of traumatic falls like ground-level hip fracture between 81% and 276% [46].

The majority of studies that have examined the association between the SSRI class of antidepressants and falls have found a significant association, but the single-randomized controlled trial found in a comprehensive, systematic review of falls and SSRIs was underpowered with 142 subjects and did not find a statistically significant association (OR 1.56, 95% CI 0.63–3.83) [47]. Although the consistency of

Table 5.4 Examples of anticholinergic medications

Medication class	Medication name	Anticholinergic activity[a]	Examples of safer alternatives
Antipsychotic			
Atypical	Olanzapine	H	Aripiprazole
	Quetiapine	M	
	Risperidone	M	
	Ziprasidone	M	
Typical	Haloperidol	M	
	Trifluoperazine	H	
	Chlorpromazine	H	
Antidepressant			
SSRI	Paroxetine	M	Citalopram, escitalopram
Tricyclic	Amitriptyline	H	
	Nortriptyline	H	
Antidiarrheal			
	Loperamide	M	
Antiemetic			
	Prochlorperazine	H	Ondansetron[b]
H2 blocker antacids			
	Ranitidine	M[c]	Proton pump inhibitors, H2 blocker: famotidine
	Cimetidine	M	
All first-generation antihistamines			
	Diphenhydramine[d]	H	Second-generation ("nonsedating") antihistamines: cetirizine, loratadine
	Chlorpheniramine	H	
	Clemastine	H	
	Hydroxyzine	H	
Anti-vertigo antihistamines			
	Meclizine	H	
	Dramamine	H	
Bladder antispasmodics			
	Trospium	H	Mirabegron (beta 3 agonist)
	Oxybutynin	H	Darifenacin, solifenacin[e, b]
	Tolterodine	H	
Antiparkinson disease medication			
	Benztropine	H	
	Amantadine	M	

Data extracted from Refs. [42–45]
[a]*M* moderate, *H* high
[b]May cause QTc prolongation
[c]Considered low risk by one anticholinergic scale, but has consistently been associated with delirium in older adults
[d]Diphenhydramine is also found in over-the-counter (nonprescription) sleep aids
[e]M3 selective, not associated with cognitive impairment, may cause constipation and dry mouth

Table 5.5 Drugs with often unrecognized anticholinergic activity that can add to the total anticholinergic burden

Psychiatric drugs	Cardiac drugs	Diuretics	Miscellaneous
Benzodiazepines	*Antiarrhythmics*	Furosemide	*Analgesics*
Alprazolam	Atenolol	Triamterene	Codeine
Diazepam	Metoprolol	Chlorthalidone	Morphine[a]
Clorazepate	Digoxin		*Anticoagulants*
Antidepressants	Quinidine[b]		Warfarin
Bupropion	*Antihypertensives*		Dipyridamole
Fluvoxamine	Captopril		*Anti-glaucoma*
Trazodone	Hydralazine		Timolol maleate
Antipsychotics	*Antianginal*		*Anti-inflammatory*
Haloperidol	Isosorbide		Hydrocortisone
			Anti-gout
			Colchicine
			Bronchodilator
			Theophylline[b]

Data extracted from Refs. [42–45]
[a]Not recommended in older adults due to decreased renal clearance
[b]Rarely prescribed due to high potential for toxicity and drug interactions [3–6]

Table 5.6 Pooled odds ratios (OR) and 95% confidence intervals (95% CI) for falls and traumatic falls in adults aged 60 and older

	Antidepressants OR (95% CI)	Benzodiazepines OR (95% CI)	Antipsychotics OR (95% CI)	Sedative-hypnotics OR (95% CI)
No. of studies	41	20	20	33
Any falls	1.44 (1.31–1.59)	1.31 (1.16–1.47)	1.29 (1.11–1.50)	1.40 (1.24–1.58)
Traumatic falls	2.12 (1.80–2.48)	2.24 (1.60–3.13)	2.76 (2.06–3.68)	1.81 (1.56–2.10)

Data extracted from Bloch et al. [46]

association between SSRIs and falls has been strong, observational and retrospective studies may be confounded by indication bias [47, 48]; i.e., most patients receive antidepressants for depression, and there is evidence that the depression *itself* may influence fall risk by contributing to disability [49]. To add to the complexity of understanding the association between antidepressants and falls, fall risk depends in part on having previously experienced a serious fall. In an analysis of 2948 men and women enrolled in the longitudinal Health, Aging, and Body Composition Study (Health ABC; mean age, 73.6 years), no association was found between any antidepressants and falls in subjects without a history of falls or fall-related fractures, but SSRIs were the only class of antidepressant to be significantly associated with a *recurrent* fall (OR 1.62, 95% CI 1.15–2.28), after adjustment for study site, drugs that increase risk of falls, self-reported depression, Center for Epidemiologic Studies Depression (CES-D) score, pain, sleep problems, anxiety, and comorbid conditions [50].

Teaching Points

At the present time, it remains uncertain how much SSRIs and other antidepressants independently contribute to the risk of falls, but attention should be paid to the additive effect they may have on fall risk. The Beers criteria *strongly* recommend avoidance of three or more CNS-active medications if considering SSRIs, tricyclic antidepressants (TCAs), or benzodiazepines because of an increased risk of falls and fractures; tricyclics, however, fall under the category of anticholinergic medications, which the Beers criteria recommend avoiding [51].

Antipsychotics and Metabolic Syndrome

Patients who are prescribed atypical antipsychotics experience higher rates of obesity, hyperlipidemia, diabetes mellitus, and the full metabolic syndrome[1] than those taking typical antipsychotics or mood stabilizers. Erickson et al. used pharmacy and medical claims data for older patients residing in the western USA to evaluate the association of atypical antipsychotics with an increased odds ratio of having new treatment-dependent diabetes mellitus. Those exposed to atypical antipsychotics had a 32% greater odds ratio of developing treatment-dependent diabetes mellitus compared to individuals not taking these agents [52]. Other pharmacoepidemiologic studies have provided inconsistent results regarding the association of atypical antipsychotics and diabetes mellitus; significant study heterogeneity makes it difficult to systematically review the studies via meta-analysis. At present, the preponderance of evidence suggests that clozapine and particularly olanzapine increase the risk of diabetes mellitus, whereas risperidone and quetiapine do not [53]. However, the use of typical antipsychotics as the frame of reference may be misleading. Lipscombe et al. found that geriatric patients currently receiving a typical antipsychotic had a 2.86 OR of hospitalization for hyperglycemia, compared to a 1.52 OR for current users of an atypical antipsychotic [54]. Significant hyperglycemia can develop in just days [55], especially in patients with obesity or a prior history of diabetes mellitus.

Teaching Points

Atypical antipsychotics have been associated with the development of the metabolic syndrome, and both atypical and typical antipsychotics have been associated with the development of hyperglycemia, which can occur within days of the start of treatment. In the inpatient setting, psychiatrists should monitor the fasting blood glucose after starting an antipsychotic, especially if the patient has risk factors for diabetes mellitus, such as a history of hyperglycemia, obesity, or other elements of the metabolic syndrome. A logical approach for older outpatients newly started on an antipsychotic is to obtain a fasting blood glucose after 1 week and 1 month and to ask the patient or informant about symptoms of hyperglycemia, such as polydipsia, polyuria, and new fatigue. The patient also should be monitored for weight gain.

1 The metabolic syndrome is defined as meeting at least 3 of the 5 criteria: abdominal obesity, hypertriglyceridemia, low high-density-lipoprotein cholesterol, hypertension, and a fasting blood glucose >100 mg/dL (5.55 mmol/L).

Psychotropic Medication and Hyponatremia

Definition of Hyponatremia

Hyponatremia is defined as a serum sodium concentration of < 135 mEq/L (135 mmol/L). Symptomatic hyponatremia is determined by its severity and the rate of decline; if insidious or chronic, some patients remain asymptomatic with a sodium below 120, although 120 or below generally is considered a critical value. Mild hyponatremia can present with nonspecific fatigue, headache, nausea, and muscle cramps, but as the sodium drops, the rate of flow of water into neurons and glia increases as a result of the widening concentration gradient, causing cerebral edema. A rapid lowering of the serum sodium into the 120 seconds (mEq/L/mmol/L), or a serum sodium of ≤ 120 mEq/L (120 mmol/L), may precipitate neuropsychiatric symptoms such as delirium, lethargy, restlessness, and abnormalities of gait and may result in seizures, coma, and ultimately death due to brain swelling. Hyponatremic seizures represent a medical emergency and require transfer to the emergency department or medical intensive care unit.

Clinically significant hyponatremia can be caused by net salt excretion by the kidney, as occurs from diuretics; by volume depletion with avid water retention from physiologically elevated antidiuretic hormone (ADH; also called vasopressin) and/or free water replacement without adequate replacement of salt; by net water retention due to physiologically elevated ADH as seen in cirrhosis and heart failure; from water intoxication during purposeful, rapid consumption of excessive amounts of water; and by *inappropriate* elevation of ADH, known as the syndrome of inappropriate antidiuretic hormone (SIADH). SIADH most commonly results from the action of medications on the CNS; many offending drugs are psychotropics.

Hyponatremia Associated with Psychotropic Medication

Data showing an association between antidepressants and hyponatremia in older adults have been gleaned through observational and case-control studies, leaving the results vulnerable to bias. With these limitations in mind, studies suggest that the greatest risk of hyponatremia occurs with SSRIs and selective norepinephrine reuptake inhibitors (SNRIs), with lower risks for tricyclic antidepressants (TCAs) and the remaining classes of antidepressants. Coupland et al. analyzed a large regional database of 40,516 patients 65 and older to evaluate the relative odds ratio of hyponatremia among different classes of antidepressants and adjusted for age, sex, depression severity and duration, use of medications known to affect serum sodium, and comorbid conditions. Compared to not taking antidepressants, patients prescribed SSRIs were significantly more likely to develop hyponatremia (OR 1.52, 95% CI 1.33–1.75); the respective ORs for TCAs and all other antidepressants considered together did not achieve statistical significance [56]. Using serum sodium level < 130 mEq/L

(< 130 mmol/L) as the cutoff, the incidence of hyponatremia with SSRIs has been reported between 0.06% and 2.6%, compared to 0.08–4% for SNRIs and 0.01–0.33% for TCAs [57]. The wide range reflects the heterogeneity of the studies. Among older adults using SSRIs and SNRIs (the highest-risk antidepressants; TCAs should not be a first-line antidepressant in the geriatric population), the risk of hyponatremia rises with age and sex, concurrent use of other agents that may affect serum sodium, and comorbidities that affect water handling by the body [57] (Fig. 5.2). Age likely is a proxy for age-associated decline in renal function and concomitant reduction in the ability to excrete free water.

The phenothiazine and butyrophenone classes of antipsychotics have infrequently been associated with SIADH. The anticholinergic effect of phenothiazines and the resulting dry mouth may also lead to increased fluid intake, augmenting the sodium-lowering effect of any inappropriate ADH secretion [58, 59].

Diagnosis and Management of SIADH

In the presence of symptomatic hyponatremia, urine and serum electrolytes and urine and serum osmolality should be obtained *statim*. In the absence of neuroendocrine or renal dysfunction, hyponatremia should lead to net urinary excretion of free water, but in SIADH, the urine osmolality is inappropriately high. Diuretics cause hyponatremia by salt and free water excretion, usually resulting in low urine osmolality. Severe mental status changes related to very low sodium, and particularly hyponatremic seizures, represent a medical emergency. The sodium should be rapidly increased by 4–6 mEq/L (mmol/L) but not more than 9 mEq/L (mmol/L) over 24 hours and 18 mEq/L (mmol/L) over 48 hours with the goal of raising the sodium to > 125 mEq/L (mmol/L). Initially, this rise can be achieved by intravenous 3% saline, given as a bolus of 100 ml over 1 hour. Hypertonic saline should only be administered under close medical supervision on a medical inpatient unit or in the emergency department. In severe cases (e.g., seizures, coma), a rate of rise faster than the above parameters leads to overly rapid shifts in fluid and electrolytes within the CNS and may cause myelinolysis. Mildly symptomatic hyponatremia, consisting of lethargy or mild confusion, should be treated by aggressive fluid restriction of 800 to 1000 ml of fluids per 24 hours. Normal saline (0.9% sodium chloride solution) should *not* be used to raise serum sodium. In SIADH, sodium handling by the kidney remains normal. Consequently, the excess salt is excreted, but the remaining free water is absorbed, potentially worsening the hyponatremia. Asymptomatic hyponatremia between 125 and 135 mEq/L (mmol/L) can be treated with a slightly more liberal fluid restriction of 1500 ml/24 hours. In SIADH, physiologic handling of sodium is not affected in the

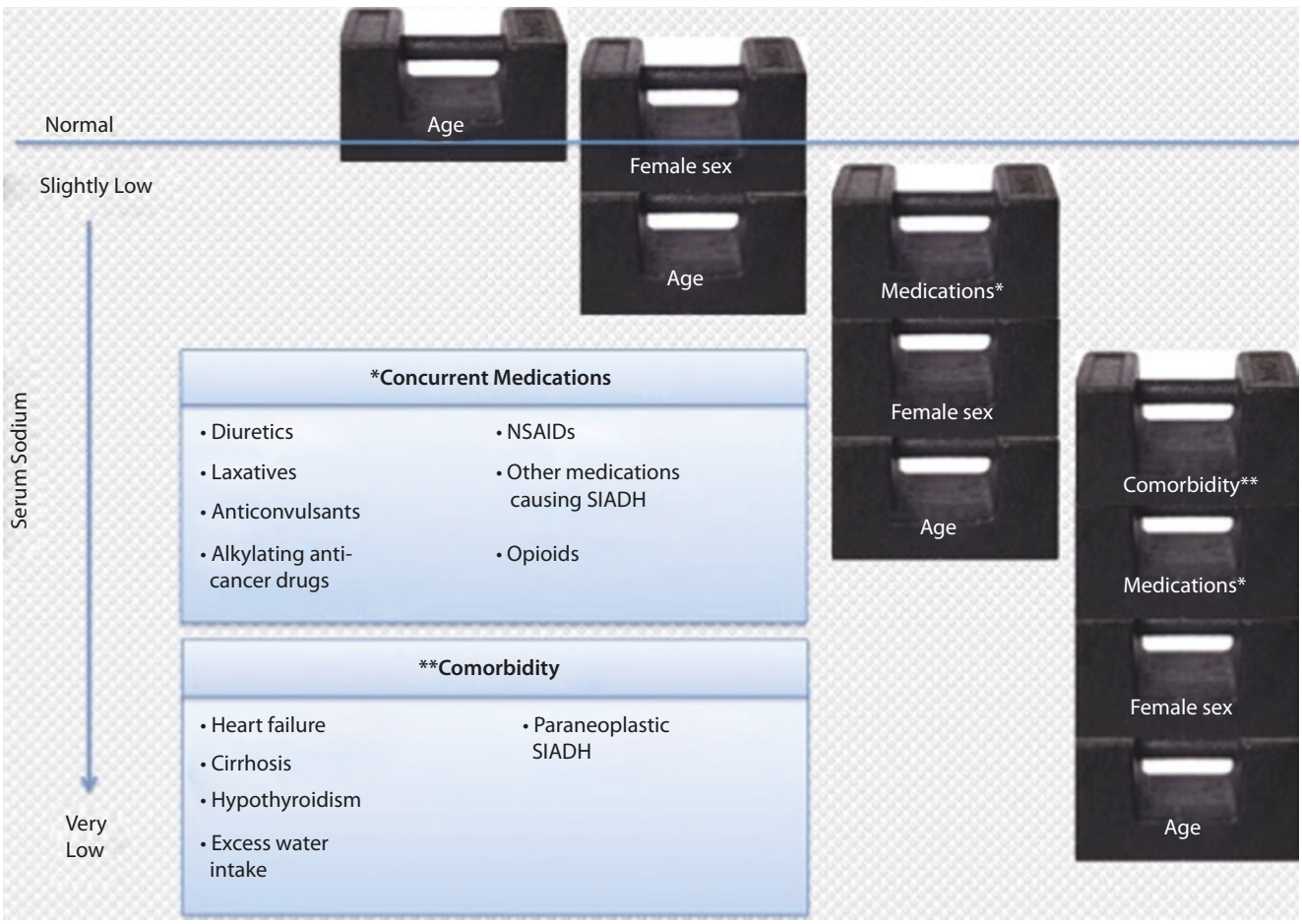

Fig. 5.2 Risk factors for hyponatremia in the older patient

presence of healthy kidneys. However, when there is underlying salt wasting (i.e., inappropriate sodium excretion causing an inappropriately high urinary sodium for the degree of hyponatremia, as might happen with chronic use of loop diuretics), salt tablets can be added to the fluid restriction. Patients susceptible to heart failure or with cirrhosis generally should not receive salt tablets, and hypertonic saline should be administered cautiously while monitoring for signs and symptoms of fluid overload.

Teaching Points

A number of classes of psychotropic medications, particularly SSRIs and SNRIs, can cause SIADH, leading to potentially serious hyponatremia that may be compounded by the concurrent administration of other sodium-lowering drugs, as well as heart failure and cirrhosis, which stimulate the kidney to retain salt and water. Delirium and seizures in conjunction with hyponatremia constitute a medical emergency requiring prompt treatment. Asymptomatic and mildly symptomatic hyponatremia can be managed by fluid restriction. More severe cases may require the addition of 3% (hypertonic) saline to bring the serum sodium to ≥ 125 mEq/L (mmol/L).

The Adverse Effects of Lithium in Older Patients

Despite its well-known potential toxicity, lithium remains a first-line mood stabilizer treatment for bipolar disorder, as well as an augmentation agent for treatment-resistant unipolar depression. Elevated levels and long-term use of lithium can lead to chronic kidney disease, polyuria, and nephrogenic diabetes insipidus with difficulty concentrating urine.

Lithium concentrates in the thyroid gland and inhibits its release of thyroid hormone, thereby increasing the risk of development of a goiter and hypothyroidism. Lithium enters the CNS and concentrates in both the hypothalamus and the pituitary gland, resulting in exaggerated release of thyroid stimulating hormone. In spite of the suppressive effect of lithium on thyroid hormone release, it infrequently can induce hyperthyroidism, possibly by directly damaging follicular cells, causing the release of stored thyroid hormone [60].

Rarely, lithium has been associated with hyperparathyroidism, although the exact mechanism remains unclear. Lithium appears to act on the calcium-sensing receptor, raising the level of serum calcium necessary to turn off the secretion of parathyroid hormone. It is also possible that in some cases lithium unmasks a previously subclinical hyperparathyroid state [61].

Acute lithium toxicity can lead to fever, altered mental status, and coma; cognitive changes have a good prognosis with recovery in 6–12 months, at least in younger patients. Irreversible loss of cerebellar Purkinje cells can result from acute or subacute toxicity, leading to cerebellar symptoms, including intention tremor, ataxic gait, and dysarthria. In chronic lithium use, cerebellar injury can develop with therapeutic lithium levels [62].

Age-associated physiologic changes increase the risk of lithium toxicity. Decreasing muscle mass and reduced production of creatinine can mask age-associated declines in the glomerular filtration rate. Healthy younger adults can compensate for the polyuria from nephrogenic diabetes insipidus by increasing their fluid intake, but the thirst response is blunted in older adults, predisposing them to a net loss in intravascular volume that may result in prerenal azotemia (elevated blood urea nitrogen to creatinine ratio) and dehydration, with a resulting increase in the serum lithium concentration and a upward spiraling risk of lithium toxicity. The signs and symptoms of lithium toxicity can be mistaken for age-associated conditions and the side effects of other medications. Dry mouth from dehydration can be mistakenly attributed to anticholinergic medication or sicca syndrome, a slight tremor or unstable gait to Parkinson disease or peripheral neuropathy.

Common comorbid conditions among older adults or their treatment increase the risk of lithium toxicity; intravascular volume depletion from the polyuria of uncontrolled diabetes mellitus or from the use of loop diuretics predispose to lithium toxicity. Nonsteroidal anti-inflammatory drugs for pain can impair renal function, increasing the risk of lithium toxicity. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB) for hypertension or heart failure may reduce kidney perfusion and the glomerular filtration rate, causing lithium levels to rise. Delirium resulting from lithium toxicity or from hypernatremia from unrecognized nephrogenic diabetes insipidus may be attributed to comorbid bipolar disorder, psychotic disorder, major depressive disorder, or another cause, rather than to the side effects of lithium. Chronic use of loop diuretics (e.g., furosemide, bumetanide, torsemide) and ACE inhibitors each has been associated with a ≥ 60% relative risk increase of hospitalization for lithium toxicity in older adults. The risk is highest during the first month of use [63], underscoring the need to closely follow lithium levels each time an agent that may affect hydration status or renal function is prescribed.

Teaching Points

Both chronic use of lithium and acute lithium toxicity can impair the water-retaining effect of ADH on the renal tubule, leading to nephrogenic diabetes insipidus, and can lead to acute and chronic cerebellar dysfunction causing disabling dysarthria, tremor, and ataxic gait, contributing to fall risk. Chronic administration of lithium can induce hypothyroidism and (less commonly) hyperthyroidism and has also been linked to hyperparathyroidism. In older patients, these risks of lithium toxicity are magnified due to the age-associated decline in renal function,

Teaching Point (Continued)
comorbid conditions that lead to the use of medications that further compromise kidney function or predispose to dehydration, and other age-associated conditions. It therefore is critical that lithium levels be closely monitored in older patients and, whenever possible, that lithium be administered at the lowest effective dose. If possible, alternatives to lithium should be sought.

5.1.8 Adverse Reactions Meriting Special Consideration

Neuroleptic Malignant Syndrome and Serotonin Syndrome: Recognition and Management

Neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are potentially life-threatening adverse drug reactions that belong to a group of dysautonomias whose symptoms overlap, making differentiation often difficult. NMS is considered an idiosyncratic reaction to dopamine blocking agents (most commonly antipsychotic medication) that may appear unpredictably during the course of treatment. Changes in antipsychotic agent, high doses, the rapidity and magnitude of upward titration, and co-administration of a mood stabilizer such as lithium increase the risk for NMS [64]. In contrast, SS represents direct dose-dependent toxicity from serotonergic agonists. Both syndromes can present with hypertension, tachycardia, hyperthermia (> 40 °C), autonomic dysfunction, mental status changes, and increased motor tone. To further complicate differentiation, not all features of either syndrome need be present for a clinical diagnosis. Figure 5.3 shows the overall similarities and differences between NMS and SS. Due to similarities in presentation [65], differentiating the two requires a careful review of medication exposure (including over-the-counter and "street" drugs) and examination for key differentiating features.

An important differentiating exam finding is hyperreflexia progressing to clonus in SS compared to typically decreased reflexes in NMS. In the psychiatric patient, the co-administration of both an antipsychotic and a serotonergic antidepressant has become commonplace, being used in cases of refractory depressive disorders (with or without psychotic features), psychotic disorders with concurrent depressive symptoms, and severe agitation and emotional dysregulation in major neurocognitive disorders. The combination of an antipsychotic (typical [phenothiazine derivative, butyrophenone] or atypical) with a SSRI or SNRI increases the risk of SS and should be made cautiously in the older adult, using the lowest possible effective dose of each drug. Other commonly used medications in the geriatric population have serotonergic properties, and given the prevalence of polypharmacy in older adults, the psychiatrist should carefully review the patient's medication list for these serotonergic drugs before starting an antipsychotic, SSRI, or SNRI (Table 5.7). Because clinicians may understandably be reluctant to stop all serotonergic drugs indefinitely when they are providing substantial benefit to the patient, it is helpful to determine the onset of serotonin toxicity in relation to the initiation or dose increase of a serotonergic agent in order to identify the immediate precipitant of the toxicity. However, this association should not be considered definitive, and in cases of moderate-severe SS, all serotonergic agents should be held, even if this places the patient at risk for serotonin withdrawal.

Neuroleptic Malignant Syndrome

NMS appears to be caused by the depletion of dopamine in the CNS or by the blockade of dopamine type 2 (D_2) receptors. Central dopaminergic blockade has been posited as the best possible explanation; antipsychotic drugs block dopamine receptors in multiple regions of the CNS, including the basal ganglia, hypothalamus, corpus striatum, and spinal areas. All antipsychotics, not just high-affinity D_2 receptor drugs like haloperidol and risperidone, have been implicated in NMS, including clozapine, quetiapine, aripiprazole, and olanzapine. High doses and a faster rate of upward titration increase the risk of NMS. More than half of reported cases have involved the co-administration of two or more psychotropics [64], but it is unclear whether this association represents potentiation or simply reflects the severity of the underlying psychiatric illness. Of note, the abrupt withdrawal of dopaminergic drugs in patients with Parkinson disease has been linked to NMS or at least to a NMS-like syndrome.

Serotonin Syndrome

There are no reliable data on the incidence of SS because of its rarity coupled with lack of recognition of milder cases. However, the widespread use of SSRI and SNRI antidepressants, together with the expanding pharmacopoeia of medications that either are serotonin agonists or that interfere with the metabolism of SSRIs, SNRIs, or MAO inhibitors, suggests that the incidence is likely to rise. Approximately 40% of cases of SS arise from a single agent [66], with the rest resulting from increased CNS serotonin levels due to the administration of multiple serotonin agonists. Table 5.7 lists medications that can increase brain serotonin levels. Many older patients receive opioids for chronic pain plus a SSRI or SNRI, either for a concurrent depressive disorder or as an adjunctive analgesic to reduce the daily opioid dose. This practice can place the patient at risk for SS. Non-phenanthrene opioids should be avoided or discontinued whenever possible in patients receiving a serotonergic psychotropic medication; non-phenanthrene opioids include tramadol, methadone, propoxyphene, meperidine, and fentanyl. The phenanthrene opioids, such as hydrocodone, morphine, and codeine, can be used safely with serotonin antidepressants [67]. Serotonergic pain

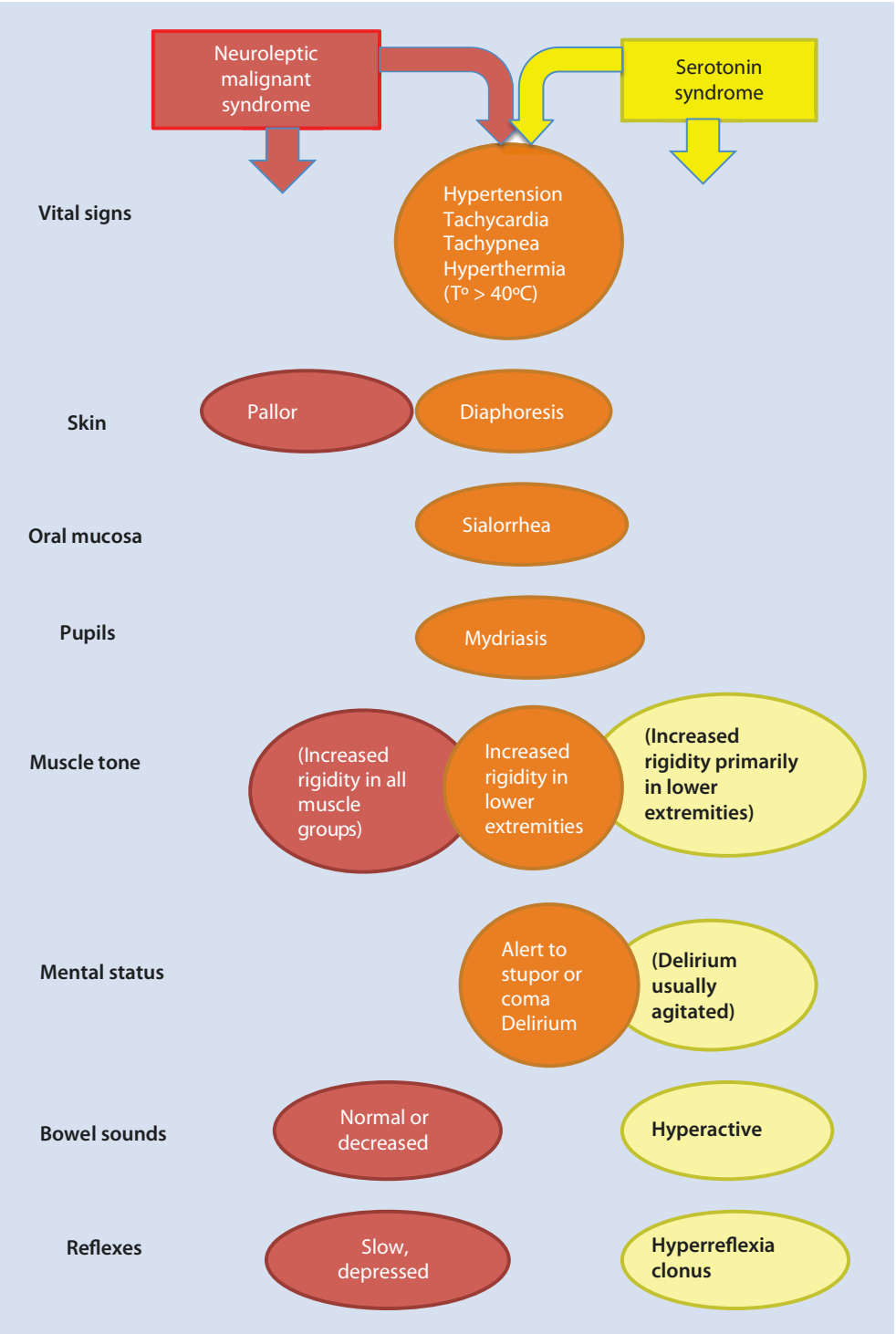

Fig. 5.3 Similarities and differences between neuroleptic malignant syndrome and serotonin syndrome

medications by themselves have been associated with SS, especially tramadol [66].

Dextromethorphan (a cough suppressant found in many over-the-counter cold remedies) also can precipitate SS. The macrolide antibiotic erythromycin (but not the second-generation macrolide, azithromycin) inhibits the metabolism of SSRIs, as can the anticonvulsant carbamazepine. Because the oxazolidinone class of antibiotics (linezolid, tedizolid phosphate) are weak MAO-B inhibitors, they have the potential to induce SS in patients receiving a serotonin-enhancing antidepressant [68].

SS can present insidiously across a continuum of severity with only one or a few of the characteristics. Mild, subacute cases can be missed, the symptoms being attributed to common morbidities in older adults (e.g., hypertension, infection) or to the comorbid psychiatric disorder in the case of akathisia and anxiety disorder. In more severe cases, tremor can be suppressed by hypertonicity (Fig. 5.4) [69].

Table 5.7 Drugs that can precipitate serotonin syndrome

Drug Class	Drugs
Antidepressants	SSRIs
	SNRIs
	Trazodone
	Tricyclic antidepressants
	MAOIs
	St. John's Wort *(Hypericum perforatum)*
Anxiolytics	Buspirone
Mood stabilizers	Lithium
	Valproic acid
	Carbamazepine
Amphetamines and derivatives	Dextroamphetamine
	Methylphenidate
	Sibutramine (Meridia; withdrawn in USA)
	3,4-methylenedioxymethamphetamine (ecstasy)
	Methamphetamine
Analgesics	Fentanyl
	Meperidine
	Tramadol
Muscle relaxants	Cyclobenzaprine
Antiemetics	Ondansetron
	Metoclopramide
Antimigraine drugs	Triptans
	Ergot alkaloids
Miscellaneous	Cocaine
	Linezolid
	Tedizolid
	5-Hydroxytryptophan
	Tryptophan

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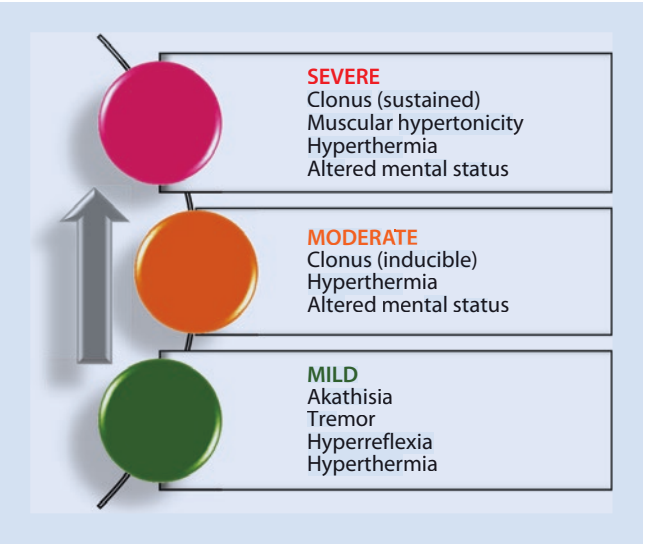

Fig. 5.4 The spectrum of signs and symptoms in serotonin syndrome

Management of Neuroleptic Malignant Syndrome and Serotonin Syndrome

NMS and severe cases of SS are medical emergencies requiring close medical and nursing management and should be transferred to the emergency department or to the intensive care unit. Care for NMS is largely supportive and begins with the discontinuation of the antipsychotic. Although NMS is idiosyncratic with an unpredictable occurrence, patients who have had it are vulnerable to a recurrence if rechallenged with an antipsychotic; the rate of recurrence upon later rechallenge may be as high as 30–50% [64]. Thus, simply reducing the dose of antipsychotic is not recommended as part of the initial treatment, placing clinicians in the dilemma of placing their patient at risk of another episode of NMS or eliminating a mainstay of pharmacological management of psychotic disorders. As all antipsychotics have been linked to NMS, switching agents also do not necessarily reduce risk of recurrence, although subsequent prescribing of antipsychotics for patients upon recovery from NMS should favor lower D_2 blocking agents (e.g., quetiapine, clozapine) to mitigate the risk of recurrent NMS. Bromocriptine and amantadine are dopamine agonists that have been used to counteract the D_2 blockade in NMS, but bromocriptine increases the risk of SS and may worsen psychotic symptoms. Amantadine may cause delirium in older patients. Intermediate-acting benzodiazepines may be necessary to control severe agitation, despite the risk of exacerbating or prolonging delirium.

For SS, the first step in treatment is eliminating the offending drugs or at least minimizing the doses; the lower the serotonergic burden, the faster the recovery. Even when the precipitating agent appears to have been identified (e.g., SS after tramadol started for chronic pain in a patient taking duloxetine for depression and diabetic neuropathy), both agents should be stopped or reduced to hasten recovery, despite the risk of serotonin withdrawal. Cyproheptadine, a serotonin ($5\text{-}HT_{2A}$) and histamine (H1) antagonist used to treat the symptoms of carcinoid syndrome, has been shown in case reports to mitigate the symptoms of SS, provided the patient is able to take per os. Positron emission tomography scans have demonstrated that cyproheptadine 4 mg and 6 mg every 8 hours can block 85% and 95%, respectively, of $5\text{-}HT_{2A}$ receptors in the prefrontal cortex [70]. While it has the potential to prophylactically protect against SS in patients in whom multiple serotonergic agents are essential [70], there are no randomized trials to verify its efficacy, and its anticholinergic properties render it problematic for older patients.

In both NMS and SS, vital signs should be monitored frequently. Severe hyperthermia (> 40 °C) can induce seizures and irreversible brain damage and requires aggressive external cooling with ice packed around the patient or a cooling blanket. Severe muscle rigidity induced by involuntary isotonic muscle contractions is found in both conditions, but can be especially severe in NMS. The tonic muscle contractions lead to rhabdomyolysis, which, in turn, can precipitate acute renal failure because of the renal tubular toxicity of the myoglobin released into the circulation by damaged muscle. Muscle relaxants therefore are needed when muscle rigidity is present. Dantrolene is more effective than benzodiazepines and is associated with a relatively lower risk of inducing delirium. Serum electrolytes and a complete blood count should be obtained in all patients and serially monitored. A creatine kinase level (CK) should be monitored. CK >1000 U/L (16.7 μkat/L) reflects muscle injury severe enough to induce renal tubular injury. During rhabdomyolysis, intravascular volume depletion exacerbates the renal tubular injury. While the CK remains > 1000 U/L (16.7 μkat/L), intravenous fluids should be infused at a rate of 150–200 ml/hour to generate a urine output > 100 cc an hour to dilute and wash out the myoglobin. In older patients, this infusion rate can lead to significant volume overload and heart failure and therefore may require the concurrent use of diuretics. In severe rhabdomyolysis, alkalinization of the urine can reduce the binding of myoglobin to the renal tubules and reduce the risk of renal failure.

Teaching Points

Neuroleptic malignant syndrome (NMS) and serotonin syndrome (SS) are rare but potentially life-threatening reactions to antipsychotics and serotonergic drugs, respectively. In milder cases, the symptoms can be mistaken for other age- and disease-associated conditions unless considered in the differential diagnosis. NMS is idiopathic and not exposure dependent; rechallenge with any antipsychotic in the future exposes the patient to a 30–50% risk of recurrence. SS, in contrast, is dependent on the total serotonergic burden. Medications from a variety of classes of drugs have serotonergic activity that, when combined with known serotonin agonists like SSRIs and SNRIs, can precipitate serotonin syndrome. For both conditions, treatment is supportive after discontinuation of the offending medications.

QTc Prolongation and Risk of Ventricular Arrhythmias

The corrected QT interval (QTc) lengthens with age, so that drugs that prolong this interval can cause a dangerously long QTc interval that predisposes the patient to potentially life-threatening ventricular tachycardia that begins as *torsades de pointes* (TdP), named for the apparent "pivoting" of the tachycardia around the baseline and also characterized by variations in the amplitude of the QRS complex (Fig. 5.5). The threshold

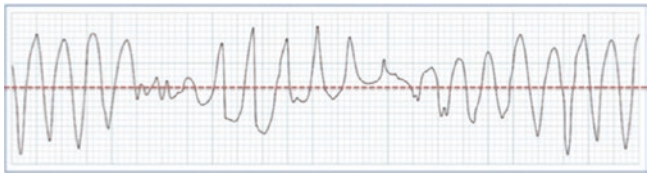

Fig. 5.5 Torsades de pointes arrhythmia

of QTc that should raise concern about TdP risk is > 450 milliseconds in men and > 470 milliseconds in women. In addition to congenital QTc syndrome, a prolonged QTc can be seen in bradycardia and with electrolyte abnormalities (hypocalcemia, hypokalemia, and hypomagnesemia). Both hypokalemia and hypomagnesemia can result from the chronic use of loop diuretics and thus can be seen in patients with heart failure; heart failure with reduced ejection fraction (HFrEF) independently increases the risk of ventricular tachycardia.

Although case reports suggest an association between QTc prolongation and phenothiazines, haloperidol and its cousin, droperidol, and the second-generation antipsychotics (risperidone, quetiapine, ziprasidone, and clozapine), epidemiologic evidence has not shown a consistent, predictable class effect of these drugs. The actual incidence of TdP-associated sudden death is very low [71]. Of the atypical antipsychotics, olanzapine and aripiprazole have the least effect on QTc. Fluoxetine and citalopram have been linked to QTc prolongation, with citalopram doing so in a dose-dependent manner, leading to a recommendation that 20 mg of citalopram be the maximum safe dose in older patients. Although escitalopram has not been clearly linked to QTc prolongation, the fact that it is the s-enantiomer of citalopram lead Health Canada to advise caution when used in older patients [72]. Sertraline and paroxetine are associated with a lower degree of risk. Among older-generation antidepressants, tricyclics as a class can cause TdP when taken in overdose, but their relationship to QTc prolongation at therapeutic levels remains unclear [73].

A number of common medications are known to prolong the QTc and independently increase the risk of TdP and sudden death and are therefore relatively contraindicated for co-administration with QTc-prolonging psychotropic medication. Of importance are the macrolide antibiotics (erythromycin, clarithromycin, and azithromycin), multiple antiarrhythmic medications (amiodarone, dronedarone, sotalol, procainamide, quinidine, disopyramide), chloroquine (an antimalarial commonly used as an immunomodulator), the antihistamine astemizole, the commonly employed antiemetic ondansetron, and methadone. There are case reports of the cholinesterase inhibitors, donepezil and galantamine, causing QTc prolongation, but the association is not definitive. However, citalopram is commonly prescribed for depression or the management of dementia-associated agitation in patients with major neurocognitive disorders who are taking a cholinesterase inhibitor, so awareness of the association is important.

General guidelines for prescribing a QTC-prolonging medication are provided in Fig. 5.6.

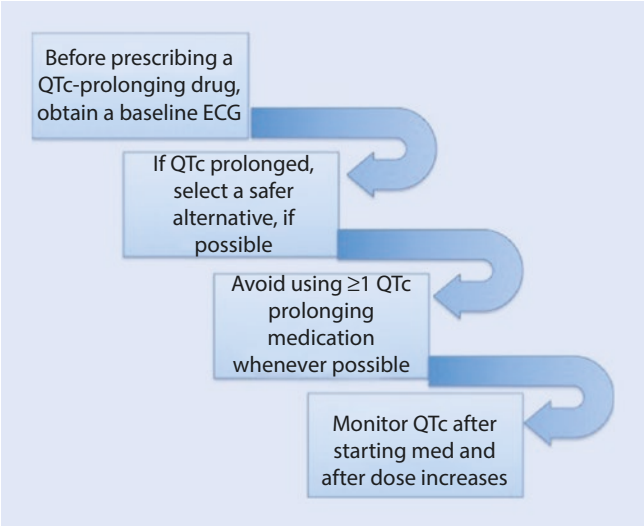

Fig. 5.6 Guidelines for prescribing drugs that prolong the QTc

Teaching Points

All classes of antipsychotics and some SSRI antidepressants have been linked to prolongation of the corrected electrocardiographic QT interval (QTc), which in turn has been associated with an increased risk of torsades de pointes, ventricular tachycardia, and sudden death. Among the antipsychotics, aripiprazole and olanzapine are believed to have the least relative effect on the QTc, and among the SSRI antidepressants, sertraline and paroxetine appear to have a lower relative risk of QTc prolongation. Because of citalopram's dose-dependent effect on the QTc, the maximum recommended daily dose in older adults is 20 mg. Multiple commonly prescribed medications affect the QTc, necessitating a careful medication reconciliation before prescribing a QTc prolonging drug. Whenever possible, only one QTc-prolonging drug should be prescribed at one time.

Selective Serotonin Reuptake Inhibitors and Risk of Bleeding

Serotonin reuptake inhibitors can reduce platelet serotonin by up to 90%, potentially compromising hemostasis by inhibiting an important mediator of platelet aggregation [65]. SSRIs have been associated with an increased risk of gastrointestinal bleeding [74] and add to the risk associated with concomitant use of aspirin and nonsteroidal anti-inflammatory drugs. SSRIs have also been associated with an increased risk of stroke from subarachnoid hemorrhage [75]. SSRIs therefore should be prescribed cautiously in patients taking an anticoagulant or antiplatelet agent for comorbid conditions such as deep venous thrombophlebitis, atrial fibrillation, carotid artery disease, and coronary heart disease.

Teaching Point

The inhibition of serotonin by SSRIs affects platelet aggregation and potentially increases bleeding risk. Care must be exercised when considering a SSRI (and presumably also a SNRI) in patients with a history of gastrointestinal bleeding, intracranial hemorrhage, or taking other platelet inhibitors or an anticoagulant.

5.2 Case Studies

The following case-based studies reflect issues of polypharmacy in older adults and the specific adverse drug events that need to be actively considered when prescribing psychotropic medications, as well as the communication among prescribing clinicians and the active use of pharmacy profiling that are recommended to facilitate safe medication prescribing and monitoring.

5.2.1 Case 1

Case 1 History

Ms. G., a 67-year-old woman, was brought to the emergency department by paramedics after a shop owner called the police about a woman in a wheelchair who was acting strangely. When found, she was seated in her wheelchair outside in the cold rain and disoriented, agitated, and incoherent. In the emergency department her initial vital signs were blood pressure 136/101 mm Hg, heart rate 121 beats/minutes and regular, respiratory rate 20 breaths/minutes, and O_2 saturation 98% on room air. Her temperature was 37.2 °C (98.9 ° F). Because of her agitation, she was given haloperidol 5 mg IV x 1, followed later by midazolam, 0.5 mg IV, and lorazepam 2 mg IV, which made her somnolent but arousable. Her past medical history, per the electronic medical record (EMR), was notable for a history of chronic obstructive pulmonary disease, epilepsy, osteoarthritis, a "psychiatric illness" believed to be bipolar disorder, hypertension, and severe osteoarthritis, which led her to rely on a wheelchair. However, her last EMR entry was 14 months earlier. Per her records, she lived in an apartment with a roommate. She had a 25+ pack-year smoking history and a history of ethanol abuse. Her outpatient medications were listed as clonazepam 0.5 mg twice daily, amlodipine 10 mg daily, losartan 100 mg daily, and citalopram 20 mg daily. Because of altered mental status, computerized tomography of the head was obtained and was negative except for mild periventricular white matter changes. After stabilization in the emergency department with placement of an intravenous line delivering 5% dextrose in normal saline at 125 ml/hour, she was admitted to the medical service.

On examination, she was a chronically ill-appearing, lethargic, disheveled woman appearing older than her listed age. She was flushed throughout her body. She was febrile to 38.2 °C, blood pressure 107/43 mm Hg, heart rate 125 beats/minutes and regular, respiratory rate 28 breaths/minutes, and

O_2 saturation 98% on room age. Her oral mucus membranes were dry, heart exam revealed regular rate and rhythm, and her lungs were clear to auscultation. On neurological examination, she had diffusely increased muscle tone, greater in the lower extremities. When she held her arms out straight, there was a fine hand tremor. Her biceps and ankle reflexes were 3+ with 16-beat clonus of the right ankle and sustained clonus of the left ankle when flexed abruptly. She had 20° flexion contractures of both knees, and there was marked involuntary resistance to further flexion. On mental status examination, she was arousable only with deep sternal rub and would follow one-step commands only for a few seconds before drifting off to sleep. She could not provide a coherent history.

Her alcohol level was 44 mg/dL (9.52 mmol/L). Her complete blood count was notable for a hemoglobin of 9.7 g/dL (97 g/L); her white cell count was within normal limits. Her blood urea nitrogen was low at 6 mg/dL (2.14 mmol/L), and her creatinine was 0.6 mg/dL (53 µmol/L). Her urinalysis was a dirty specimen with lots of squamous epithelial cells and many bacteria per high-power field; urine dipstick was 1+ nitrite positive and heme positive without red cells. Urine was sent for culture and sensitivity. A gas chromatography toxicology screen returned 12 hours after admission, positive for citalopram and methamphetamines.

The following morning, the patient was more arousable, although still delirious based on the Confusion Assessment Method. Her temperature was 38.5 °C (101.3 °F) and blood pressure 162/94 mm Hg. Her muscle tone remained increased, especially in the lower extremities, but was improved from the night before. Because of her fever and "dirty" urine, she was empirically given 1 g of ceftriaxone for a presumptive urinary tract infection.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. Was the management of her agitation appropriate?

? Question 2. What is her presumptive diagnosis and what is the appropriate management going forward?

Case 1 Answers

Case 1 Answer 1 (Question 1—Was the management of her agitation appropriate?)

The patient's was reportedly uncooperative, yelling, and resisting care in the emergency department. She was given a "cocktail" consisting first of haloperidol, followed by a short- and then intermediate-acting benzodiazepine. Based on her examination findings of increased tone, tremor, borderline hyperreflexia, and clonus, serotonin syndrome (SS) and neuroleptic malignant syndrome (NMS) should have come to mind. Her core temperature was within normal limits, but she had been outside in the cold rain and might have been expected to be relatively hypothermic. Her blood pressure was low, but she was also volume depleted. SS was suggested by the prescription of citalopram, a serotonergic antidepressant. She had a history of psychiatric illness and had not been seen at the medical center for over a year. Presence of an antipsychotic could not be excluded without a toxicology screen. Since NMS could not be ruled out as the cause of her neurological and motor findings, it was inappropriate to empirically administer haloperidol. Although benzodiazepines could exacerbate her confusion and confound monitoring of her mental status, they were appropriate tranquilizers in this setting. Moreover, they act as mild muscle relaxants and could help mitigate her increased motor tone, although likely were not given for that reason. Benzodiazepines, however, are second-line muscle relaxants after dantrolene. One further clue that this was SS and not NMS was her reflexes. She showed 3+ reflexes at the ankles, which is brisk but not abnormal. In older adults the ankle reflexes are commonly diminished, so 3+ can be considered borderline hyperreflexic. Hyperreflexia helps distinguish SS from NMS, in which the reflexes typically are suppressed. However, on early presentation this distinction should not have been considered definitive and haloperidol ideally should not have been administered in the emergency department.

Case 1 (Continued)

After the presumptive diagnosis of serotonin syndrome made in the morning after admission, a creatine kinase (CK) level returned at 3660 U/L. The infusion rate of the normal saline was increased to 200 ml/hour to increase her urine output to approximately 150 ml/hour. She was monitored every 4 hours for signs and symptoms of fluid overload, and after 16 hours of forced diuresis, she became dyspneic and was found to have an increased respiratory rate to 36 breaths/minutes, jugular venous distention, and crackles 1/3 up her posterior lung fields. A single dose of intravenous furosemide 40 mg was administered with improvement in her symptoms. Her urine culture at 24 hours showed no growth. Her creatinine had doubled from 0.6 mg/dL (53 µmol/L) to 1.2 mg/dL (106 µmol/L).

On hospital day 3, she was more alert, conversant, and cooperative, but remained disoriented to time and place. Her clonus was reduced to 4 beats, her motor tone was minimally increased, her ankle reflexes were 1+, and her tremor had disappeared. Normal saline was continued, but the rate was reduced to 100 cc/hour when her CK level dropped to 1820 U/L. By hospital day 4, her CK dropped below 1000 U/L and the IV infusion was stopped. Her serum creatinine remained stable at 1.2 mg/dL (106 µmol/L). A psychiatric consultation found that she had decisional capacity, with a Mini Mental State Exam score of 28/30, missing only the day of the week and the day's date. They confirmed that she had been taking citalopram 10 mg daily as an outpatient and recommended restarting the SSRI before she developed withdrawal symptoms. Although the medical team strongly recommended discharge to a skilled nursing facility for rehabilitation, she insisted on being discharged back to her

apartment. The team asked the social worker to report her to Adult Protective Services for possible self-neglect. She was discharged home on hospital day 5 with a creatinine trending downward at 0.9 mg/dL (89 μmol/L).

Case 1 Answer 2 (Question 2—What is her presumptive diagnosis and what is the appropriate management going forward?)

The constellation of signs and symptoms plus her toxicology screen confirm the diagnosis of moderately severe serotonin syndrome. The formal diagnosis was not made until early in the second hospital day due to the delay in obtaining the results of the toxicology screen. However, the presence of severe muscle rigidity and heme positivity without hematuria should have raised immediate concern for rhabdomyolysis. A creatine kinase level should have been obtained much earlier and muscle relaxants started empirically. Cyproheptadine, a serotonin (5-HT_{2A}) and histamine (H1) antagonist, would have been the preferred choice, although as an antihistamine, it has anticholinergic side effects that could have contributed to Ms. G.'s delirium. Dantrolene could have been used for the muscle spasms, which carries a lower delirium risk than diazepam, which, for muscle relaxation, would have required doses that would have significantly sedated her and clouded evaluation of her mental status. The patient's fever easily could have been caused by the rhabdomyolysis. Her initial IV fluid rate should have been higher, given her volume depletion and need to prevent renal tubular toxicity by myoglobin.

Case 1 Analysis This case illustrates that serotonin syndrome can easily be missed, with the symptoms in Ms. G. masked by agitation and limited cooperation, resulting in her motor findings initially being overlooked. Her initial agitation was attributed to her underlying psychiatric illness and later to her use of amphetamines, although agitation is a key component of serotonin syndrome (Fig. 5.4). Even when her motor findings were noted, the team failed to suspect rhabdomyolysis until the following morning, at which time appropriately aggressive forced diuresis was initiated. However, by that time myoglobin-induced acute kidney injury already had taken place. Cyproheptadine arguably should have been given, although her motor rigidity and rhabdomyolysis improved without it. Her serotonin syndrome likely was precipitated by recreational methamphetamine use, adding to the serotonergic agonism of her SSRI (Table 5.7).

5.2.2 Case 2

Case 2 History

Ms. A. was a 72-year-old woman with a history of left non-small cell lung carcinoma with brain metastasis. She had received combination therapy with chemotherapy and cranial radiation and was clinically stable without apparent tumor recurrence. She was a former heavy smoker, now abstinent for 10 years. Medical history also included coronary artery disease with congestive heart failure, hypertension, hyperlipidemia, hyperthyroidism, and recurrent urinary tract infections. Shortly after diagnosis of the CNS metastatic spread of lung cancer, she developed major depressive disorder and was treated with citalopram, 20 mg per day. Before starting citalopram, her serum sodium level was 130 mEq/L (mmol/L) (normal, 135–145 mEq/L [mmol/L]); pretreatment MoCA was 27 out of 30, and Hamilton Depression Inventory score was 20, consistent with a diagnosis of major depressive disorder. She had sleep and appetite disturbances and mild difficulties with concentration, but had no evidence of psychotic symptoms or suicidal ideation.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What surveillance is indicated for mild hyponatremia (without delirium) in a patient on SSRI treatment?

Question 2. What can explain the presentation of delirium and hyponatremia in this patient?

Question 3. What medication options are considered for depression in a patient who has recovered from SSRI-associated SIADH?

Case 2 Answers

Case 2 Answer 1 (Question 1—What surveillance is indicated for mild hyponatremia (without delirium) in a patient on SSRI treatment?)

Continuing periodic monitoring of her electrolyte panel and cognitive status is indicated in the context of depression management. Within 1 month of starting citalopram, Ms. A. developed cognitive impairment with reduced level of consciousness and was acutely unable to accomplish activities of daily living. Due to acute mental status changes in a cancer patient, she was admitted to the hospital for comprehensive evaluation. Magnetic resonance imaging of her brain showed decreased size of the heretofore documented metastatic lesions, without evidence of edema. She had mild cortical atrophy and white matter disease but no evidence of stroke or any other acute CNS process. Serum sodium was 121 mEq/L(mmol/L); the rest of the renal panel was normal. Serum osmolality was 268 mOsm/kg, urine osmolality was 472 mOsm/kg, and urine sodium was 131 mEq/L (mmol/L). Liver-associated enzymes were normal, as were TSH, B_{12}, calcium, and vitamin D levels.

A psychiatric consultation-liaison service examination revealed mild somnolence (RASS −1; drowsy on approach with prompt full arousal to speech with sustained eye contact), blunted and perplexedly dysphoric affect, no suicidal/homicidal ideations, and no psychosis. Thought processes

were mildly perseverative with some tangentially. MoCA score was 18 out of 30, with deficits in recall memory, orientation, and concentration most prominently noted. The rest of the psychiatric consultation was unremarkable.

Case 2 Answer 2 (Question 2—What can explain the presentation of delirium and hyponatremia in this patient?)

Ms. A. was diagnosed with delirium due to SIADH/hyponatremia, attributable to citalopram, with additional risk factors of lung cancer and CNS metastatic disease. Citalopram was immediately discontinued, and electrolyte levels and volume status were monitored daily. Her level of consciousness and cognitive function gradually improved, with normal level of consciousness (RASS 0; alert, calm) and improved MoCA (score of 25, with residual deficits in recall and concentration) within 6 days. She was discharged on hospital day 7, with a serum sodium level of 130 mEq/L (mmol/L) and renormalized serum and urine osmolality. Her mood continued to be mildly depressed, and she was prescribed mirtazapine 7.5 mg po qhs with a plan for monitoring of renal panels every 2 weeks for 3 months for surveillance for possible recurrence of SIADH.

Case 2 Answer 3 (Question 3—What medication options are considered for depression in a patient who has recovered from SSRI-associated SIADH?)

Most antidepressants have been at least anecdotally associated with SIADH, though the risk appears most dramatic for SSRI and SNRIs. Based on the current state of the literature, these classes of antidepressants are likely best avoided in these patients, with other antidepressants used, but with continued vigilance for recurrence of SIADH.

Case 2 Analysis The syndrome of inappropriate antidiuretic hormone (SIADH) is associated with systemic demographic and illness factors (e.g., increased age, malignancy, pulmonary disease, brain lesions) and medications (e.g., thiazide diuretics, vincristine, cyclophosphamide). Many classes of psychotropic medications have been associated with SIADH (e.g., SSRIs, SNRIs, mirtazapine, carbamazepine, antipsychotics, tricyclic antidepressants, monoamine oxidase inhibitors). With sufficiently low serum sodium, patients may develop delirium as the presenting syndrome. Clinical evaluation reveals hyponatremia, normal blood urea nitrogen and creatinine levels, a normal volume status, decreased serum osmolality, and increased urine osmolality. If sodium levels are 120–134 mEq/L (mmol/L), reversal of the provocative stimulus, fluid restriction, and monitoring of electrolyte and fluid status may be adequate to reverse hyponatremia. More severe hyponatremia may require cautious administration of hypertonic saline, with or without a loop diuretic to remove excess salt and water. Excessively rapid correction of severe hyponatremia may result in central pontine myelinolysis.

In this patient's case, the SSRI-associated SIADH risk was potentiated by lung cancer with CNS metastatic disease. The precipitous drop in sodium level shortly after SSRI initiation and a similarly brisk return toward eunatremia after SSRI discontinuation correlated with onset and later resolution of her delirium. For continued antidepressant treatment, choice of a non-SSRI antidepressant (in this case mirtazapine or bupropion) may minimize risk of SIADH recurrence, but continued vigilance (especially during the first 3 months of the new treatment) is needed for surveillance. At any time during antidepressant treatment, a presentation of delirium mandates immediate assessment of serum sodium, serum and urine osmolalities, assessment of fluid status, and search for other possible causes of SIADH.

5.3 Key Points: Pharmacotherapy, Safe Prescribing and Adverse Drug Events

- Age-related changes in drug metabolism and action increase the vulnerability of older patients to adverse drug reactions.
- Polypharmacy, arising from age-associated multimorbidity, adds to the risk of adverse drug events (ADEs), as does the prescription of potentially inappropriate medications (PIMs).
- Often overlooked are important interactions between drugs and over-the-counter supplements and food-drug interactions.
- Older adults are particularly vulnerable to complications from anticholinergic drugs, which span numerous classes of medication and include numerous psychotropic medications.
- Lithium continues to be prescribed to older adults but is associated with an increased risk of toxicity because of age-related changes.
- Falls and fall risk increase with age and have also been associated with psychoactive drugs, especially antidepressants.
- Other adverse reactions to which older patients are more susceptible include QTc prolongation and risk of ventricular tachycardia, hyponatremia from drugs inducing the syndrome of inappropriate antidiuretic hormone (SIADH), and bleeding from serotonergic drugs.
- Neuroleptic malignant syndrome and serotonin syndrome, although rare, are life-threatening conditions that can easily be missed in their early stages because the symptoms mimic other conditions commonly seen in older patients.
- Tables 5.8 and 5.9 provide a summary of the common adverse drug events by class and the key points to remember regarding psychotropic medications for the older adults.

Table 5.8 Summary of common adverse drug events by class of psychotropic medication

Drug class	Examples	Side effect concerns	Conditions associated with increased risk for adverse events	Comments
Antipsychotics	Phenothiazines	EPS/parkinsonism	Parkinson disease and other parkinsonian disorders (e.g., Lewy body disease)	Avoid antipsychotics with higher D_2 receptor potency to minimize risk of drug-induced parkinsonism (D_2 receptor potency: risperidone > olanzapine > quetiapine)
		Anticholinergic effects	(See conditions listed for anticholinergic effects of tricyclics)	Concomitant use of other anticholinergic drugs
	Haloperidol	Orthostatic hypotension	Parkinsonian disorders	High incidence of autonomic dysfunction in Parkinson disease
			Known orthostatic hypotension	Caution in patients on antihypertensives
	Atypical antipsychotics		Pre-existing orthostatic hypotension	Orthostatic hypotension affects ~1/3 of patients ≥ age 75
		Seizures		May lower seizure threshold
		Excess sedation		May contribute to falls and fall-related injuries
		QTc prolongation	Known QTc prolongation, history of ventricular tachycardia	Use with caution with SSRIs and SNRIs, especially citalopram, as well as with macrolide antibiotics, cardiac medications like amiodarone
		Falls and fall-related injury	History of falls	Use caution when using concurrently with antidepressants, benzodiazepines, anticonvulsants, which increase fall risk
		Glucose intolerance and weight gain	Diabetes mellitus	Concurrent use of mirtazapine may exacerbate weight gain
			Obesity	
Antidepressants	Tricyclics (e.g., amitriptyline)	Anticholinergic side effects	Glaucoma	May precipitate acute, vision-threatening rise in intraocular pressure in narrow-angle glaucoma
			Delirium	Use cautiously with other anticholinergic medications (see Table 5.4)
			Benign prostatic hypertrophy	May precipitate urinary retention
		Increased fall risk	History of falls	
	SSRIs, SNRIs	SIADH	History of hyponatremia	Concurrent use of sodium-lowering medications (e.g., diuretics) or drugs also associated with SIADH (e.g., opioids)
		Increased risk of bleeding	Recent history of intracranial hemorrhage	Avoid or use with caution in patients taking anticoagulant or patients taking platelet inhibitor (e.g., aspirin)
			Recurrent gastrointestinal bleeding	
		Serotonin syndrome		Use with caution with other serotonergic agents
		QTc prolongation	Known QTc prolongation, history of ventricular tachycardia	Use with caution with SSRIs and SNRIs, especially citalopram, as well as with macrolide antibiotics, cardiac medications like amiodarone.

(continued)

Table 5.8 (continued)

Drug class	Examples	Side effect concerns	Conditions associated with increased risk for adverse events	Comments
	Paroxetine, fluoxetine (SSRIs)	Drug-drug interactions		Prolonged half-lives (especially fluoxetine). May interact with drugs metabolized by CYP450 pathway
	Bupropion	Lowers seizure threshold	Active seizure disorder	Use with caution with other drugs which may lower seizure threshold. Concomitant use of SSRI or SNRI increases risk of serotonin syndrome
			Recent intracranial injury or stroke	Period of increased seizure risk
Anxiolytics	Benzodiaz-epines	Sedation	Unsteady gait	Cumulative effect with other CNS depressants
		Increased fall risk	History of falls	
		Cognitive impair-ment	Pre-existing cognitive impairment	
		Delirium	Advanced age	
		Drug dependence	Known benzodiazepine dependence/abuse; known alcohol depen-dence/abuse	Shorter-acting benzodiazepines (e.g., alprazolam) have higher risk of drug dependence
Sedative-hypnotics	Non-benzodiaz-epine, benzodiazepine receptor-binding drugs	Daytime sedation Increased fall risk	Unsteady gait History of falls	Cumulative effect with other CNS depressants
	Zolpidem			
	Temazepam			
	Flurazepam			
	Estazolam			
	Eszopiclone			
	Triazolam			
Mood stabilizers	Carbamazepine	Sedation	Unsteady gait	Narrow therapeutic index; levels may be increased by CYP3A4 inhibitors
		Fatigue	History of falls	Use with caution with other drugs that may lower serum sodium (e.g., SSRIs, diuretics)
		Ataxia		
		Increased fall risk		
		Blurred vision		
		Hyponatremia (SIADH) Hepatotoxicity Blood dyscrasias	History of hyponatremia Liver disease Anemia, neutropenia	
	Valproic acid	Hepatotoxicity	Liver disease	Cumulative effect with other CNS depressants
		Hyperammonemia	Urea cycle enzyme deficiency	

Table 5.8 (continued)

Drug class	Examples	Side effect concerns	Conditions associated with increased risk for adverse events	Comments
		Pancreatitis	History of pancreatitis	
Cognitive enhancers	Cholinesterase inhibitors			
	Donepezil Rivastigmine Galantamine	Gastrointestinal intolerance (anorexia, nausea, diarrhea)		If symptoms resolve after lowering dose or stopping, may not return if rechallenge with same drug or different drug from same class
		Vivid dreams		
		Fatigue		
		Bradycardia (heart rate < 60)		Exaggerates neurocardiogenic dysautonomia seen in Alzheimer disease
		Syncope		Avoid or use with caution when taking drugs which slow heart rate or affect cardiac conduction (beta blockers, digoxin, verapamil)

Adapted from Hirsch et al. [11]

Table 5.9 Summary of teaching points on Adverse Drug Events (ADEs)

Keys to safe prescribing for the older patient
Safe prescribing of psychotropic medication to older patients is especially challenging because of the prevalence of age-associated changes in pharmacokinetics and pharmacodynamics and polypharmacy caused by multimorbidity, increasing the risk of ADEs
All clinicians should be familiar with at least one tool to identify potentially inappropriate medications in the older patient, which are associated with an excessive risk of adverse reactions compared to benefits when safer alternatives exist
All older patients seen in psychiatric consultation require a careful review of their medications and assessment of the risk for drug interactions and side effects before prescribing
Medication review should include over-the-counter medications and unregulated supplements, which can have significant interactions with prescribed drugs
The patient's diet is important and may affect drug absorption, kinetics, and the risk of ADEs
In older adults, adverse events not only can be life-threatening (torsades de pointes, neuroleptic malignant syndrome, and serotonin syndrome), but can lead to injuries, functional impairment, disability, impaired quality of life, and premature mortality (falls and syncope)
Safe prescribing equals prudent prescribing

5.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following antipsychotics has the highest risk of diabetes mellitus?

A. Olanzapine
B. Haloperidol
C. Quetiapine
D. Aripiprazole
E. Risperidone

Answer: A

Whereas all atypical antipsychotics have been associated with the development of the metabolic syndrome, both typical and atypical antipsychotics have been associated with the development of hyperglycemia. Among the given options, olanzapine is associated with the highest risk of diabetes mellitus (statement A) (see ▶ section Antipsychotics and Metabolic Syndrome for further details).

MCQ 2. Which of the following antipsychotics has the highest degree of anticholinergic effect and thus would be problematic in delirium?

A. Clozapine
B. Haloperidol
C. Risperidone
D. Olanzapine
E. Aripiprazole

Answer: A

It is difficult to predict the likelihood of anticholinergic side effects occurring with various doses of antipsychotics. However, the atypical antipsychotics clozapine and olanzapine have significant affinity for the muscarinic receptors, while haloperidol, risperidone, and aripiprazole do not. Therapeutic doses of clozapine, and to a lesser extent olanzapine, are associated with clinically relevant anticholinergic activity; therefore, the correct answer is A.

MCQ 3. Which of the following mood stabilizers used for bipolar disorder has a risk of hyperammonemia, which may present as delirium?

A. Lithium
B. Carbamazepine
C. Oxcarbazepine
D. Olanzapine
E. Valproate

Answer: E

Although cases of carbamazepine and olanzapine-induced hyperammonemia have been reported [76, 77], oxcarbazepine did not show significant effects on the increase in blood ammonia level. Lithium is known to cause renal, not hepatic dysfunction. However, the use of valproate frequently results in hyperammonemia and delirium. Valproate-induced hyperammonemic encephalopathy and delirium may even occur in patients with normal liver function, despite normal doses and serum levels of valproate. Therefore, statement E is correct.

MCQ 4. Which of the following SSRIs is most likely to induce problematic drug-drug interaction?

A. Sertraline
B. Escitalopram
C. Citalopram
D. Fluoxetine

Answer: D

Of the SSRIs, fluoxetine is generally not recommended for treatment in older adults because of its long half-life, prolonged side effects, and drug-drug interactions. Although not included as an answer option, paroxetine is also generally not recommended in older adults as it has the greatest anticholinergic effect of all the SSRIs, similar to that of some tricyclics (desipramine and nortriptyline). The SSRIs considered to have the best safety profile in older adults are sertraline, escitalopram, and citalopram, which have the lowest potential for drug-drug interactions based on their cytochrome P450 interactions, whereas fluoxetine, paroxetine, and fluvoxamine have higher risks of drug-drug interactions. Therefore, statement D is the correct answer.

MCQ 5. What mechanism is causative of the orthostatic hypotension seen with quetiapine?

A. Dopamine-4 blockade
B. Dopamine-2 blockade
C. Histamine-1 blockade
D. Alpha-2 agonism
E. Alpha-1 blockade

Answer: E

Quetiapine has affinity for D_2, 5-HT_{1A}, 5-HT_{2A}, H1, and alpha-1 receptors. Alpha-1 antagonism can cause orthostatic hypotension (statement E). Quetiapine is a strong antagonist at histamine H1 receptors, which is linked to sedative effects and weight gain, not orthostatic hypotension. The other mechanistic options (dopaminergic, alpha-2 agonistic) do not cause orthostatic hypotension.

MCQ 6. Which of the following is a common metabolic complication of lithium?

A. Hyperthyroidism
B. Hypothyroidism
C. Hyperparathyroidism
D. Hypoparathyroidism
E. Glucose dysregulation

Answer: B

Chronic administration of lithium can commonly induce hypothyroidism and less commonly hyperthyroidism. Lithium use has also been linked to hyperparathyroidism, but not hypoparathyroidism. Lithium therapy has not been associated with glucose dysregulation. Therefore, the correct answer is B.

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Somatic Therapies: Electroconvulsive Therapy

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6.1 Background

6.1.1 Introduction

Electroconvulsive therapy (ECT) is a biological treatment which involves the electrical induction of seizures as treatment for psychiatric disorders. Among various indications for its use, ECT remains the gold standard treatment for major depressive disorder.

6.1.2 History of ECT

In 1934, the Hungarian neuropsychiatrist Ladislas Joseph von Meduna chemically induced repeated seizures using camphor in a small series of patients with schizophrenia. He used this to support his theory of the biological antagonism between schizophrenia and epilepsy [1].

In 1937, the Italian neuropsychiatrists Ugo Cerletti and Lucio Bini began to induce seizures experimentally with electrical stimuli in patients with severe psychosis in an attempt to overcome problems associated with camphor, such as pain and variable efficacy [1]. ECT quickly replaced pharmacoconvulsive therapy throughout the world given its greater tolerability.

The use of ECT peaked from the early 1940s through the mid-1950s, when pharmacological antipsychotic and antidepressant medications were discovered and came into clinical use. It was around this time that ECT also became the subject of highly negative portrayals in the media and its use gradually began to decline [2].

By the mid-1980s, innovations in ECT technique, including the use of anesthesia, oxygenation, muscle relaxation, and seizure monitoring, led to a growing acceptance of this treatment modality. Physicians began to realize that some patients were intolerant to pharmacological agents and/or had symptoms that were treatment-refractory. The rapid onset of action of ECT compared to alternative treatments also further contributed to its newly increased use. Presently, over 100,000 patients annually receive ECT treatments in the USA [3].

6.1.3 The Electrical Stimulus

The goal of ECT is to induce a generalized tonic-clonic seizure via the delivery of an electrical stimulus. Ideally, this is done in a way that minimizes adverse effects, particularly with respect to memory disturbance. The electrical stimulus is given using alternating current, with a variety of waveforms. A waveform refers to the shape of the stimulus as a function of time. Historically, sine wave used to be the most common waveform used in ECT; this has been replaced by brief pulse and ultrabrief pulse waveform in modern ECT protocol.

Sine-wave currents are characterized by a continuous stream of electricity that flows in alternate directions (alternating current). Like sine wave, brief pulse is also bidirectional, but instead of the continuously undulating sine wave, brief pulse consists of a series of rising and falling rectangular pulses of current which are separated by brief periods of no baseline electrical activity.

Pulse width refers to the duration of each pulse. Wider pulse widths are less efficient at inducing seizures and are therefore associated with higher seizure thresholds. They are also associated with a greater impact on cognition than narrower pulse widths. Stimuli between 0.5 and 2 milliseconds are called brief, and those less than 0.5 milliseconds are known as ultrabrief. The number of pulses per second is referred to as the frequency of stimulus and is measured in Hertz (Hz). Seizure threshold refers to the total amount of electricity required to induce an adequate seizure and is an integral part of stimulus dosing in ECT. Evoking a generalized seizure using a brief pulse waveform typically requires much less stimulus intensity compared to a sine-wave stimulus.

The electrical stimulus is characterized by current, voltage, and impedance. Current refers to the number of electrons per second flowing through the ECT device, stimulus cables, electrodes, and the patient. Voltage is the force that drives the flow of electrons during the stimulus, and impedance refers to the level of resistance to the current flow that needs to be overcome. The greater the impedance, the greater the voltage that is required for the flow of electrons.

The primary source of impedance is scalp tissue that underlies the electrodes. Most of the electrical stimulus is dissipated in the scalp and skull; only a small fraction of stimulus energy actually reaches the brain. Impedance can be too high when the stimulus electrodes are in poor contact with the skin, when there is faulty connection of the electrodes, or when the scalp is poorly prepared for ECT. Modern devices have safety mechanisms so that the user cannot deliver the stimulus if the impedance is too high. It is possible for the impedance to be too low, indicating a short circuit. Too-low scalp impedance can occur when the ECT electrodes are placed too close together or when a conducting medium like electrode gel forms a low impedance pathway between the electrodes.

All modern ECT devices utilize a bidirectional, constant-current, brief pulse stimulus waveform. This waveform is more efficient than the older sine wave for inducing seizures and allows ECT to be administered with fewer adverse cognitive effects [4]. The use of the ultrabrief pulse, which is a more efficient way to induce seizures stimulus, is associated with less memory impairment. It may also be associated with a slightly more delayed and less robust antidepressant effect, although evidence to support its use is accumulating [5]. ◘ Figure 6.1 shows examples of waveforms used in ECT.

6.1.4 Electrode Placement

The electrical stimulus can be delivered through a variety of electrode placements. Standard electrode placements used in modern ECT practice will be described further.

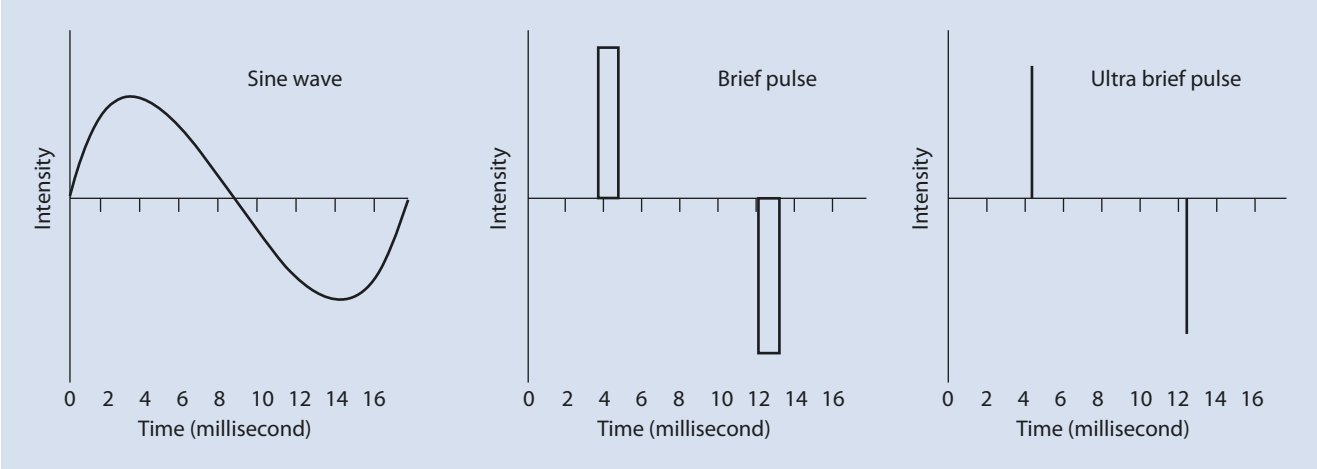

Fig. 6.1 Examples of waveforms used in ECT

In bifrontal placement, the center of each electrode is placed 5 cm above the outer canthus of the eye along a vertical line perpendicular to a line connecting the pupils. In bitemporal placement, the center of the stimulus electrodes is applied 2–3 cm (1 inch) above the midpoint of the line connecting the outer canthus of the eye and the external auditory meatus on each side of the patient's head. In right unilateral (d'Elia) placement, one electrode is positioned as in bitemporal on the right side, and the center of the other electrode is placed 2–3 cm to the right of the vertex of the skull, on a line connecting the tragus of the ear on both sides (see Fig. 6.2).

Stimulation on the right side of the brain spares the dominant hemisphere from direct stimulation, thus perhaps sparing verbal memory. This works for right-handed patients. However, even in patients who are left-handed, language function is usually located on the left side of the brain. Because language function is predominantly located in the left hemisphere in approximately 98% of right-handed people and in 70–90% of left-handed people, it is reasonable to perform unilateral ECT on the right side, even in left-handed patients. If the patient experiences unusual severe confusion or memory impairment after the first few treatments, consideration can be given to switching to left unilateral electrode placement. A simple test of hemispheric dominance can be done by comparing the time elapsed following an ECT treatment until the patient can name simple objects [6].

Fig. 6.2 Right unilateral electrode placement

6.1.5 Stimulus Dosing

The seizure threshold is the amount of energy necessary to evoke a generalized seizure. For a therapeutic seizure, the minimum recommended duration of the seizure is 20 seconds of motor response or 25 seconds of electroencephalogram (EEG) seizure. This is a rule of thumb to which there are exceptions. Shorter seizures late in the treatment course may still be effective despite their short duration, and shorter seizures at higher stimulus intensities can also be effective. Determination of treatment adequacy is based on clinical outcome rather than the number of seconds of seizure activity. Seizures tend to be shorter in older patients and to diminish in length over the course of treatment [7]. Seizure duration may also be affected by other parameters including dose of the anesthetic agent used and the amount by which the stimulus exceeds the seizure threshold.

There are many factors which influence an individual's seizure threshold, including age, sex, placement of stimulus electrodes, concomitant psychotropic medications, and

anesthetic agents. These are listed in Table 6.1. Age is one of the principal factors affecting seizure threshold; there is, however, significant interindividual variation in this parameter.

There are various methods of determining the dosing of the electrical stimulus. The preferred method in most cases is stimulus dose titration, in which the seizure threshold is determined empirically by a series of stimuli of increasing intensity, and the treatment is given at a predetermined multiple of the seizure threshold (1.5 × threshold for bitemporal/bifrontal ECT, 6 × threshold for right unilateral ECT). This method allows for the most accurate determination of the energy required for effective ECT for an individual, minimizing the energy administered and therefore minimizing cognitive side effects. It is, however, associated with some risks. It requires multiple subconvulsive stimuli, which increase the risk of bradycardia or asystole. It may also mean that the first treatment is less effective. This method requires efficiency on the part of the ECT practitioner to ensure that the patient has a seizure during the first treatment session. On average, however, only one restimulation is necessary at the first treatment [8].

Other methods of determining the dose of ECT include age-based dosing in which the dose of ECT is estimated based on a patient's age and on the desired electrode placement and fixed high dose, in which all patients receive the same dose of stimulus, usually at a relatively high level (e.g., 50–100% of the device's maximum output intensity) [9]. These techniques do not match stimulus intensity with seizure threshold and may result in stimulation of many patients at doses much higher than seizure threshold, as well as potentially underdosing patients receiving right unilateral ECT. They are associated with greater simplicity on the part of users, however, and reduce the risk associated with subconvulsive stimuli.

Table 6.1 Factors influencing seizure threshold

Factor	Lower seizure threshold	Higher seizure threshold
Age	Younger	Older
Sex	Female	Male
Brain disease	Irritative	Diffuse, nonirritative
Electrode placement	Unilateral	Bilateral
Electrode application	Good application	Poor application
Medication	Alcohol or benzodiazepine withdrawal Amphetamines Lithium Tricyclic antidepressants Reserpine	Anticonvulsants Barbiturates Benzodiazepines
Seizure activity	Seizures within last few minutes	Seizures within last few days

Older patients are more vulnerable to the cognitive side effects of ECT and are also more likely to have conditions associated with risk for cardiac arrhythmias. Under most circumstances, stimulus dose titration and careful collaboration with the anesthesiologist regarding the management of bradyarrhythmia risk are the recommended approaches for older patients.

6.1.6 Seizure Monitoring

Following delivery of the electrical stimulus, monitoring of the generalized seizure is done by observing both the ictal motor response and the EEG activity. In the first phase of the ictal motor response, a gradual, sustained tonic contraction usually occurs within a few seconds after termination of the stimulus and may last from a few seconds to many seconds. It is then followed by the clonic phase characterized by rhythmic alterations in flexion and extension that decrease in frequency and then terminate. This phase typically lasts longer than the tonic phase.

Motor activity can be influenced by the dose of muscle relaxant, usually succinylcholine, and intensity of the electrical stimulation. Response to stimuli barely above threshold may sometimes be decreased or absent, and convulsive movements may not always end simultaneously in all locations [10]. The American Psychiatric Association in 1990 recommended that the end of the motor convulsion be determined by the longest-lasting motor activity observed anywhere in the body [11].

Two EEG leads are generally monitored, one on each side of the head. In this way, seizure activity in both hemispheres is monitored separately. Electrodes are placed over the prefrontal and mastoid areas on the same side of the head. Contact between the electrode and scalp must be optimized by cleaning the recording electrode sites. ECT devices generally begin recording following the administration of the electrical stimulus.

Preictal baseline recordings often consist of mixed fast and slow activity that may be higher in amplitude than that observed during the waking state. Following the electrical stimulus, sometimes a brief preictal period of low amplitude fast activity may be observed. This may be followed by rhythmic activity of low to moderate amplitude, known as the epileptic recruiting rhythm, associated with the early stages of seizure generalization. Both the preictal and epileptic recruiting rhythm phases are frequently absent. Often the earliest phase of the seizure is characterized by high frequency polyspike activity. It coincides with tonic and early clonic components of the motor response and lasts 10–15 seconds. During the clonic phase, this polyspike activity evolves into a repetitive polyspike and slow wave complexes, synchronous with clonic movements. The frequency of these discharges is usually 3–5 Hz and diminishes gradually in frequency as the clonic phase progresses toward termination. In this phase, the amplitude and regularity of the polyspike and slow wave pattern gradually diminish and may end abruptly. The

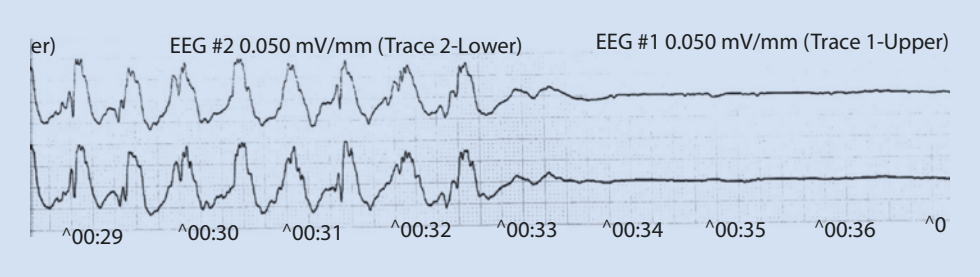

Fig. 6.3 EEG seizure termination

postictal phase begins immediately following EEG seizure termination and usually appears flat. A sample EEG seizure termination appears in Fig. 6.3.

6.1.7 Mechanism of Action

The exact mechanism by which ECT exerts its antidepressant and antipsychotic actions remains unknown. It is widely hypothesized that ECT works by promoting the increased availability of neurotransmitters including serotonin, norepinephrine, and dopamine at the synapse with subsequent modulation of postsynaptic receptors, analogous to the mechanism of action of many antidepressants. Anticonvulsant effects of ECT may also be central to the antidepressant properties of ECT [12]. It is also suggested that there is a correlation between both decreased cerebral blood flow and increased interictal prefrontal EEG and clinical response to ECT [13]. Restoration of normal patterns of activity in brain networks may play an important role in the mechanism of efficacy of ECT.

6.1.8 Cardiovascular Response to ECT

Following the initial electrical stimulus, parasympathetic activation occurs due to the direct stimulation of the brainstem nuclei. This results in a drop in blood pressure and transient sinus bradycardia (which lasts several seconds). As soon as the seizure begins, sympathetic nervous system activation begins which causes blood pressure and heart rate to increase dramatically. This continues until the end of the clonic phase when parasympathetic system is reactivated. Upon the patient's awakening, these events are then followed by a second phase of sympathetic hyperactivity. Usually, vital signs return to baseline within minutes of the end of the ictal period.

6.1.9 Pre-ECT Evaluation

ECT operating psychiatrists, medical consultants, and anesthesiologists must work collaboratively both prior to and during a course of ECT. Basic components of the pre-ECT evaluation should include a thorough psychiatric history including history of previous response to ECT; a medical history and physical examination with focus on cardiovascular, respiratory, neurological, and musculoskeletal systems; a history of dental problems and examination for loose or missing teeth; and a history of anesthesia use both personally and within the family [14]. Any personal or family history of complications from anesthesia should be noted. Although there is no specific set of routine investigations recommended, laboratory tests generally performed include a complete blood count, serum chemistry with sodium and potassium, as well as an electrocardiogram. A chest x-ray is indicated in patients with cardiovascular or pulmonary disease or with a history of smoking [15].

Decisions regarding additional investigations prior to ECT should be individualized. Testing of cerebral functioning including electroencephalographic (EEG), neuroimaging, or neuropsychological assessments can be considered where there are specific concerns. Spinal radiographs should also be considered in patients with known or suspected spinal disease. When the risks of ECT in the setting of the existing systemic medical disease are unclear, further testing and/or consultation should be considered.

An evaluation of the risks of cognitive impairment should be considered in every case pre-ECT. The Mini Mental State Examination (MMSE) is the most commonly used bedside rating scale to monitor global cognitive changes [16]. It may however not be very sensitive to changes in anterograde or retrograde amnesia [17]. Other, more sensitive tests such as the Montreal Cognitive Assessment (MoCA) also have limitations with respect to the time associated with administration, learning effects, and lack of specificity to autobiographical memory loss. The pre-ECT cognitive evaluation and the patient's values and preferences should guide recommendations about treatment technique in terms of electrode placement, treatment frequency, dosing, and medications to be avoided. Cognition and autobiographical memory should be monitored during ECT, both by clinical history and by objective measures according to the clinician's judgment.

6.1.10 Informed Consent

Informed consent in the geriatric population requires special consideration because decisional capacity to consent to ECT treatment may be compromised from cognitive dysfunction or severe psychiatric illness [18]. The process of informed consent begins with the provision of information about the ECT treatment and signing of the consent document. Written consent is the standard for ECT. This process continues throughout the entire course of ECT treatment; it should be made clear that the patient or their surrogate

(substitute) decision maker can withdraw consent at any time. It is the responsibility of the operating psychiatrist to ensure that the appropriate information has been conveyed regarding risks and benefits specific to that patient and that the patient has had a chance to ask questions about the procedure. The physician should provide information about the nature of the condition being treated; a description of how, when, and where ECT will be performed; typical numbers of treatment sessions; and the expected benefits and possible risks of ECT including death, cardiac complications, and cognitive impairment. Information should also be provided about practical considerations during the course of ECT, including taking nothing by mouth after midnight prior to the day of treatment and that emergency treatment may be necessary if the patient has a complication during an ECT treatment. The physician should also confirm that the patient has understood the information provided as well as appreciates the benefits and risks of other reasonable alternative treatments or no treatment. Consent to ECT must be voluntary and must be obtained from the patient unless the patient is considered decisionally incapable. In some jurisdictions, surrogate consent for involuntary ECT for a decisionally incapable patient is not allowed under the law, and a formal judicial consent may be needed. For incapable patients, surrogate consent should be obtained prior to treatment with ECT in accordance with the legal requirements of the local jurisdiction. The discussion should be documented in the patient's medical record.

6.1.11 Management of Medications

In treatment of major depressive disorder, combining ECT with an antidepressant such as venlafaxine or nortriptyline can improve remission rates by approximately 15% [19]. Some psychotropic medications are probably best avoided or maintained at the lowest possible doses during ECT. Lithium may increase the risk of delirium or prolonged seizures, and so in general it is preferable to discontinue this medication prior to ECT sessions. Data from case series suggests that lithium continuation during a course of ECT can be done without is held 24–36 hours before each ECT treatment session. The decision to continue lithium during a course of ECT, particularly in specific patients with a "brittle" depressive disorder, should be carefully considered by the treating psychiatrist [20]. Due to the anticonvulsant property of benzodiazepines and antiepileptic medications, it can be more difficult to induce a seizure, and efficacy of ECT may be decreased. If it is impossible to discontinue benzodiazepines during ECT, their action can be reversed with flumazenil just prior to the procedure, with careful attention to the possibility of withdrawal. The use of anticonvulsants during ECT depends upon the indications for use and upon the particular drug in question. ECT can be done in the presence of anticonvulsant medications, with careful observation of the adequacy of the seizure in ECT and of the patient's clinical response. If possible, the use of anticonvulsant medications should be minimized during ECT. Where it is deemed necessary to continue anticonvulsants during ECT, using the minimum effective dose and timing the ECT procedure to coincide with trough levels of the drug can be helpful strategies. Other drugs that lower seizure threshold (e.g., clozapine, bupropion, tricyclic antidepressants) may slightly increase the risk of prolonged seizures, especially when used in combination. It is usually safe to consider such medications during ECT, but caution should be exercised regarding high doses and polypharmacy.

Most medications scheduled to be administered in the morning are held until after the procedure. However, antihypertensive medications, cardioprotective medications, and anti-reflux medications are usually given in the morning prior to the procedure with sips of water. Diuretics should not be given prior to ECT because of the risk of incontinence and/or bladder rupture. Decisions regarding pre-ECT medications should be made in collaboration with the anesthesiologist.

6.1.12 Use of ECT in Geriatric Psychiatry

A large proportion of patients receiving ECT are in the geriatric age range [21]. Several factors may be attributed to the higher rate of ECT utilization in the older population. Depressive disorders can increase in severity and frequency with increasing age as the natural history of major depressive illness progresses [22]. There is also an association between high relapse rates and later onset of illness [23]. Due to age-related pharmacokinetic changes, geriatric patients have a lower tolerance to medications and are sometimes unable to tolerate adequate pharmacotherapy. In comparison to pharmacotherapy, ECT may pose less risk of complications in older patients [11]. Geriatric patients also tend to have a better response to ECT, with higher rates of response and remission than their younger counterparts. Finally, older patients have less physiological reserve and can quickly deteriorate into life-threatening situations when they stop eating and drinking and become bedbound or immobile in the context of severe depressive disorder.

6.1.13 Diagnostic Indications and Efficacy

Major Depressive Disorder

Late-life depressive disorder is a serious and growing psychiatric problem. It is a common psychiatric disorder in older adults and is associated with substantial morbidity and mortality. It also impairs quality of life and creates a substantial strain on families and communities.

The efficacy of ECT in major depressive disorder is well established [24]. It is effective in treating both melancholic and severe non-melancholic depressive disorder [25] as well as bipolar depression [26]. It has particular efficacy in treating

major depressive disorder with psychotic features [27] and is a first-line treatment for this indication. Data from comparative trials show that ECT-related antidepressant effects are greater than any pharmacologic agent, including monoamine oxidase inhibitors, heterocyclics, and serotonin reuptake inhibitors [28]. When major depressive disorder is resistant to pharmacotherapy, 50% or more respond to ECT [29]. ECT has a rapid effect and high remission rates of 75% [30] compared to 25–35% remission rates with pharmacotherapy [31]. Many older adults either fail to respond to antidepressant medications or experience intolerable side effects when taking antidepressants, so ECT can be particularly useful in this group.

Older patients with depressive disorder treated with ECT exhibit better clinical outcomes than younger patients. This was supported by the Consortium for Research in Electroconvulsive Therapy (CORE) study, which divided patients by age into groups of 18–45 years, 46–64, and 65–85 years. While 70% of the patients aged 18–45 years achieved remission, 90% achieved remission in the two older-aged samples [24]. ECT is effective in older patients with depressive disorders regardless of the age of onset. However, a 2016 prospective study of older patients found that ECT was somewhat more effective for late-onset depressive disorder than for early onset [32]. Vascular changes on MRI did not influence the chances of response to ECT.

Major depressive disorder with psychotic features has a poorer prognosis than nonpsychotic depressive disorder, is less responsive to antidepressants, and is associated with a substantially larger suicide rate (five times the rate of suicide in nonpsychotic depressive disorder). ECT has particular efficacy for depressive disorder with psychotic features, with higher remission rates and earlier improvement of symptoms [27]. It is considered first line for this indication. In a prospective trial of ECT in geriatric patients, psychotic symptoms were a predictor of response to ECT in this older group [32]. Delusions and other psychotic features also have a higher prevalence in late-onset major depressive disorder with age 60 years and older.

The time course of response to ECT can be variable and may be longer for geriatric patients [33]. ECT should therefore not be abandoned when a rapid response is not seen. The average number of treatments needed to achieve remission is between 6 and 12; however, some patients may require longer courses.

A study on the effect of ECT on mortality and clinical outcome in geriatric unipolar depression showed that older adults with major depressive disorder who received ECT lived longer and had a greater clinical improvement compared to patients who received treatment with pharmacotherapy only [34].

The Prolonging Remission in Depressed Elderly (PRIDE) [35] study evaluated the efficacy and tolerability of continuation ECT plus medication compared to only medication in depressed geriatric patients after a successful course of ECT. In phase 1 of the study, an acute course of right unilateral ultrabrief pulse ECT was combined with venlafaxine treatment. Of these patients, 70% met response criteria, and 61.7% of all patients met remission criteria. Among patients who remitted, the mean decrease in Hamilton Depression Rating Scale (Ham-D) score was 24.7 points, and the mean number of ECT sessions to achieve remission was 7.3. This corresponds to approximately 2.5 weeks of ECT, given 3 times weekly. Right unilateral ultrabrief pulse ECT, combined with venlafaxine, was shown to be a rapidly acting and highly effective treatment choice for depressed geriatric patients, with excellent safety and tolerability. Data from this study supports the efficacy of ECT to treat severe depressive disorder in geriatric patients and the rapidity of its action. In older patients, the presence of suicidal ideation or refusal to eat and drink increases the necessity for intervening rapidly. In these circumstances, ECT continues to be the treatment of choice.

Bipolar Disorder

Pharmacotherapy is the first-line treatment for bipolar disorder, as most patients with manic episodes can be managed with medications. However, some patients may be unable to tolerate adequate pharmacotherapy for age-related reasons. Lithium can be hard for older patients to tolerate for both pharmacokinetic and pharmacodynamic reasons. Older patients may experience lithium neurotoxicity (e.g., sedation, delirium, amnesia) even when lithium levels remain in the therapeutic range [36]. The use of anticonvulsants can also be limited by tolerability issues. Depressive episodes in bipolar disorder can be difficult to treat, and manic and depressive episodes can become more frequent and more difficult to treat as patients age. ECT is an alternative treatment option for geriatric patients with bipolar disorder who cannot tolerate pharmacotherapy and is useful in depressed, manic, and maintenance phases of the disorder [37].

The treatment of bipolar disorder in late life with ECT is informed primarily by the literature in the general adult population, although some of these trials included older patients. ECT is effective for bipolar depression with no difference in the degree of improvement in depressive episodes in bipolar disorder compared with unipolar depressive disorder [38]. It is effective regardless of electrode placement, with significantly more rapid clinical improvement and a shorter treatment course in bipolar disorder than in unipolar depressive disorder [39]. Several studies suggest that depressive episodes in bipolar disorder require fewer treatments with ECT than unipolar depressive disorder to achieve comparable benefits [38].

Remission rates for mania are greater than for depressive episodes in bipolar disorder after an acute course of ECT [40]. ECT had a favorable treatment outcome compared with conservative treatment in a case-control study of adult inpatients. The average length of hospital stay was 6.5 days in the ECT group and 15.3 days in the control group. Overall, symptom improvement was 96% in the ECT group and 44% in the

control group [41]. Results from a literature review found that 80% of medication-resistant patients in manic episodes achieved remission or had a significant clinical improvement following an acute course of ECT [42]. Mixed (manic and depressive) states in bipolar disorder might be more difficult to treat as evidenced by increased number of ECT treatments in a group with mixed states compared to depressive episodes [43]. In patients with frequent mood episodes, maintenance ECT can contribute to stabilization when pharmacotherapy is insufficient.

Other Disorders

Schizophrenia

In the West, ECT is used primarily for depressive and bipolar disorders. However, worldwide, schizophrenia is an important indication for ECT. In schizophrenia, several studies suggest that antipsychotic medications and ECT have comparable efficacy [44]. In clinical practice, it is most commonly used in treatment-resistant schizophrenia. Evidence also suggests that for treatment of acute psychotic episodes, a combination of antipsychotic medications and ECT may have greater efficacy than either ECT or medications alone [44]. The combination of clozapine and ECT is particularly effective for treatment-resistant schizophrenia. No evidence indicates that ECT has efficacy for the treatment of negative symptoms of schizophrenia. Case reports suggest that presence of depressive symptoms appears to increase the likelihood of response to ECT in patients with schizophrenia [45]. In older patients with schizophrenia, ECT is most commonly employed in cases of severe treatment resistance or intolerance of pharmacotherapy.

Catatonia and Neuroleptic Malignant Syndrome (NMS)

Older patients with major depressive disorder have the highest risk of catatonia [46]. ECT has been shown to be an effective and safe treatment for delirious mania with catatonic features [47]. For schizophrenia patients with catatonia who relapsed after a positive response to acute ECT, a combination of continuation ECT and antipsychotics has been shown to maintain symptom improvement [48]. Combination of benzodiazepines and ECT has also been shown in case reports to be effective for NMS, malignant catatonia, and residual or refractory catatonia [49].

Parkinson Disease and Dyskinesias

ECT is safe, effective, and well tolerated in geriatric patients with Parkinson disease and parkinsonism. It is most often used for treatment of comorbid depressive disorder but may have benefits for the motor symptoms of Parkinson disease in addition to its effects on depressive disorder. It is also effective for patients who develop psychotic symptoms or who develop antipsychotic-induced intractable movement disorders, despite discontinuation of the provocative agents [50]. It is also a useful treatment strategy when medication management for Parkinson disease fails or is not tolerated [51]. Practical considerations, such as the availability of maintenance ECT and the willingness of neurologists to employ it, may limit its use for Parkinson disease without other neuropsychiatric complications.

Major Neurocognitive Disorder (Dementia)

Major neurocognitive disorder is one of the major causes of disability in the geriatric population and is commonly complicated by behavioral disturbance. Behavioral disturbances include restlessness, wandering and hoarding, verbal or physical aggression, anxiety, depression, psychosis, and repetitive vocalizations. Some behavioral disturbances can occur in up to 90% of patients with major neurocognitive disorder. These patients may develop major depressive disorder, which can respond to ECT despite the presence of the underlying neurocognitive disorder. ECT can be used in this context when appropriate, e.g., in cases of treatment resistance or in cases where urgent treatment is required. When underlying depressive or psychotic symptoms are successfully treated with ECT, cognitive deficits may improve in some (but not all) patients with major neurocognitive disorder and concurrent major depressive disorder [52]. These patients are more vulnerable to a transient worsening of cognition during ECT, however. An emerging literature based on case series has identified ECT as a potentially effective intervention for severe, treatment-resistant agitation in patients with major neurocognitive disorder [53].

Poststroke Depressive Disorder

ECT is generally well tolerated and effective for geriatric patients with poststroke depressive disorder. Five randomized, placebo-controlled antidepressant trials for poststroke depressive disorder established that antidepressants could reduce the frequency and severity of crying episodes, but the efficacy of treating other depressive symptoms was limited [54]. A retrospective study reviewed charts of 20 geriatric patients who received ECT for poststroke depressive disorder and found that 95% of patients improved with ECT [55]. However, careful consideration should be given to the risks of increased intracranial pressure, which will inevitably occur during ECT. Factors to consider are the amount of time elapsed since the stroke, presence of anticoagulation, hemorrhagic versus ischemic stroke, and presence of cerebral aneurysms.

6.1.14 Side Effects in Geriatric Patients

Older adults may be at greater risk because of a higher prevalence of medical comorbidity, but older age itself is not a risk factor for mortality associated with ECT. There are no absolute contraindications to the use of ECT [11]. When considering the medical risks of ECT, however, the cardiovascular system and the central nervous system are two organ systems that are of critical importance; certain conditions do increase the risk of mortality (See Table 6.2).

Table 6.2 Conditions associated with increased risk in ECT

Brain lesions with increased intracranial pressure (space-occupying cerebral lesion like tumor, hematoma)
Cerebral aneurysm and other cerebrovascular malformations
High anesthetic risk (American Society of Anesthesiologists level 4 or 5)
Pheochromocytoma
Poorly compensated congestive heart failure
Recent intracerebral stroke/hemorrhage
Recent myocardial infarction
Severe cardiac valvular disease
Severe chronic obstructive pulmonary disease, asthma, or pneumonia

Mortality rates associated with ECT have declined from 2 to 10 per 100,000 ECT treatments in the 1990s to less than one per 100,000 ECT treatments in more recent studies [56]. Headaches and muscle pain are the most common side effects of ECT, usually lasting up to several hours. This may be caused by the depolarizing muscle relaxants used with ECT, most commonly succinylcholine. Other side effects include dry mouth, nausea, and fatigue. The most serious adverse effects related to ECT in the geriatric population are cardiac or pulmonary complications, post-ECT delirium/confusion, and persistent autobiographical memory impairment. Fractures during the procedure, although rare in contemporary ECT, can occur with severe osteoporosis; careful attention should be paid to the adequacy of muscle relaxation. Falls can also be a particular concern in the peri-ECT period when ECT is given to older adults.

Cardiac Complications

Patients with cardiac disease have significantly higher rate of cardiac complications during ECT compared to those without. A preexisting cardiac abnormality strongly predicts the type of cardiac complication that may occur with ECT. Physiological changes in heart rate and cardiac output during ECT challenge the cardiovascular system and occasionally in vulnerable patients lead to transient cardiac arrhythmias, particularly bradycardia, premature ventricular contractions, and/or sinus arrest. The risks of arrhythmias can be lowered in susceptible patients by pretreatment with appropriate medications, e.g., atropine and glycopyrrolate, in collaboration with the anesthesiologist.

Patients with preexisting hypertension who are unable to tolerate the hypertensive challenge during ECT may also have an increased risk of transient cardiac ischemia or myocardial infarction. Electrocardiogram (three leads) is monitored during the procedure as part of the administration of anesthesia. In addition, patients should be monitored clinically after the procedure for signs and symptoms of cardiac disease. A 12-lead electrocardiogram should be considered if cardiac complications are suspected. Uncontrolled hypertension should be treated prior to administering ECT as transient autonomic changes during ECT are usually well tolerated in older adults with controlled hypertension. There is no evidence that ECT causes sustained increased blood pressure either in hypertensive or non-hypertensive patients during ECT. Treatment for congestive heart failure should be optimized before ECT, as complication rates increase dramatically for patients with ejection fraction less than 25%. Surgical treatment may be required to correct anatomic problems associated with large aneurysms or severe valvular heart disease before ECT. Geriatric patients with unrepaired small abdominal aortic aneurysms (range 3–5.2 cm), descending aortic aneurysm, and aortic valve stenosis ($\leq$ 1 cm^2) under rigorous medical management can be successfully treated with ECT [57].

Other potential cardiotoxic effects during ECT include anoxia (prevented by adequate ventilation and muscle relaxation), rapid increase in serum potassium induced by the action of succinylcholine, or (rarely) reactions to generalized anesthesia.

Pulmonary Complications

Treatment of chronic obstructive pulmonary disease pre-ECT is essential to optimize lung capacity. Patients with obstructive sleep apnea are at increased risk of airway obstruction following the ECT procedure; anesthesiology should be consulted, and patients should bring their CPAP device with them for use in the recovery area if necessary.

Prolonged apnea during ECT may occur when succinylcholine is used as a muscle relaxant in patients with a history or family history of pseudocholinesterase deficiency. In those cases, nondepolarizing muscle relaxants can be used as an alternative. Based on individual needs, patients with active asthma should use their inhalers shortly before ECT treatment. Theophylline has been associated with a higher risk of prolonged seizures during ECT and should be avoided as a concomitant medication [58]. Theophylline is used relatively rarely in contemporary practice, but some older patients may still be taking this drug.

Postictal and Interictal Confusion

Most patients experience some transient confusion lasting a few minutes to a few hours after they wake up from an ECT treatment. Delirium and confusion post-ECT is usually transient and reversible. Geriatric patients with underlying neuropsychiatric conditions, such as major or mild neurocognitive disorder, Parkinson disease, and stroke have a higher risk of developing delirium and confusion immediately post-ECT. Other factors that may contribute to post-ECT delirium include benzodiazepine withdrawal and co-administration of ECT with pharmacological agents such as bupropion, lithium, dopaminergic drugs, and theophylline. If a patient becomes agitated, postictal sedation with a short-acting benzodiazepine such as midazolam or with a small dose of haloperidol may be necessary. Reassurance, avoidance of cognitive demands during the acute postictal period, and discontinuation of potentially offending agents

are usually all that is necessary for treatment. Post-ECT delirium with agitation tends to recur and may require prophylactic medication such as midazolam immediately following the ECT procedure, prior to moving to the recovery area. Sometimes, when a state of postictal confusion does not fully resolve, it may accumulate and develop into an interictal confusional state. In such cases, ECT may be withheld or frequency of treatments reduced to allow for cognitive recovery.

Cognitive Impairment

Memory disturbances consist of anterograde amnesia (difficulty retaining newly learned information) as well as retrograde amnesia (difficulty recalling information learned before the course of ECT). Anterograde amnesia tends to resolve over a period of days to weeks after a course of ECT. Resolution of retrograde amnesia may not be complete for some memories covering the period of ECT and is most severe for those events occurring closer in time to ECT.

Following acute treatment with ECT, cognitive deficits associated with a major depressive episode, such as impaired decision-making and working memory, tend to improve in patients as the depressive episode resolves, as they do with pharmacological treatments. A systematic review of 27 studies examined the impact of ECT on cognition in depressed older patients and concluded that apart from evidence of interictal slowing of information processing speed, there were mixed results regarding the impact of ECT on other cognitive domains. The study recommended that physicians regularly administer brief focused cognitive tests before, during, and after ECT treatment to monitor progress [59]. There is no standard brief cognitive test that accurately captures ECT-related cognitive changes; most clinicians use standard available measures such as the MMSE or MoCA.

A prospective, naturalistic study on the effectiveness of bifrontal and right unilateral ECT, which assessed depressed geriatric patients at baseline, immediately post-ECT and 3-month post-ECT, found no difference in the efficacy of ECT between the formula-based ECT groups at any time but marked differences in cognitive impairment associated with different ECT techniques [60]. Worse cognitive impairment was associated with sine wave compared with brief pulse; post-ECT cognitive deficits were greater with bilateral than right unilateral electrode placement, and retrograde amnesia for autobiographical material was greater with bilateral electrode placement than right unilateral placement in a 3-month follow-up. Most patients who received right unilateral ECT showed cognitive improvement compared to their baseline by 3 months. More cognitive side effects were also associated with higher stimulus intensity over the seizure threshold.

In a randomized controlled study comparing the effect of ECT on autobiographical memory, right unilateral ultrabrief pulse ECT was found to have better post-ECT autobiographical and anterograde memory side effect profile than right unilateral brief pulse ECT [61].

Bifrontal ECT has been thought to have a favorable cognitive profile, like right unilateral ECT. However, data supporting this have been mixed. A randomized controlled study of 65 depressed geriatric patients comparing bifrontal and right unilateral ECT found that overall the cognitive effects of ECT were similar [62]. However, a large multicenter trial in a mixed-age population did not confirm an advantage for bifrontal ECT [63]. Administration of a large number of ECT sessions (over 100 during lifetime), spread out over several courses, did not result in long-term cognitive impairment in a placebo-controlled study of cognitive function [64].

6.1.15 Continuation ECT and Maintenance ECT

Continuation ECT is intended to prevent relapse in first 6 months after remission with acute or index ECT. Maintenance ECT is intended to prevent recurrence in the period 6 months and longer after the index course of acute ECT. They are both usually provided as ambulatory treatment and indicated in patients who have an established pattern of recurrent illness and who experience symptom emergence when attempting to discontinue continuation therapy. Most patients who receive ECT are candidates for maintenance therapy, although a trial of maintenance pharmacotherapy is usually attempted first for practical reasons. In clinical practice, the distinction between continuation ECT and maintenance ECT can be blurred. Within a year of the end of an ECT course, 50–60% of depressed patients will relapse when treated with maintenance antidepressants [65]. Medication resistance during prior to the course of ECT predicts a higher rate of relapse [29].

Maintenance ECT is generally well tolerated and is as effective as maintenance pharmacotherapy in severely depressed geriatric patients after a successful course of ECT [66]. A study that assessed hospital readmission rates of older patients with severe psychiatric illness found that the number of psychiatric hospitalizations was significantly lower with 80% reduction in admissions during maintenance ECT compared to before maintenance ECT. Duration of hospital stay was significantly shorter during maintenance ECT (12 days) compared to before maintenance ECT (215 days). The average length of maintenance ECT course was 34 months. Overall, this study concluded that maintenance ECT following acute ECT significantly improved clinical outcomes [67].

Antidepressants alone reduce relapse in the post-ECT period [68]; however, the addition of lithium to an antidepressant can substantially further improve relapse rates. Sackeim et al. found that adding lithium to nortriptyline after ECT substantially reduced 6-month relapse rates (84% relapse on placebo, 60% on nortriptyline alone, and 39% on nortriptyline plus lithium) [69]. A large multicenter randomized controlled study established evidence that both continuation ECT and continuation pharmacotherapy with nortriptyline and lithium are effective in preventing relapse of depression following response to ECT. A combination of nortriptyline and lithium was equivalent to continuation ECT on a fixed dosing schedule over a 6-month period, with approximately 40% of patients relapsing over that time in both groups [69].

Attempts have been made to improve the efficacy of post-ECT maintenance treatment by allowing a flexible, symptom-titrated approach rather than a rigid fixed schedule of treatments. Phase 2 of the PRIDE study [70] compared two randomized treatment arms: a medication only arm (venlafaxine and lithium over 24 weeks); and an ECT plus medication arm (four continuation ECT treatments over 1 month, plus additional ECT as needed, using the Symptom-Titrated, Algorithm-Based Longitudinal ECT [STABLE] algorithm, while continuing venlafaxine plus lithium). The ECT plus medication group had statistically significant lower Ham-D scores than the medication only group. The difference in adjusted mean Ham-D scores at study end was 4.2. This study established that flexibly providing additional ECT treatments after achieving remission based on patient symptoms was beneficial in sustaining improvement in depression for most patients.

Maintenance ECT has shown to be effective in reducing relapse in patients with catatonic schizophrenia [71]. Combined treatment of ECT and antipsychotic drugs is superior to ECT or medication alone in relapse prevention for schizophrenia [72].

Additional ECT beyond the endpoint of an index course is valuable and feasible in maintaining the long-term antidepressant benefits of ECT in a vulnerable geriatric population. Continuing ECT after remission is beneficial in sustaining improvement in depressive symptoms for most patients. There are currently no established continuation ECT and maintenance ECT treatment schedules. Typically, treatments occur weekly during the first month post-acute ECT, then tapered to every other week in the following 1–2 months, and then tapered to monthly ECT. Frequency of treatments should be modified to meet the patient's needs and must be individualized based on clinical judgment.

6.1.16 Electroconvulsive Therapy Versus Repetitive Transcranial Magnetic Stimulation

Repetitive transcranial magnetic stimulation (rTMS) is a newer form of treatment shown to be efficacious in treating a number of disorders including severe major depression. (See ► Chap. 7.) An advantage of rTMS over ECT is that the patient does not receive anesthesia and there is no seizure induction. Therefore, it has a much safer risk profile compared to ECT. Due to its potential therapeutic efficacy and lack of side effects, use of rTMS has expanded in recent years. The effects of rTMS appear to be substantially more modest than those of ECT at the present time, although work is ongoing to optimize rTMS treatment protocols to improve response and remission rates.

The first meta-analysis in 2014 that compared ECT with rTMS included nine randomized controlled clinical trials. The study found that patients who received either rTMS or ECT had statistically significant reductions in their depressive symptoms, as measured by Ham-D. The rTMS patients had a mean reduction of 9.3 points, while ECT patients had a mean reduction of 15.4 points. When the degree of improvement between rTMS and ECT participants was analyzed, patients who received ECT showed significantly lower Ham-D scores compared to patients with rTMS. This difference became even more significant in favor of ECT when the effect size was factored into the comparison. This study confirms ECT as the leading therapeutic modality for patients with treatment-refractory depression. It also suggests the therapeutic validity of rTMS as a treatment option for depressed patients who are treatment resistant [73]. Patients who fail to respond to rTMS may respond to ECT; however, patients who fail to respond to ECT are unlikely to respond to rTMS.

6.2 Case Studies

The following case-based studies reflect the use of ECT in geriatric psychiatry, both in straightforward and in more complex cases, with or without cognitive and other medical comorbidity.

6.2.1 Case 1

Case 1 History

Mrs. A. is an 88-year-old widowed woman, who lives alone in her own home. She is a retired nurse and mother of three adult children, two of whom are still living. She has no past psychiatric history, despite the stress of losing one of her sons in a motor vehicle accident when she was 70 years old. One of her four siblings had bipolar disorder. Mrs. A. presents with anxiety, insidious in onset and worsening over several months, in the context of a recent stressor; 6 months prior to her clinical presentation, her daughter-in-law died after 1-year illness with lung cancer.

Over the past several months, she has become increasingly anxious. She has stopped singing in her community choir, as she feels she cannot recall the words to the hymns and does not want to hold her fellow choristers back. She has also withdrawn from auditing a university course for seniors in archeology, as she feels she cannot absorb the course material. She has been going out much less frequently and refuses invitations from friends to attend concerts, although she previously enjoyed this type of activity very much. When her daughter visits, she finds little fresh food in the refrigerator. The patient explains that she had not been eating much and had been relying on simple meals like toast and cereal. She has lost 5 lbs. (2.3 kg) over the past 2 months and admits that she has been spending much of her time in bed due to fatigue.

Her daughter took her to her primary care physician, who prescribed citalopram 10 mg/day for 1 week, increasing to 20 mg/day the following week. Two weeks later, the patient has a fall in the bathroom, lacerating her forehead. When brought to the emergency room, she is alert and has no focal neurological findings but is disoriented to time.

Clock drawing is abnormal; she begins placing the numbers correctly but trails off after writing the number four. In the emergency room, she has a witnessed generalized tonic-clonic seizure lasting 1 minute.

Her medical history is as follows: coronary artery disease with a myocardial infarction at age 78; hypertension, controlled; hyperlipidemia; osteoporosis with right wrist fracture at age 86; history of temporomandibular joint pain in her youth, treated remotely with a surgical intervention, currently asymptomatic for many years; and history of right total hip replacement at age 76 under general anesthesia after hip fracture. Her medications on presentation to the emergency room are perindopril, enteric-coated aspirin, rosuvastatin, atenolol, calcium, vitamin D, alendronate, and citalopram.

Investigations in the emergency room are as follows: sodium 126 mmol/L (126 mEq/L; low), potassium 4.5 mmol/L (4.5 mEq/L; normal), and hemoglobin 130 g/L (8 mmol/L; normal). Electrocardiogram showed findings consistent with old myocardial infarction, no acute changes, and a QTc of 446 milliseconds. Computed tomography (CT) of the brain revealed mild periventricular white matter changes and mild global atrophy consistent with age and two old small lacunes in the left frontal lobe but nil acute. MoCA was 15 out of 30, with multiple deficits including attention and concentration.

Her forehead laceration is repaired with sutures. She is admitted to internal medicine for hyponatremia, attributed to syndrome of inappropriate antidiuretic hormone (SIADH) caused by her selective serotonin reuptake inhibitor (SSRI). Her fall and seizure are attributed to hyponatremia. Citalopram is discontinued and replaced with mirtazapine 15 mg po qhs. Sodium gradually returns to the normal range.

After a 2-week admission in internal medicine, the patient is transferred to geriatric psychiatry service. On admission, she spends much of her time in her room. She is alert, and MoCA is improved at 19. However, she makes a poor effort, saying "I don't know" or "I can't do that" in response to several questions. She stays only briefly in the common dining area at meals, seeming vigilant and eager to leave. Questioning reveals that she is concerned that she is being watched and fears she may be taken from the hospital to prison, for a crime she will not disclose.

Case 1 Questions and Answers

Case 1 Questions

- Question 1. Name two alternative treatment approaches and the rationale for your preferred treatment recommendation?
- Question 2. Would you give an antidepressant during ECT?
- Question 3. Are there any medical conditions that increase ECT-associated risks in this patient?
- Question 4. How would you manage her nonpsychiatric medications in the peri-ECT context?
- Question 5. What electrode placement and pulse width would you choose?
- Question 6. If she responds to ECT, what would you choose as a maintenance strategy?

Case 1 Answers

Case 1 Answer 1 (Question 1—Name two alternative treatment approaches and the rationale for your preferred treatment recommendation?)

This patient appears to have major depressive disorder with psychotic features, with onset in late life. She does have a biologic vulnerability for bipolar disorder based on her family history, but we cannot make a diagnosis of bipolar disorder based on her clinical history. She appears to have been cognitively and functionally intact as recently as several months ago, and so a diagnosis of an underlying major neurocognitive disorder is less likely. There may have been a superimposed delirium due to hyponatremia (likely SIADH caused by citalopram), but this appears resolved, with an alert sensorium and an improvement in her MoCA scores. Her statements of incapacity during cognitive testing are characteristic of depression, although we cannot completely rule out residual delirium and/or major or mild neurocognitive disorder. However, the hyponatremia which is thought to be the cause of her delirium has now normalized. The clinical history, with its onset over several months, is suggestive of a depressive episode. Although she has anxious rather than depressed mood (a common presentation in older patients), she presents with anhedonia (avoids previously enjoyed activities), hypersomnia, feelings of lack of capacity, poor appetite with weight loss, low energy, and delusions of guilt. ECT is a first-line treatment for depressive disorder with psychotic features and more effective than pharmacotherapy. However, treatment with an antidepressant and an antipsychotic (assertive doses of both) could be a reasonable alternative with a somewhat lower efficacy. Since the patient is eating and drinking and is not acutely suicidal, either option could be reasonable depending on patient and family preferences once they have understood the alternatives, risks, and benefits. A study of pharmacotherapy of depressive disorder with psychotic features (STOP-PD) found a combination of sertraline 150–200 mg per day and olanzapine 15–20 mg per day to be effective in older adults with depressive disorder with psychotic features. However, caution would have to be exercised regarding sertraline for this patient, given the recent hyponatremia with citalopram; it is prudent to avoid SSRIs and to select an alternate antidepressant with a lower risk of inducing hyponatremia via SIADH [74]. The remission rate with assertive pharmacotherapy in STOP-PD was 41.9%; this is substantially lower than remission rates associated with ECT which are on the order of 80%. Therefore, ECT is the treatment of choice in this case.

Teaching Point
ECT is the treatment of choice in depressive disorder with psychotic features. However, assertive pharmacotherapy with an antidepressant and antipsychotic combined can be a reasonable alternative.

Case 1 Answer 2 (Question 2—Would you give an antidepressant during ECT?)

Most clinicians would combine an antidepressant with ECT treatment. This is in part because of the evidence which suggests a 15% improvement in remission rates when a noradrenergic antidepressant is combined with ECT [19]. Venlafaxine and nortriptyline are the best studied. This strategy also allows an adequate dose of the antidepressant to be in place when the acute course of ECT is complete, allowing for a smooth transition to maintenance pharmacotherapy. Given her recent history of hyponatremia with citalopram, however, careful monitoring of serum sodium would be crucial. Venlafaxine, like most other antidepressants, has been associated with hyponatremia. In this particular case, it was introduced gradually, with careful monitoring, and hyponatremia did not recur. Low sodium increases the risk of prolonged seizures in ECT, and ECT should be avoided until electrolyte balance is restored. There is a theoretical risk of increased cardiovascular complications when combining drugs like venlafaxine or a tricyclic antidepressants with ECT, but the risk is considered acceptable in contemporary ECT unless there are particular clinical circumstances increasing the risk of cardiac arrhythmias with a particular patient.

Teaching Point
Combining antidepressants with ECT can result in a small improvement in remission rates.

Case 1 Answer 3 (Question 3—Are there any medical conditions that increase ECT-associated risks in this patient?)

The patient's recent hyponatremia was discussed in *Case 1 Answer 2*; that risk can be managed by careful selection of antidepressants and by monitoring of serum sodium. She had a recent fall due to a seizure. The reasons for the seizure (hyponatremia) are now resolved, so that is no longer a concern. She did hit her head, but CT of the brain showed no evidence of subdural or cerebral hemorrhage post-trauma, which would raise the risk of ECT substantially. The old lacunar infarcts in the left frontal region will not affect the efficacy of ECT or its safety. (They might, however, offer an explanation of the etiology of her first depressive episode at age 88.)

Her coronary artery disease and hypertension appear to be stable and well controlled. Given her osteoporosis, there is a slightly increased risk of fracture during ECT; this can be managed with appropriate attention to muscle relaxation during the procedure. She appears to have tolerated a general anesthetic in the past with no complications. Her remote history of temporomandibular joint pain and surgery raises the possibility of a recurrence of temporomandibular joint pain with ECT; this risk should be discussed with the patient prior to the procedure. Although the muscles throughout the body are paralyzed temporarily via the depolarizing muscle relaxant succinylcholine, direct electrical stimulation of the masseter muscles cannot be avoided, and this produces a strong bite which can aggravate temporomandibular joint pain. Unilateral stimulation may decrease the strength of the bite somewhat.

Despite her multiple medical illnesses, ECT is likely safer and more tolerable than pharmacotherapy for this 88-year-old woman. Of note, she has just experienced significant morbidity due to an SSRI.

Teaching Point
Most medical conditions associated with increased risk during ECT can be stabilized and managed safely during ECT, in collaboration with other specialists including anesthesiologist.

Case 1 Answer 4 (Question 4—How would you manage her nonpsychiatric medications in the peri-ECT context?)

Her current medications are as follows: perindopril, enteric-coated aspirin, rosuvastatin, atenolol, calcium, vitamin D, and alendronate. Cardioprotective medications such as perindopril, enteric-coated aspirin, and atenolol are usually given with sips of water in the morning prior to the ECT treatment. The remainder of her medications can be held until after her treatment. Decisions regarding peri-ECT medications for an individual patient should be made in collaboration with the anesthesiologist. Other peri-ECT medication issues to consider are giving anti-reflux medications with sips of water prior to ECT, reducing benzodiazepines and anticonvulsants to the minimum effective dose, and avoiding diuretics prior to the ECT treatment.

Teaching Point
Cardioprotective and anti-reflux medications are usually given prior to ECT with sips of water; the remainder of the medications is usually held until after the treatment. Medications to be given pre-ECT include antihypertensives, antiarrhythmics, antianginals, bronchodilators (except theophylline), and antiglaucoma agents. Decisions regarding peri-ECT medications should be made in collaboration with the anesthesiologist.

Case 1 Answer 5 (Question 5—What electrode placement and pulse width would you choose?)

Right unilateral ECT given at six times seizure threshold has been shown to be as effective as bilateral ECT and to have fewer cognitive side effects. More recent data from the PRIDE study suggests that right unilateral ultrabrief pulse ECT can be fast acting and effective, with a favorable cognitive profile. The PRIDE study did include a small proportion of patients with psychotic symptoms. It is possible that in the real world, brief pulse treatments and bitemporal treatments have somewhat better efficacy. A discussion must be held with the patient and/or her surrogate decision maker regarding the risk-benefit analysis of different electrode placements and pulse widths. In a case such as this, without immediate life-threatening urgency, it would be reasonable to start with right unilateral ultrabrief pulse ECT, monitoring progress objectively, and considering a switch to brief pulse ECT or bitemporal ECT or both if there is no meaningful improvement after six treatments.

Teaching Point

Right unilateral ultrabrief pulse ECT is efficacious in older patients with depression, with or without psychotic features. Consider switching to right unilateral brief pulse ECT or bitemporal brief pulse ECT if there is no improvement after six treatments.

Case 1 Answer 6 (Question 6—If she responds to ECT, what would you choose as a maintenance strategy?)

Maintenance pharmacotherapy and maintenance ECT are both reasonable alternatives after response to an acute or index course of ECT. Relapse rates are high in the first 6 months after ECT. They can be reduced by antidepressant pharmacotherapy and reduced even more by a combination of antidepressant and lithium carbonate in the post-ECT period. Antidepressant plus lithium is equivalent to maintenance ECT at fixed intervals. Patient preference and practical considerations such as availability of maintenance ECT may dictate the choice of treatment. Symptom-titrated maintenance ECT, in which ECT is given depending on patient symptoms and avoided when there is significant cognitive impairment, may offer some advantages in the post-ECT continuation period. If lithium and maintenance ECT are combined, consider using the minimum possible lithium dose and holding the dose prior to each treatment to avoid excess confusion with the lithium/ECT combination. Gradual tapering of ECT at the end of the index course can be a helpful bridging strategy. Any antidepressant introduced in the context of recent medication-induced hyponatremia risks producing the same effect; therefore, careful monitoring of serum sodium would be indicated if antidepressant treatment is pursued.

Teaching Point

Pharmacotherapy (antidepressant plus lithium if possible) and maintenance ECT are both reasonable alternatives after an index course of ECT to maintain remission. Pharmacotherapy with an antidepressant alone is better than placebo but substantially worse than the combination of an antidepressant and lithium.

Case 1 (Continued)

The patient was treated with right unilateral brief pulse ECT with stimulus dose titration, in combination with slowly increasing doses of venlafaxine. After four treatments, she began to show some improvement, with reduced anxiety, increased socialization, and gradual disappearance of her delusions of guilt. Around treatment number 7, her daughter noticed that she seemed vague and less sociable. She did not remember most details of her hospital admission and recent events and seemed to have forgotten some important events in the preceding year, including her daughter-in-law's funeral. MoCA was 18 at this point. Once she achieved remission (after nine treatments), ECT was gradually tapered (once per week for 1 month, then once every 2 weeks for 1 month, then discontinued due to patient preference), and she was maintained on venlafaxine XR 225 mg po qAM. Hyponatremia did not recur with regular sodium monitoring. After ECT, she was put on lithium carbonate and maintained at a serum level of 0.4–0.6 mmol/L (mEq/L). MoCA was 27 out of 30 at 3 months post-ECT. The patient resumed her usual activities, including choir, university courses, and driving a motor vehicle.

Case 1 Analysis This patient illustrates a fairly typical case of late-onset major depressive disorder with psychotic features. Her advanced age and presence of psychotic features, along with the relatively short duration of illness, make her an ideal candidate for ECT. She does have some medical comorbidity, but all of it could be stabilized, optimized, and managed in collaboration with anesthesiology in order to permit the safe use of ECT. Her adverse reaction to citalopram illustrates the substantial safety issues associated with pharmacotherapy in adults in their 8th decade and beyond. ECT can be safer than pharmacotherapy for this reason.

The patient had delirium superimposed on her depression and also had a reduced score on her MoCA even when delirium had resolved. This might have been mistaken for a major neurocognitive disorder, but the clinical history was not compatible with that diagnosis. A careful history and examination are necessary to differentiate among depressive disorder, delirium, and major neurocognitive disorder. This is one of the common clinical tasks of the geriatric psychiatrist.

The patient was treated with right unilateral brief pulse ECT and responded well, ultimately attaining complete

remission and regaining her former level of functioning. However, she did develop transient cognitive impairment during ECT and sustained some autobiographical memory loss. Given the emergent findings of the PRIDE study, it might have been preferable to treat her with right unilateral ultrabrief pulse ECT. This might have reduced the impact of her ECT treatments on cognition. However, if a strategy such as this were to have been tried, it would have been imperative to monitor her progress carefully with a structured rating scale for depression, such as Hamilton Depression Rating Scale (Ham-D). If no substantial improvement were seen after six sessions, consideration would have to be given to switching to right unilateral brief pulse or bitemporal brief pulse treatments despite the risks.

This patient elected to use maintenance pharmacotherapy after ECT, following a brief taper of ECT. The use of lithium and venlafaxine was an evidence-based choice. However, a careful pre-lithium work-up and close monitoring are essential when using lithium in the frail to avoid lithium toxicity.

6.2.2 Case 2

Case 2 History

Mr. X. is a 90-year-old man from a long-term care home. He is followed by a geriatric psychiatrist in the community due to a history of recurrent, treatment-resistant depressive disorder with psychotic features and mild-to-moderate major neurocognitive disorder due to vascular disease. His psychiatrist, long-term care staff, and the patient's family noted an increase in depressive mood symptoms over a period of 2 months with prominent irritability, affective lability, poor frustration tolerance, verbal aggression, and social isolation. He was also refusing medications, food, and personal care. He was mildly suspicious about the motives of long-term care staff, but there were no overt psychotic symptoms. This presentation was in keeping with previous episodes of major depression.

Due to functional decline and symptom severity, Mr. X. was hospitalized at an acute care hospital in the community. During a one-and-a-half-month admission, the depressive symptoms failed to respond to the addition of duloxetine 60 mg daily and aripiprazole 3 mg daily. A brief course of ECT was attempted, and he responded well, but ECT was discontinued due to the patient's perceived "frailty." He was then transferred to a tertiary care hospital for consideration of the viability of a return to ECT and consideration of alternatives.

His past psychiatric history is significant for several episodes of major depressive disorder with psychotic features requiring hospitalization due to failed outpatient management and significant functional impairment. Acute and maintenance ECT had been used with success several times over the past 15 years. Although his depressive symptoms have been severe, Mr. X. has no history of suicide attempts. There is no history of hypomania, mania, or psychosis in the absence of depressive symptoms. A diagnosis of mild-moderate, major neurocognitive disorder, vascular type, was made 4 years ago. He now requires assistance with activities of daily living. He has consistently refused cognitive testing over the last several years.

Mr. X.'s medical history is quite extensive; he has had several falls secondary to intermittent hypotension and suffers from atrial fibrillation, hypertension, and congestive heart failure. He also has chronic renal failure and poor vision secondary to glaucoma and cataracts. Recent intermittent food refusal has led to a decrease in weight from 110 lbs. (50 kg) to 84 lbs. (38 kg). He now uses a wheelchair as he is too deconditioned to ambulate independently. Recent laboratory investigations that accompanied Mr. X. show that a complete blood count with differential, electrolytes, extended electrolytes, blood urea nitrogen, and creatinine are all within normal limits.

Prior to ECT, he intermittently refused prescribed medications due to irritability and suspiciousness. Following ECT, however, his adherence has improved, and his weight loss has stabilized. He is currently prescribed duloxetine 60 mg daily, aripiprazole 3 mg daily, furosemide 20 mg daily, metoprolol 100 mg twice daily, apixaban 2.5 mg twice daily, digoxin 0.0625 mg daily, and vitamin B_{12} 1000 mcg intramuscular injection every 4 weeks. Previous psychiatric medication trials have included paroxetine, citalopram, escitalopram, fluvoxamine, venlafaxine XR, amitriptyline, and clomipramine.

On mental status exam, Mr. X. is a very thin, small-statured man seen sitting in a wheelchair quietly. Eye contact is appropriate, and his speech is slow and quiet. His attitude is dismissive. He reports his mood as "so-so" and has several vague complaints about physical discomfort and the hospital staff. He is mildly irritable. His thought content is vague, and he is unable to accurately discuss recent events but alludes to some accurate details regarding his personal history. There is no evidence of psychosis, and he adamantly denies suicidal ideation. Cognition, although not formally tested, appears to be impaired. Insight and judgment are poor.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What are the indications for ECT in Mr. X.'s case?

Question 2. You are considering a return to ECT to complete the treatment of Mr. X.'s major depressive episode. Which elements of the history would you pursue further? What would your pre-ECT work-up include?

Question 3. Do aging and increased frailty affect the viability of ECT?

Question 4. It can be difficult to differentiate premorbid mood or anxiety disorder symptoms from behavioral and psychological symptoms (or neuropsychiatric symptoms) associated with a neurocognitive disorder. Can behavioral and psychological symptoms be successfully treated using ECT? What are the effects on cognition in this population?

Case 2 Answers

Case 2 Answer 1 (Question 1—What are the indications for ECT in Mr. X.'s case?)

ECT is an important treatment for severe and treatment-resistant depression when multiple pharmacological trials have failed and when a rapid response is necessary [75]. Rapid ECT initiation should be considered in cases of active suicidal ideation and behavior, severe weight loss, malnutrition or dehydration, overall worsening medical status, and psychosis.

In Mr. X.'s case, symptoms of major depressive disorder were initially causing mental suffering and are affecting his adherence to medications and preventing adequate nutritional intake. Physical deterioration in the form of a 26-lb. weight loss and the new inability to ambulate were concerning signs of declining physical health. Mr. X. was at risk for further mental and physical deterioration if his depressive symptoms did not rapidly improve. The initial indication for ECT appears to have been good. His current state, however, is somewhat improved, with less distress and a stabilization of his nonadherence to treatment and his weight loss. There appears to be less urgency to return to ECT at this point.

Mr. X. does, however, have a history of many failed medication trials for past depressive episodes and has required maintenance ECT in the past. Mr. X.'s history indicates that he has always had a robust response to ECT. A history of better response to ECT than to pharmacological management is another instance in which ECT is indicated. A return to maintenance ECT could be indicated based on past response, but the risks and benefits of this approach need to be carefully considered.

Teaching Point

ECT is the treatment of choice when there is clinical urgency and a need for a rapid response. Past response to ECT is another important indication.

Case 2 Answer 2 (Question 2—You are considering a return to ECT to complete the treatment of Mr. X.'s major depressive episode. Which elements of the history would you pursue further? What would your pre-ECT work-up include?)

Prior to initiating ECT, an evaluation by an ECT psychiatrist should be conducted to ensure that ECT is the appropriate treatment option for the patient. The consultation serves three main functions: (i) to verify that the patient has an ECT-responsive diagnosis of adequate severity to warrant the treatment, (ii) to assess the patient's general medical history and current general medical status in order to maximize safety during the treatment, and (iii) to begin the consent process [75].

Mr. X.'s current major depressive episode has resulted in significant weight loss (though this is now stabilized), and he is potentially at risk for further physical deterioration. He has only intermittently been adherent to medications and has a history of inadequately responding to pharmacological interventions. Acute and maintenance ECT have been successful at managing Mr. X.'s depressive symptoms in the past. All of these factors are indications supporting the use of ECT to treat Mr. X.'s residual symptoms of major depressive disorder and to consider a transition to maintenance ECT. Before ECT can be initiated, Mr. X.'s medical history and current medical status must be evaluated, and informed consent must be obtained.

Prior to prescribing and initiating a course of ECT, the operating psychiatrist, medical consultants, and anesthesiologists should work collaboratively prior to and during a course of ECT. A thorough psychiatric history including previous response to ECT, a medical history, and physical examination with focus on the cardiovascular, respiratory, neurological, and musculoskeletal systems must be conducted. A history of dental problems and examination for loose or missing teeth is also indicated as well as eliciting a history of experience with anesthesia use both personally and within the family [14].

Mr. X. has an extensive medical history with several cardiac and cardiovascular risk factors. His medical history includes glaucoma, cataracts, and chronic renal failure, and his cardiac and cardiovascular risk factors include intermittent hypotension, atrial fibrillation, hypertension, and congestive heart failure. There is no available information about the recent course of ECT other than that it was discontinued due to "frailty." In this case it would be important to contact Mr. X.'s last treating psychiatrist to inquire about the most recent course of ECT. Important questions to ask include: What electrode placement and pulse width was used? Were there any adverse effects? How was it tolerated? Was there perceived benefit? How many treatments did he receive, and, finally, why were the treatments discontinued? This inquiry may result in valuable information about Mr. X.'s health and inform the decision as to whether he is a suitable candidate for ECT. It is also important to review the patient's current medications as certain medications can negatively impact the efficacy of ECT, patient safety, and post-ECT recovery.

As part of the pre-ECT evaluation, a physical examination was performed and revealed the following: Mr. X.'s blood pressure was 149/88 mm Hg, and his heart rate was 77 beats/minute and irregularly irregular. Respiratory rate was 16 breaths/minute, and his oxygen saturation was 98% on room air. He did not appear to be in any distress. The cardiovascular examination revealed a 2/6 mid systolic ejection murmur in the aortic area. Capillary refill time was delayed and there was evidence of 2+ (moderate pitting) bilateral pedal edema. The lungs were bilaterally clear to auscultation. Musculoskeletal examination was significant for kyphosis. Other than diffuse, symmetrical weakness, the neurological examination was normal.

Although there are no routine laboratory tests recommended, generally performed tests include a complete blood count, serum chemistry with sodium and potassium, as well as an electrocardiogram. A chest x-ray can be considered in patients with cardiovascular or pulmonary disease or with a history of smoking [15]. Testing of cerebral functioning,

including electroencephalography and/or neuropsychological assessment, can be ordered on an individualized basis if there are specific concerns. Spinal radiographs should also be considered in patients with known or suspected spinal disease. When the risks of ECT in the setting of the existing medical disease are unclear, further testing or consultation should be considered.

Laboratory investigations were repeated as a part of the pre-ECT assessment for Mr. X. The complete blood count and differential were within normal limits. Serum chemistry was within normal limits except for a mildly elevated creatinine. An electrocardiogram revealed atrial fibrillation at a rate of 75 beats/minute. There was evidence of an old infarct, and the QTc interval was 445 milliseconds. As there was no suspected spinal disease, a spinal radiograph was not performed. A CT of the brain was available from his community hospital, where it had been performed after a fall 1 year prior to the current admission. It revealed diffuse, moderate cerebral microvascular disease and mild diffuse atrophy. There was no evidence of stroke or space-occupying lesions. In order to establish a cognitive baseline, cognitive testing was attempted, but Mr. X. was uncooperative.

A telephone conversation with Mr. X.'s last outpatient psychiatrist revealed the following information about his previous course of ECT: ECT was initiated to treat the major depressive episode as his symptoms failed to respond to medications, and he had previously been successfully treated with ECT. Due to concerns about weight loss and malnutrition, bitemporal lead placement and brief pulse width were used in an effort to elicit a rapid response. Mr. X. showed improvement after three treatments and continued to improve clinically over the course of eight treatments. He became less suspicious, and adherence to medications and food intake improved. He seemed less irritable and more consistently able to enjoy visits from his family, although some irritability and negativity persisted.

His last outpatient psychiatrist went on to explain that during his eighth ECT treatment, he developed a supraventricular tachycardia in the ECT suite and subsequently had respiratory arrest in the ECT recovery area; he was rapidly resuscitated with no sequelae. The incident was reviewed with his outpatient psychiatrist, ECT psychiatrist, and the anesthesiologist. Risks and benefits of ongoing treatment were reviewed, and Mr. X.'s surrogate decision maker was contacted. The treating team and Mr. X.'s surrogate decision maker felt that the risks outweighed the benefits of treatment and ECT was discontinued. It was at this point that he was referred to the tertiary care center for consideration of the viability of a return to ECT.

Patients with systemic medical conditions that predispose them to increased risk during ECT may benefit from a specialist consultation to comment further on their suitability. Due to his recent cardiac event during ECT, Mr. X. was referred to cardiology to assess the cardiac risks associated with a potential return to ECT. After an evaluation, the cardiologist stated that Mr. X. remained at high risk for future adverse events if ECT were continued. After consultation with his surrogate decision maker, lithium 150 mg at night was initiated for relapse prevention, with an aim to maintain serum levels around 0.4 mmol/L (mEq/L).

Teaching Point

In general, ECT is safe and effective in even the frail geriatric patients. There are circumstances, however, when the risks are deemed to outweigh the benefits and consideration of alternatives is necessary. These situations involve consultation, collaboration, and consideration of the values and priorities of the patient.

Teaching Point

An antidepressant in combination with lithium is a more effective strategy for relapse prevention than an antidepressant alone. The tolerability of this approach must be considered on an individual basis.

Case 2 Answer 3 (Question 3—Do aging and increased frailty affect the viability of ECT?)

Frailty is a common clinical syndrome in older adults that carries an increased risk for poor health outcomes including falls, incident disability, hospitalization, and mortality (See ► Chap. 1 for further details on frailty). It is defined as a clinically recognizable state of increased vulnerability resulting from aging-associated decline in reserve and function across multiple physiologic systems such that the ability to cope with every day or acute stressors. Frailty is associated with increasing age and has been estimated to affect up to 12% of older individuals in the USA [76].

There is no upper age limit for the use of ECT; older age is a positive predictor of response to ECT. In a study of ECT in the very old, 86.3% of patients had a favorable response to ECT, and the rate of complications was 22.7%, lower than the previously cited rates of 27–77% [77]. In geriatric patients with depression, ECT results in faster and higher remission rates compared to depression treatment with pharmacotherapy [78].

However, ECT in older adults does present some challenges. While older age itself is not a risk factor for mortality associated with ECT, older adults may be at greater risk because of a higher prevalence of medical comorbidity (See ► Chap. 1). There are no absolute contraindications to the use of ECT, but when considering the medical risks, the cardiovascular system, the respiratory system, and the central nervous system are of importance.

Conditions associated with increased risk during ECT include brain lesions with increased intracranial pressure, hematoma, cerebral aneurysm, and other cerebrovascular malformations. High anesthetic risk (American Society of Anesthesiologists level 4 or 5), pheochromocytoma, poorly compensated congestive heart failure, recent intracerebral stroke/hemorrhage, recent myocardial infarction, severe cardiac valvular disease, severe chronic obstructive pulmonary

disease, asthma, or pneumonia may also predispose to increased risk with ECT.

Patients with cardiac disease have a significantly higher rate of cardiac complications during ECT compared to those without disease due to physiologic changes in heart rate and cardiac output during ECT. Vulnerable patients may experience transient cardiac arrhythmias or sinus arrest. Controlling hypertension and optimizing congestive heart failure treatment prior to ECT may help prevent transient ischemic changes and rates of complications. Surgical treatment may be required to correct anatomic problems associated with large aneurysm or severe valvular heart disease before ECT. Although complication rates are higher than among younger patients, they must be interpreted in the context of the illness and potential complications of alternate treatments, as well as the potential consequences of no treatment at all [78].

Mr. X. is an example of a patient who has had a robust response to ECT but in whom increasing age and cardiac risk factors pose an increased risk. While it is likely that he will once again respond to treatment, the risk of a serious adverse event is higher than when ECT was used in the past. Important factors to consider in such cases are (i) the urgency of the required treatment, (ii) the availability and viability of other treatment options, and (iii) the nature of the risk associated with ECT.

For Mr. X., this evaluation would include an examination of his current medical and psychiatric status. Is he at risk for acute physical deterioration due to refusal of oral intake or medication nonadherence? Does the level of mental suffering need to be urgently addressed? Is he at risk for acute harm to himself or others? Other treatment options and their relative risks and benefits in comparison to ECT must be considered. In this case, all treatment trials should be reviewed. Have all possible medications been tried? Is there anything that has had modest benefit in the past than can be revisited? And finally, if Mr. X. were to be treated with ECT, what are the adverse outcomes that may result?

Mr. X. has had significant weight loss and deconditioning because of the major depressive episode, now partially treated. Although he has deteriorated physically, his vital signs are stable, and the laboratory investigations are generally within normal limits except for a mildly elevated serum creatinine indicating dehydration. Therefore, he is likely not at an acute risk for systemic medical decompensation. Psychiatric evaluation reveals no suicidal or homicidal ideation. His affect remains irritable, and his thought content is somewhat negative, but he remains improved after the ECT course. His weight loss has stabilized, and his adherence to treatment is more consistent. Finally, the extent of the risk associated with ECT must be considered. History and physical examination reveals cardiac disease and a history of a serious cardiac incident and respiratory arrest during the last ECT treatment. These factors increase the likelihood of adverse events with ECT.

Clinically, one must assess whether Mr. X.'s symptoms warrant the use of a procedure with the risk of severe cardiac and respiratory complications and potentially even death. As Mr. X. is not acutely medically compromised and his psychiatric symptoms are not causing severe distress, the risks of ECT were judged to outweigh the risks of ongoing medical management at the present time. However, if his clinical status deteriorated rapidly and emergent treatment with ECT was necessary, the risks and benefits of treatment with ECT might be analyzed differently. In the face of a life-threatening clinical situation, a return to ECT might make sense despite the associated risks. A return to ECT would need to be discussed carefully with Mr. X.'s surrogate decision maker, and informed consent would need to be obtained prior to initiating treatment.

Teaching Point

There are no absolute contraindications for ECT, but some conditions are associated with increased risk. ECT can be done in most patients, but the benefits must be weighed against the potential risks. Collaborative decision-making with patients and surrogate decision makers is essential.

Case 2 Answer 4 (Question 4—It can be difficult to differentiate premorbid depressive or anxiety disorder symptoms from behavioral and psychological symptoms (or neuropsychiatric symptoms) associated with a major neurocognitive disorder. Can behavioral and psychological symptoms be successfully treated using ECT? What are the effects on cognition in this population?)

Major neurocognitive disorder is one of the major causes of disability in the geriatric population. Behavioral and psychological symptoms of major neurocognitive disorder refer to the distressing, non-cognitive symptoms of major neurocognitive disorder, which includes agitation or restlessness, wandering and hoarding, verbal or physical aggression, anxiety, depression, psychosis, and/or repetitive vocalizations. It can be observed in up to 90% of patients with major neurocognitive disorder.

A growing body of literature has identified ECT as an effective intervention for severe refractory agitation in patients with major neurocognitive disorder [53, 79, 80]. However, trials comparing the efficacy of ECT and antipsychotic drugs for treatment of patients with major neurocognitive disorder with severe behavioral disturbances have yet to be done [81].

There has been concern surrounding the cognitive ability of geriatric patients receiving ECT, but cognitive impairment per se should not necessarily exclude recommendations for ECT in geriatric patients. Certain geriatric patients with baseline cerebral impairment may be at greater risk of more prolonged disorientation and/or the development of

transient delirium with ECT [78, 81]. These adverse effects are generally transient and reversible in most cases, ranging from a few days to a few months. Older age, preexisting cognitive impairment, co-administration of ECT with other drugs, and medical comorbidities may also be contributing factors. In some patients with major neurocognitive disorder and concurrent major depressive disorder, treating underlying depressive or psychotic symptoms with ECT may actually improve cognitive deficits [52].

In the cognitively intact geriatric population, data suggests that the cognitive effect profile of ECT in older adults is comparable to that in mixed-age populations. Following an initial and transient decline, baseline impairment, often due to the depressive disorder itself, is usually reversed after an acute course of ECT. Overall, ECT is thought to be safe and effective in treating patients with neurocognitive disorder due to Alzheimer disease and severe behavioral disturbances, major depressive disorder, manic episodes, and psychotic symptoms [81].

Case 2 Analysis When used in older adults, the frail, and medically ill population, ECT treatment is often met with additional challenges. When considering ECT in such a patient, first and foremost one must consider the indications for ECT, including the growing body of evidence for its use and safety in behavioral and psychological symptoms associated with major neurocognitive disorder.

A thorough history and physical examination are especially important in this patient population. ECT has been shown to be an effective treatment in very old and frail individuals, but this population is also more likely to be afflicted with medical comorbidities predisposing them to increased risks during ECT. Although there are no absolute contraindications for the use of ECT, when risk factors such as cardiovascular, pulmonary, and neurological disease are present, the risks and benefits of treating with ECT must be weighed carefully. One must weigh the risks of untreated psychiatric illness with the medical risks associated with ECT, and additional caution must be taken. Consultation with general medicine, psychiatry, anesthesia, and other specialist colleagues may be indicated in order to make a fully informed decision when ECT is being recommended. If the clinical situation necessitates the use of ECT in a high-risk patient, the risks and benefits must be clearly discussed and documented with the surrogate decision maker.

In this case study, Mr. X. had clear psychiatric indications for the use of ECT. Old age, frailty, and cognitive impairment are not contraindications for the use of ECT, but a thorough history and physical examination in this case revealed a likelihood of increased risks with the procedure. Although he continued to experience significant symptoms of major depressive disorder, the risks of treating with ECT outweighed the potential benefits. If his clinical status deteriorated further and emergent treatment became necessary, informed consent would need to be obtained from the surrogate decision maker following a careful discussion of the risks.

6.3 Key Points: Electroconvulsive Therapy

- ECT is a safe and effective treatment for depressive disorder in the geriatric population, including frail and very old patients.
- Older patients with depressive disorder respond better to ECT than do younger patients.
- ECT is a treatment of choice for depressive disorder with psychotic features, a common presentation in the geriatric patients.
- ECT can be particularly useful in situations in which a rapid response is required, for example, in patients who are not eating and drinking or when there is severe suicidality.
- ECT has efficacy in disorders other than depressive disorders; these include psychotic disorders, catatonia, Parkinson disease with or without psychotic symptoms, depressive disorder due to Parkinson disease or stroke, and depressive disorder in the context of major neurocognitive disorder.
- There is an emerging literature on the use of ECT for treatment of behavioral disturbance in the context of major neurocognitive disorder.
- There are no absolute contraindications to ECT; however, there are numerous medical conditions associated with increased risk. The risk-benefit ratio of ECT must be considered by the treating psychiatrist in collaboration with anesthesiologists and medical consultants prior to embarking on a course of ECT treatment.
- Ultrabrief right unilateral ECT appears to be effective in older patients and to have a favorable profile of cognitive side effects. However, if this form of ECT is ineffective, other forms such as brief pulse ECT and/or bitemporal ECT with more robust efficacy and a larger evidence base should be considered.
- Right unilateral ECT must be given at doses substantially exceeding seizure threshold (e.g., six times) in order to be effective.
- Bitemporal brief pulse ECT is the form of ECT with the most definitive efficacy but can be associated with significant autobiographical memory disturbance.
- Stimulus dose titration, with dosing based on seizure threshold, is the preferred method of determining the electrical dosing of ECT. However, in some circumstances, an increased risk of bradycardia or asystole with multiple subconvulsive stimuli, an age-based dosing method or fixed high dose may be preferable.
- After a successful series of ECT treatments, some form of maintenance treatment is required to prevent relapse, which is common and occurs early after termination of ECT.
- Maintenance ECT for depressive disorders is as effective as maintenance pharmacotherapy with a noradrenergic antidepressant in combination with lithium. Maintenance treatment with an antidepressant alone is less effective.
- Symptom-titrated maintenance ECT, combined with pharmacotherapy, may be required to prevent relapse.

6.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Electroconvulsive therapy (ECT) has been shown to have efficacy in treating several psychiatric disorders. ECT is *not* effective for which of the following conditions?

A. Acute manic episode
B. Depressive episode in bipolar disorder
C. Depressive disorder with melancholic features
D. Negative symptoms of schizophrenia
E. Depressive episodes with catatonia

Answer: D

Although ECT was first utilized as a treatment for schizophrenia, the development of effective antipsychotic medications in the late 1950s eventually led to its decline in use for this illness. Studies suggest that antipsychotic medications and ECT have comparable efficacy and combination of antipsychotic medications and ECT may have greater efficacy than either ECT or medications alone. No evidence indicates that ECT has efficacy for the treatment of negative symptoms of schizophrenia. ECT has been shown to have efficacy equal to lithium or antipsychotic medication, has a response rate of up to 80%, and has a significant advantage over lithium in patients who have not responded to lithium or antipsychotic medication. ECT is effective in treating both melancholic and severe non-melancholic subtypes of depressive disorders. It is also equally effective in treating major depressive disorder (with or without psychotic features) and bipolar disorder. Catatonia associated with both depressive or bipolar disorders and schizophrenia also responds well to ECT. Therefore, statement D is the correct answer.

MCQ 2. Which of the following statements is true regarding seizure induction during ECT in the geriatric population?

A. Age-based dosing should be used routinely to avoid subconvulsive stimuli.
B. Increased age is associated with higher seizure thresholds.
C. Intravenous caffeine prior to stimulation is recommended to facilitate seizure induction in older adults.
D. EEG tracings in older patients are associated with higher amplitudes.

Answer: B

Stimulus dose titration is the dosing method of choice despite the risk of subconvulsive stimuli, to minimize excessive dosing of electrical energy and consequent cognitive impairment. Intravenous caffeine is not recommended due to questionable efficacy and cardiotoxicity. Older patients' EEG tracings tend to have lower amplitudes due to increased cerebrospinal fluid and skull thickness. Seizure threshold in older adults is high due to increased thickness of skull, thereby increasing their risk of being unable to receive stimulus of adequate intensity during ECT; thus statement B is correct.

MCQ 3. Which of the following medications should be avoided or maintained at the lowest possible level during ECT treatment?

A. Olanzapine
B. Venlafaxine
C. Lithium
D. Aspirin
E. Propranolol

Answer: C

Lithium may increase the risk of delirium or prolonged seizures and is best held the night prior to ECT. Given the cardiovascular changes that occur during ECT, regular antihypertensive medications should be taken as usual by the patient prior to ECT. Antidepressant medications should be chosen that have relatively fewer effects on the cardiac function. Tricyclic antidepressants and venlafaxine have been associated with cardiac toxicity but are still routinely used with ECT; caution should be exercised particularly at high doses, and consideration should be given to electrocardiogram monitoring. There have been no concerning findings with the use of olanzapine or aspirin just prior to receiving ECT. Therefore, the correct answer is C.

MCQ 4. Regarding maintenance pharmacotherapy, which of the following is true after an initial treatment of ECT for major depressive disorder?

A. Following treatment with ECT, optimal maintenance pharmacotherapy includes an antidepressant in combination with lithium.
B. Maintenance pharmacotherapy should not be used in combination with maintenance ECT.
C. When patients receive antidepressants alone as maintenance pharmacotherapy following successful treatment with ECT, the estimated rate of relapse after 6 months is 20%.
D. Maintenance pharmacotherapy is superior to maintenance ECT following a successful ECT course.

Answer: A

Evidence suggests that a combination of antidepressants and lithium may be more effective in maintaining remission than an antidepressant drug alone; thus statement A is true. The PRIDE study suggests synergy between maintenance ECT and maintenance pharmacotherapy, and statement B is untrue. Roughly 80% of patients successfully treated for major depression with ECT relapse within 6 months without any maintenance treatment. When patients receive antidepressants alone as maintenance pharmacotherapy after successful ECT, the 6-month relapse rate is approximately 60%, and thus statement C is untrue. Efficacy of maintenance ECT

over a 6-month period was found to be comparable to combination pharmacotherapy with lithium and nortriptyline, and therefore statement D is untrue.

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Somatic Therapies: Repetitive Transcranial Magnetic Stimulation (rTMS) and Deep Brain Stimulation (DBS)

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7.1 Background

7.1.1 Somatic Therapies

Biological treatments for psychiatric disorders comprise pharmacotherapy as well as numerous non-medication somatic therapies. In the early twentieth century, these included fever therapy (pyrotherapy), insulin coma, and frontal lobotomy, as well as electroconvulsive therapy (ECT) [1]. Of these older treatments, only ECT is still in use [2], although other types of psychosurgery continue to have a limited role in modern psychiatry [3]. In the past three decades, additional forms of neuromodulation have become available, including repetitive transcranial magnetic stimulation (rTMS), deep brain stimulation (DBS), magnetic seizure therapy (MST), vagal nerve stimulation (VNS), trigeminal nerve stimulation (TNS), transcranial direct current stimulation (tDCS), and focal electrically administered seizure therapy (FEAST) [4]. This chapter will limit its discussion to rTMS and DBS; the remainder of these newer neuromodulation treatments remains largely investigational or has limited availability for clinical use in most settings. ECT is a well-established and effective treatment for depressive disorders in older patients and will be discussed in a separate chapter. Emerging evidence exists for efficacy of rTMS in this population, although optimal rTMS treatment protocols are still in evolution for the older adult. DBS remains an investigational treatment at present. In this chapter, the use of rTMS and DBS in older patients will be outlined and explored.

Neuromodulation techniques are primarily used to treat major depressive disorder, although limited evidence exists for other indications. Late-life depressive disorder is a common problem associated with significant functional impairment and poor quality of life [5]. In community settings, the prevalence is up to 5%, and it is more common in medical settings and in long-term care. Subsyndromal depression is much more common and is associated with a similar degree of disability [6]. Late-life depressive disorder is associated with white matter hyperintensities in approximately 50% of patients [7], and a distinct subtype of depression in late life, so-called vascular depressive disorder, has been proposed [8]. This subtype has been associated with treatment resistance [9].

In general, antidepressants have been shown to be effective in the treatment of late-life depressive disorder. However, as many as 50% of patients do not achieve remission [10]. Older patients may have difficulty tolerating pharmacotherapy due to changes in drug metabolism with aging, increased end-organ sensitivity to the effects of drugs, multiple medical comorbidities, and drug-drug interactions. Psychotherapy may be difficult to implement due to cost, availability, transportation, and the impact of systemic medical or cognitive comorbidity. Therefore, somatic therapies are of particular importance in geriatric psychiatry.

7.1.2 Repetitive Transcranial Magnetic Stimulation (rTMS)

History of rTMS

Transcranial magnetic stimulation (TMS) was originally developed in the 1980s, by Anthony Barker et al. at the University of Sheffield. It was designed as a tool to study functioning of the brain and nerves. Early studies in depression were small, open label, and done mainly with treatment-resistant patients, but results were suggestive of efficacy [11]. Since the first pilot studies in the 1990s, larger studies have been conducted with careful attention to sham stimulation and blinding. In addition, stimulation protocols have trended toward longer treatment durations, higher treatment intensities, and greater cumulative numbers of magnetic pulses [12]. With this evolution, there have been more consistent demonstrations of the effect of rTMS in generating response and remission in depressive disorders in the adult population [13]. rTMS is now considered a first-line treatment in adults who have failed at least one trial of an antidepressant. Newer protocols are being developed with more complex stimulation patterns, e.g., theta-burst stimulation, with the hope of generating increased efficacy with shorter treatment times. A 2014 meta-analysis concluded that high-frequency rTMS is associated with clinically meaningful antidepressant effects and few side effects, reported response rate in this meta-analysis was 29.3%, and remission rate was 18.6% [14]. This is much lower than response and remission rates with ECT but still is clinically significant. rTMS treatment is now accepted as an evidence-based treatment for depressive disorders by multiple international authorities [15]. The Clinical TMS Society was founded in 2011 and is a source of consensus-based treatment recommendations [16]. Some (but not all) early studies showed that older age was a negative predictor of response. However, more recent studies (post-2007) with more modern parameter settings show equivalent efficacy to younger adults [13].

Methods of Stimulation

rTMS is administered with a treatment coil, which is an electrical wire coil (encased in plastic) which is placed on the scalp surface. A current which varies in time is discharged within this coil. This generates a brief dynamic pulsed magnetic field. The scalp and the skull are transparent to the magnetic field and pose no barrier to it. However, neural tissue is conductive, and when the magnetic field reaches the brain, it induces current flow. Because the skull does not impede the magnetic field, TMS can induce relatively large currents in the brain which are relatively focal, and specific areas of the brain can be targeted for stimulation. In repetitive transcranial magnetic stimulation (rTMS), a series of repetitive brief magnetic pulses constitute the treatment [17].

In rTMS, the patient remains awake throughout the treatment, and no general anesthesia is required. An illustration of an rTMS treatment apparatus appears in ◘ Fig. 7.1. Patients

Fig. 7.1 An example of an rTMS treatment apparatus (© 2017 NeuroQore, Inc. | Mehran Talebinejad | mt@neuroqore.com, used with permission)

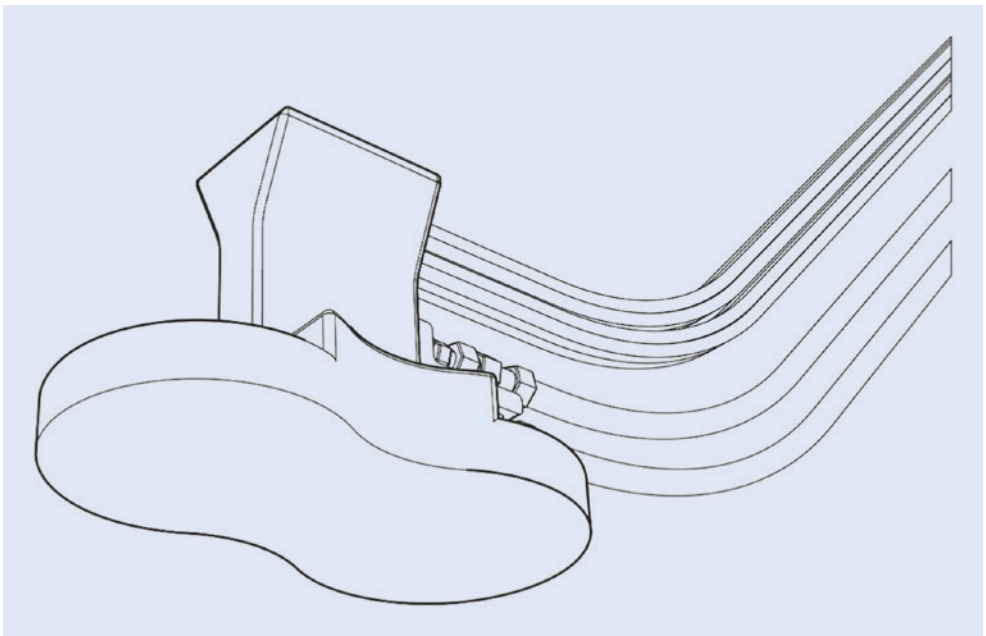

Fig. 7.2 A figure-8 rTMS coil (© 2017 NeuroQore, Inc. | Mehran Talebinejad | mt@neuroqore.com, used with permission)

are generally seated in a reclining position, and the coil is applied to the scalp at the appropriate location. Treatments are usually administered by a trained technician, under the supervision of a physician. Appropriate emergency medical equipment and assistance should be available at all times [18]. Hearing protection is worn by both patient and technician, as the device generates a loud clicking sound when in operation which can be loud enough to damage hearing with prolonged exposure [19]. Sometimes patients listen to music or audio recordings involving meditation or relaxation [15]. Sessions can be of very short duration in some newer treatment protocols (e.g., theta burst) but more commonly last 20 minutes to 1 hour. Treatments are typically administered 5 days per week [20]. The peak magnetic field is comparable to that generated by an MRI device but brief and focal instead of continuous and large [16]. Several thousand amperes of current in the coil are required to produce a magnetic field sufficiently intense and large to generate neuronal depolarization [21].

Multiple devices and coil shapes are available for use, with regulatory approval depending on the local jurisdiction. Details are available from their respective manufacturers (e.g., Neuronetics, NeuroQore, Brainsway, Magstim, MagVenture) [16]. The figure-8 coil is the most common; it consists of two round coils placed side by side to form the shape of the numeral 8. This arrangement has the effect of producing a focal magnetic field for stimulation. An illustration of a figure-8 coil appears in Fig. 7.2. Another coil, sometimes called a double-cone coil, is shaped to accommodate the curvature of the skull. An H-shaped coil that fits around the head in a helmet-like configuration produces a

focal magnetic field which penetrates somewhat more deeply into the brain than the figure-8 coil. The clinical significance of these different coil shapes remains to be determined [20].

Different stimulation frequencies produce significantly different effects on the brain. Stimulation at a frequency lower than 1 Hz (low-frequency TMS, sometimes abbreviated LF-rTMS) produces cortical inhibition. Frequencies above 1 Hz (typically 10–20 Hz) produce neuronal excitability and are referred to as high-frequency rTMS (HF-rTMS) [16].

Another important parameter in rTMS is the intensity of the stimulus. It is typically described in proportion to the motor threshold of the individual. The motor threshold is defined as the lowest intensity of stimulation that, when applied to the motor cortex, causes a standard contraction of a muscle in at least 5/10 consecutive trials [20]. Earlier studies of rTMS typically used lower intensities, e.g., 80–100% of threshold; more modern studies tend to use higher intensities [13].

There are many variables in rTMS. When describing rTMS treatment, it is important to include the following parameters: site of stimulation, coil shape and orientation relative to the scalp, method of site determination, stimulus intensity, stimulus frequency, number of daily sessions, duration of daily sessions, intertrain interval, specific pattern of stimulation (e.g., theta burst), total pulses per session, cumulative pulses per treatment course, and total duration of treatment. These are summarized in Table 7.1 [22, 23]. Conventionally, there is repetition of individual pulses at a preset interval; theta-burst stimulation is an investigation protocol involving a repetition of short bursts of pulses at a preset interval and can be associated with shorter duration of treatment session [24].

The site of rTMS stimulation was originally determined by finding the motor cortex and moving 5 cm anterior. The motor cortex was found by observing contraction of muscles in the thumb in response to brain stimulation. This method of locating the dorsolateral prefrontal cortex (DLPFC) has proved inaccurate in many cases. Therefore, alternate methods have been developed to determine the appropriate site for stimulation. These include methods that account for difference in skull size (e.g., the F3 method) and the use of neuronavigation. In the F3 method, skull measurements are used to locate the target. In neuronavigation, the patient's magnetic resonance imaging (MRI) scan is used to determine the site of stimulation. No clear evidence exists to suggest that neuronavigation is superior to the F3 method [23].

Published safety parameters describe the current consensus on the upper limits of safe application of rTMS in terms of combinations of stimulus intensity, intertrain interval, and frequency [18]. These safety guidelines should not be exceeded in clinical practice.

Table 7.1 The rTMS stimulation parameters [22, 23]

Parameter	Example
Site of stimulation	Left DLPFC Right DLPFC Bilateral stimulation (simultaneous or sequential)
Coil shape	Figure-8 Double-cone H-type Other
Target location	Measurement-based (5 cm) method Neuronavigation BeamF3
Stimulus intensity (% motor threshold)	80–120% 120% is upper limit of current safety guidelines Theta burst typically delivered at 80%
Stimulus frequency (Hz)	1 Hz or below—low frequency Above 1 Hz (typically 10–20 Hz)—high frequency
Number of daily sessions	1
Duration of daily sessions	20 minutes—1 hour Theta burst protocols are shorter; e.g., 6 minutes
Intertrain interval/ specific pattern	Theta burst Paired pulse Quadripulse
Pulses per session	1600 pulses per session
Cumulative pulses	24,000 pulses over a 3-week period
Total duration of treatment	2–6 weeks

Note: DLPFC dorsolateral prefrontal cortex

Mechanism of Action

The precise mechanisms underlying the neural effects of rTMS are largely unknown. rTMS may preferentially activate neural elements oriented horizontally to the brain surface [21]. In addition to the immediate stimulation or inhibition of the cortex (depending on frequency), there are interhemispheric effects on similar circuits on the non-stimulated side of the brain and persistent effects on the brain due to long-term potentiation [25]. Bashir et al. showed that low-frequency stimulation of the nondominant hemisphere in older subjects produced less facilitatory effect in the dominant (unstimulated) hemisphere. Their conclusion was that this may suggest reduced cortical plasticity and interhemispheric communication in those older subjects [21]. Investigations such as this one may help to shed light on possible explanations for the sometimes-reported lower response rates in older patients.

rTMS in the General Adult Population

rTMS is an established treatment for depressive disorders in the adult population [14]. There is also evidence that rTMS is effective as a treatment for treatment-resistant depressive disorder in adults, although greater degrees of treatment resistance are associated with lack of response [22].

The Clinical TMS Society has provided a consensus-based review and treatment recommendations [16]. They summarize the existing trials, including three large multicenter randomized controlled studies in an aggregate sample of rTMS in treatment-resistant depression in adults. Their conclusion was that daily rTMS to the left DLPFC had substantial evidence for efficacy and safety when patients were treatment resistant or unable to tolerate conventional treatments. There is less evidence for low-frequency stimulation of the right DLPFC and for bilateral protocols involving both high-frequency stimulation of the left DLPFC and low-frequency stimulation of the right DLPFC, but research in this area is ongoing [26].

Real-world open-label data from a rTMS clinic in Australia described outcomes for treatments of 167 patients (adults, no older patients) over a period of 6 years [27]. In that cohort, 28% achieved remission, 12% achieved response, and 23% achieved partial response. Of their responders, the average reduction in scores on the Hamilton Depression Rating Scale (Ham-D) was 15.05 points. Age did not predict response, but degree of treatment resistance was negatively associated with response. Of these, 41 patients returned for a second course of rTMS; 21 patients ultimately went on to maintenance rTMS, at intervals of 1–4 weeks. The courses of rTMS were well tolerated. In this sample, there were no seizures and no switches to manic episodes. Most patients (69%) had no side effects. The most common side effects included localized discomfort, mild headaches, and fatigue posttreatment. Some concern, however, has been raised about the small magnitude of treatment response [28] and about the durability of the effect of rTMS [29]. Higher treatment intensities (e.g., 120% of motor threshold) and longer treatment periods (e.g., 3–6 weeks) may be necessary for efficacy [22]. The search for more robust and consistently effective treatment protocols is ongoing in contemporary rTMS research.

Trials Including Older Patients

Several of the earlier studies of rTMS included older subjects. Some demonstrated efficacy with no age-related effects. The data on efficacy in older subjects was mixed, however, with other studies showing that younger patients responded better; i.e., older age was negatively associated with treatment response [13]. For example, a 2006 meta-analysis, which pooled data from six clinical trials with a total of 195 patients, found that prior treatment resistance and age were significant negative predictors of response to rTMS [30]. These trials included patients up to age 91 years. This confirmed earlier work by Figiel et al., which showed a 56% response rate in younger patients, compared to a 23% response rate in older patients [31]. The reasons for the differential response of older patients may have included a duration of treatment effect; older patients may have required longer courses. There may also have been a confounding effect of other brain disorders. A controlled trial of 24 older patients (mean age, 62 years) failed to demonstrate an effect of ten sessions of stimulation of the left DLPFC at 100% of motor threshold [32].

In this context, several subsequent studies excluded patients over the age of 65 years. However, the literature suggested that older patients might require higher intensity of treatment to account for the effects of age-related frontal cortical atrophy. By adjusting for measured prefrontal atrophy with increased stimulus intensity (average 114% of motor threshold, range 103–141%), a significant antidepressant effect could be produced [33]. In this study of 18 treatment-resistant older patients with depressive disorders, 27% responded to treatment, and 22% achieved remission.

In addition to increased stimulus intensity, older patients may require longer courses of rTMS [13]. Several large randomized controlled trials published after 2007 have *not* found age to be a negative predictor of response [13]. Developing effective treatment protocols for older patients is a focus of contemporary rTMS research. Modern treatment parameters for older patients currently under investigation include higher stimulus intensities (e.g., 120% of motor threshold), coils with slightly deeper penetration (e.g., H-type coils), bilateral treatment protocols, and longer treatment courses.

Trials Specific to Older Patients

There have been relatively few randomized controlled trials of rTMS solely in older adults [34]. These are summarized in ◘ Table 7.2 [12, 32, 35, 36]. A preliminary trial of rTMS for late-life depressive disorders was published in 2001 [12]. In this study, 20 patients over the age of 50 (mean age, 60.7 years) were treated with stimulation over the left DLPFC at 80% of motor threshold for a total of five sessions. Scores on Ham-D improved by 39.7%, response rate was 30%, and remission rate was 20%. However, this was a negative trial, as the treatment results were not significantly different from results in the sham group. This study did have significant limitations, including a small sample size, underdosing, and an imperfect method of sham control. This study did find that responders had greater volumes in the prefrontal cortex than nonresponders, suggesting a possible explanation for the failure of some older adults to respond to rTMS. Another early trial by of rTMS in older patients with treatment-resistant depressive disorder found no significant effect of high-frequency left prefrontal rTMS in 24 treatment-resistant subjects [32].

In contrast to these studies, another earlier trial of high-frequency left prefrontal rTMS for poststroke depressive disorder showed efficacy after 2 weeks of treatment, with no demonstrable age-related effects on treatment response [35]. The same group reported in 2008 on the results of a larger trial with two separate experiments in patients with vascular depressive disorder. These trials involved a larger number of subjects and were able to demonstrate efficacy with a higher stimulus intensity (110%) and a longer duration of treatment (15 sessions). Among the older subjects, active rTMS was only significantly effective in the prolonged treatment condition. Age was a negative predictor of response. In this trial, greater antidepressant response to rTMS was associated with larger volume of gray matter in the frontal area. The

Table 7.2 Randomized controlled studies of rTMS specific to older patients [12, 32, 35, 36]

Authors, year	Type of depression	Total subjects	Mean age (SD)	Age range (years)	TMS parameters	% improvement on Ham-D scores	Response rate (%)	Remission rate (%)	Treatment more effective than sham	Age-related findings
Jorge et al. (2008) part 1	Vascular	30	62.9 (7.2) (active group)	50 and older	L, 10 sessions, 10 Hz, 110%, 1200 pulses	33.1	33.3	13.3	Yes	More treatments improved response
Jorge et al. (2008) part 2	Vascular	62	64.3 (9.4)	50 and older	L, 15 sessions, 10 Hz, 110%, 1200 pulses	42.4	39.4	27.3	Yes	Older patients benefited more from prolonging treatment; age was negative predictor of response
Jorge et al. (2004)	Post-stroke	20	63.1 (8.1)	Not reported	L, 10 sessions, 10 Hz, 110%, 1000 pulses	38	30	10	Yes	No
Mosimann et al. (2004)	Mid/late-life	24	62 (12)	41–80	L, 10 sessions, 20 Hz, 100%, 1600 pulses	20%	26.6	Not reported	No	No
Manes et al. (2001)	Late-life	20	60.7 (9.8)	50 or older	L, 5 sessions, 20 Hz, 80%, 800 pulses	39.7	30	20	No	No

Note: Ham-D Hamilton Depression Rating Scale, *L* left

treatment was well tolerated, with no significant side effects or impact on cognition [36]. In fact, patients who were receiving active rTMS showed improvement in speed of performance on the Trails B test, independent of response to rTMS. This finding suggests the possibility that rTMS could enhance cognition independent of its effect on depression.

In addition to the studies previously described, there have been several open trials of rTMS in late life. These are summarized in Table 7.3 [33, 37–39]. Collectively, these studies showed reduction in Hamilton Depression Rating Scale (Ham-D) scores of 31.6–48.6%, response rates of 28–58.5%, and remission rates of 10–29.2%. Note that all but one of these studies defined response as a 50% reduction in pretreatment Ham-D and remission as a Ham-D below 8; the exceptional study [38] used a more permissive criterion for response of at least a 25% improvement in Ham-D and treated for only 2 weeks. Nahas et al. attempted to compensate for age-related atrophy in the prefrontal cortex by adjusting the stimulus intensity, based on MRI data for each participant. In that study, patients with depressive disorder with late-life onset responded less well than patients with early-onset depressive disorder. White matter hyperintensities did not have a demonstrable impact on treatment response [33].

Indications for rTMS

Major Depressive Disorder

The primary indication for rTMS is major depressive disorder. It is considered a first-line treatment for patients who have failed at least one trial of an antidepressant medication

Table 7.3 Open-label studies of rTMS specific to older patients [33, 37–39]

Authors, year	Type of depression	Total subjects	Mean age (SD)	Age range (years)	TMS parameters	% improvement on Ham-D scores	Response rate (%)	Remission rate (%)	Age-related findings
Hizli Sayar et al. (2013)	Late life	54	66.57 (5.77)	60–83	100%, LDLPFC, 18 sessions, 25 Hz, 1000 pulses	48.6	58.5	29.2	None reported
Abraham et al. (2007)	Late life	20	66.8 (6.4)	60–80	100%, LDLPFC, 10 sessions, 10 Hz, 1600 pulses	31.6	30	10	None reported
Nahas et al. (2004)	Late life	18	61.2 (7.3)	55–75	114% (103–141%), LDLPFC, 15 sessions, 5 Hz, 1600 pulses	35.2	28	22	Stimulus intensity adjusted for DLPFC atrophy; less response with late-onset depression
Fabre et al. (2004)	Vascular	11	67.9 (6.7)	56–77	100%, 16 sessions, 5 Hz,	35%	45	Not reported	Worsened verbal fluency

Note: Ham-D Hamilton Depression Rating Scale, *LDLPFC* left dorsolateral prefrontal cortex

[40]. Greater degrees of treatment resistance are associated with lack of response to rTMS, so it may be preferable to use rTMS earlier in the treatment course of major depressive disorder. As discussed above, older age has been associated with poor response to rTMS, but emerging data suggests that older adults may require higher stimulus intensities and longer courses of treatment for a positive response. Taking this into account, it would be reasonable to consider rTMS for an older adult with major depressive disorder, either early onset or late onset.

Bipolar Depression

Ten out of 23 randomized controlled trials described in a 2016 systematic review included patients with bipolar depression (an episode of depression within bipolar disorder), usually a very small proportion of the overall sample (under 20%) [29]. There have been relatively few controlled trials specific to bipolar depression. Sequential bilateral rTMS was tried in this population in 49 patients (mean age 47.9 years, standard deviation 11.9) and failed to separate from sham treatment in a 4-week trial [41]. The very limited efficacy data (two randomized controlled trails) prior to this study was mixed. The efficacy of rTMS in bipolar depression thus remains unclear.

Depressive Episode with Psychotic Features

Depressive episode with psychotic features is a common presentation in older patients. Evidence to date suggests that a depressive episode with psychotic features responds less well to rTMS [13]. A meta-analysis comparing ECT and rTMS, conducted in 2014, found that ECT was superior to rTMS for this presentation of depressive disorder [42]. As available data is limited, however, it remains possible that longer or more intense treatment protocols of rTMS might be more effective for this subtype of depressive disorder.

Vascular Depressive Disorder

rTMS has been studied in vascular depressive disorder and found to be safe and effective in this context [36]. It remains unclear if the presence of subcortical vascular changes affect response to the treatment, either positively or negatively. White matter hyperintensities did not have a demonstrable impact on treatment response in one of the early trials of rTMS in late-life depressive disorder [33]. However, if there is ischemic damage in the frontal cortex, rTMS should be avoided due to the risk of provoking a seizure in this context [36].

Depressive Disorder in the Context of Major or Mild Neurocognitive Disorder (Formerly Dementia) with Behavioral Disturbances

There is no data regarding the safety and efficacy of rTMS in the context of depressive disorders comorbid with major or mild neurocognitive disorder [36]. The use of rTMS in mild and major neurocognitive disorder is currently being explored, and there is some preliminary data regarding the tolerability of the procedure in this context [9]. There may also be practical concerns in more severe major neurocognitive disorder, as the patient must cooperate with the procedure and sit quietly in one position for a significant period.

Depressive Disorder in Parkinson Disease and Parkinson Plus Syndromes

There is a case report of a significant response of depressive disorder in a 62-year-old man with progressive supranuclear palsy and major depressive disorder with low-frequency stimulation of the right DLPFC. A 2-week randomized controlled trial of multifocal rTMS in 61 patients with Parkinson disease and depressive disorder was negative [43]. However, a randomized controlled trial of high-frequency (5 Hz) stimulation of the left DLPFC for 2 weeks in 22 patients with depressive disorder and Parkinson disease showed a significant response and remission rate. This was consistent with a limited previous literature (four randomized controlled trials) regarding rTMS for depression associated with Parkinson disease [44]. rTMS may be effective for depression in this population.

Depressive Disorder with Traumatic Brain Injury

Traumatic brain injury is theoretically associated with increased risk for seizures with rTMS and is thus considered a relative contraindication for rTMS. There, however, is a small literature exploring the use of rTMS in this population. Six patients with traumatic brain injury received high-frequency left rTMS of the DLPFC in a feasibility study for headache, and there were no adverse effects [45]. Nielson et al. reported on a case on the use of rTMS in a 48-year-old man who had intracranial titanium plates and screws following traumatic brain injury [46]. He was treated with low-frequency stimulation of the right DLPFC. The stimulus site was determined by neuronavigation, and the titanium plate was considered far enough away from the site of stimulation. Another case of use of rTMS in traumatic brain injury was reported by Fitzgerald et al. [47] who recommended reviewing neuroimaging and neurosurgical reports and excluding subjects taking medications that lower seizure threshold. The safety of rTMS in patients with traumatic brain injury remains unclear.

Major and Mild and Neurocognitive Disorders

In a trial of rTMS for vascular depressive disorder, Jorge et al. found a significant increase in performance speed, independent of improvement in depression [36]. rTMS is now being investigated for potential utility in the context of neurocognitive disorders. Ahmed et al. conducted a trial of rTMS in 45 patients with mild, moderate, and severe major neurocognitive disorder due to Alzheimer disease. In this trial, high-frequency left stimulation was compared to low-frequency right and sham. The high-frequency left group showed statistically significant improvement in mood, functioning, and activities of daily living [9].

An industry-funded study combined rTMS and cognitive training in an open-label study of 30 patients with mild-to-moderate major neurocognitive disorder due to Alzheimer disease [48]. Targets of stimulation were the left inferior frontal gyrus (Broca area), left superior temporal gyrus (Wernicke area), left and right DLPFCs, and left and right parietal somatosensory association cortices. There was a statistically significant improvement in cognitive measures such as MMSE, ADAS-Cog in this preliminary work. Lee et al. showed similar results in a trial of 27 patients [49]. Drumond Marra et al. showed some improvement in memory in a randomized controlled trial of rTMS (high-frequency left DLPFC) in 34 older patients with mild cognitive impairment, although other cognitive functions remained unchanged [50]. This work remains exploratory and investigational at present.

Other Psychiatric Disorders

The use of rTMS is being explored in the general adult population for various anxiety disorders (including generalized anxiety disorder, panic disorder, and social anxiety disorder), obsessive-compulsive disorder, and posttraumatic stress disorder. The data supporting a general anxiolytic effect or a specific effect on particular anxiety disorders is limited at present, and this use remains investigational. It may be necessary to target different brain regions (e.g., orbitofrontal cortex and supplementary motor area in obsessive-compulsive disorder). No specific data exists regarding the treatment of anxiety disorders in older adults with rTMS [51]. A case report exists of successful treatment of burning mouth syndrome in a 64-year-old patient with high-frequency rTMS to the left DLPFC over a 2-week period [52].

Side Effects of rTMS

In general, rTMS is a well-tolerated treatment with few side effects. The most typical side effects are mild headache (10%) and discomfort at the site of stimulation (6%) [53]. Patients develop tolerance to the scalp discomfort; it may require beginning treatment at a lower stimulus intensity and then gradually increasing so that the patient can tolerate the appropriate dose [53].

The main risk associated with rTMS is induction of a seizure. Seizures are rare, occurring at a rate of about 1/30, 000 treatment sessions [16]. Other reported serious side effects include syncope and rare induction of hypomania. Facial twitching, local redness, drowsiness, and dizziness have also occurred. There have been anecdotal reports of insomnia, joint pain, vertigo, and hostile thoughts.

Naturalistic data from a 7-year real-world clinical experience in Australia have been reported; these data involve a total of 205 patients, 262 courses of rTMS, and a total of 6155 treatments (81.4% acute courses, 18.6% maintenance courses). In this group, 69.4% had no side effects, and only 4.3% reported side effects that interfered with functioning [15]. This finding is consistent with Rossi et al. in 2009, where side effects commonly reported were mild and mostly localized discomfort at the site of stimulation and headaches. In that study, only 8.0% of patients dropped out because of side effects or lack of efficacy [18]. Risks associated with rTMS can be minimized by using a pretreatment clinical screening questionnaire [18].

rTMS and Cognition

rTMS has not been demonstrated to impair cognition in any domain [13]. One early study in older patients found decreased verbal memory [54], but most studies have found

rTMS to have no other effects on cognition or to have a positive effect. An early study of older patients with vascular depression found an improvement on speed of performance in the Trails B task; this improvement was independent of improvements in depressive disorders, suggesting a possible independent effect of stimulation of the left DLPFC on cognition.

High-frequency rTMS has been reported to exert facilitator effects on various cognitive functions. Kim et al. treated 16 healthy older subjects with high-frequency stimulation over the left DLPFC and then assessed changes in inhibitory control using a modified Stroop task [55]. Five daily stimulations improved reaction times. Nadeau demonstrated gains in several cognitive domains (language, visuospatial function, and verbal episodic memory) with right high-frequency stimulation of the DLPFC [54]. This effect was independent of improvement in depressive symptoms. These more recent findings echo the findings of Moser et al., who demonstrated improved executive functioning in 19 middle-aged and older patients with treatment-resistant depressive disorder with 1 week of high-frequency left-sided stimulation in a randomized controlled trial [56].

The clinical significance of these studies showing improvements in cognition is uncertain at present, and exploratory work is ongoing to examine the possibility that rTMS could be helpful for patients with cognitive decline [49]. However, impairment of cognition does not appear to be a side effect of rTMS with current treatment parameters.

Contraindications and Safety Considerations

There is only one absolute contraindication to rTMS: the presence of metallic hardware in close contact with the coil used to administer the stimulus [18]. This might include cochlear implants, medication pumps, internal pulse generators, DBS electrodes, or any other ferromagnetic implants. The magnetic pulses generated by the coil have the potential to cause such devices to malfunction. Some authors have also suggested that rTMS should be avoided in patients with cardiac pacemakers or an implanted defibrillator, for similar reasons [36]. There is, however, one case report of successful use of rTMS in a patient with a cardiac pacemaker in a 72-year-old patient [57].

Induction of a seizure is a major significant risk associated with rTMS. Disorders with the potential to lower seizure threshold are associated with increased seizure risk when high-frequency rTMS is given. These include epilepsy, brain lesions (e.g., vascular, traumatic, infectious, metabolic, tumors), concomitant medications which lower seizure threshold, sleep deprivation, and heavy alcohol use. Consideration should be given to reducing or eliminating factors which lower seizure threshold and to the use of concomitant anticonvulsant medication in such circumstances [18]. It is important to respect established safety protocols when using rTMS in a clinical setting, to reduce the risk of seizure. Novel protocols may be associated with increased seizure risk and should be considered investigational at present [58].

Practical Considerations

rTMS is not currently available in all jurisdictions, and clinicians may have variable experience with its use. Local issues of insurance reimbursement/financial coverage and access may have a significant impact on the use of rTMS, independent of the evidence supporting its use. As with all medical treatments, informed consent prior to the treatment is important, and it should be mentioned that there are more effective treatments for refractory depressive disorder, including ECT. Patients should also be educated and informed about the equipment and the procedure, as they will be required to sit in a relatively fixed position with little opportunity to observe the rTMS device during the initial treatment session.

rTMS may be done with or without concomitant antidepressants. It should be noted that many psychotropic medications, including antidepressants and antipsychotics, may alter the seizure threshold. Therefore, if medications change during rTMS, consideration should be given to reassess the patient's motor threshold [16]. Most rTMS-induced seizures have occurred in patients taking medications known to reduce the seizure threshold. If a patient is on such a medication, or is withdrawing from a central nervous system depressant such as a benzodiazepine, caution should be exercised regarding the risk of seizure induction with rTMS [18]. Some evidence suggests that starting a new antidepressant medication at the same time as a course of rTMS improves response rates [40].

Several methods of locating the target for stimulation have been described. Earlier studies determined the location of the motor cortex by observing thumb movement and then used a standard measurement to determine the stimulus location. This method has been found to be inaccurate in 30% of cases [16]. Neuronavigational methods of determining the location of stimulation are accurate, but have not been shown to be more effective than placement strategies that adjust for skull size (e.g., stimulation at the BeamF3 site) [23].

Treatment is usually administered 5 days per week, for a total duration of 4–6 weeks. It can be appropriate to extend treatment beyond 6 weeks if there is only a partial improvement and no clear plateau. If the patient has shown no response after 6 weeks, the patient is unlikely to respond, although a case could be made for continuing for a specific individual. This may be particularly relevant for older patients, who may respond more slowly to antidepressant treatments in general and to rTMS in particular [13]. There is no known toxicity related to cumulative exposure to rTMS. Progress and response to rTMS should be monitored with an objective rating scale to assist with making these treatment decisions [16].

Durability of Effect and Post-rTMS Maintenance

In a 6-month continuation study of adult responders to rTMS, patients were maintained on pharmacotherapy and followed over time; 12.9% relapsed, and 38.4% of patients had worsening symptoms. When adjunctive rTMS was restarted, 84.2% of these patients regained their previous benefit [11]. Mean

time to relapse was 164 days (+/− 4 days). This was consistent with previous studies [41]. In the general adult population, the duration of the rTMS effect in responders may be around 4–6 months.

One study of older patients with vascular depressive disorder who responded to rTMS followed patients on continuation citalopram for 9 weeks. In this study, 4 of 13 patients relapsed within 9 weeks on the antidepressant, a 30% relapse rate [59]. This is a somewhat higher than results reported in younger populations. However, the numbers in this study are small, and it is not clear if this represents a real difference in relapse rates in this population.

In the absence of clear evidence-based protocols for discontinuation of rTMS and maintenance treatment, consensus recommendations for the adult population suggest that when discontinuing rTMS, to gradually reduce the frequency of treatments over 3 weeks and then stop [16]. In a large multicenter NIMH-funded trial, treatments were reduced to three times per week for 1 week, then to two times per week for 1 week, and then to one time per week for 1 week, and then treatments were discontinued [22]. If patients show worsening of symptoms or relapse after discontinuation, a return to rTMS is likely to result in a return to previous levels of improvement.

Maintenance rTMS can also be an option for patients who relapse often; expert consensus suggests administering treatments at a frequency between once per week and once per month, according to patient symptoms [16]. In a naturalistic Australian study, 21 of 167 (12.6%) patients went on to require maintenance rTMS after relapsing [27].

ECT Versus rTMS for Depressive Disorders

A summary of the literature to date concludes that rTMS is less effective than ECT for depressive disorder [40]. This finding particularly holds true in the presence of psychotic features [42]. Patients who have not responded to ECT are unlikely to respond to rTMS [40]. The two treatments should be considered as complementary. rTMS has demonstrated efficacy for depressive disorder earlier in the course of treatment resistance, and it is better tolerated and often more acceptable to patients than ECT. Simpson et al. conducted an economic analysis of the timing of rTMS use in treatment-resistant depressive disorder and found that using rTMS early in the treatment course instead of switching medications was a more cost-effective strategy [60]. As rTMS becomes more generally available, it may take on a more important role in the managing of treatment-resistant depression. However, ECT remains the most effective treatment for major depressive disorder at present, especially for treatment-resistant depressive disorder, and depressive disorder with melancholic and/or psychotic features [61].

Future Directions for rTMS in Older Adults

rTMS is now an accepted treatment for depressive disorders in the general adult population [40]. Current evidence suggests that older patients may respond as well as younger ones, with adequate intensity and duration of treatment, regardless of age of onset of depression [13]. However, many questions remain unanswered. Future research will need to elucidate optimal treatment protocols for effectiveness and from an economic perspective. Other unanswered questions include the impact of vascular changes, the long-term durability of the antidepressant effect of rTMS, and the ideal ways to combine rTMS with antidepressant medications and psychotherapy. The role of rTMS in treating other psychiatric disorders common in older patients, such as neurocognitive disorders, anxiety disorders, psychotic disorders, and somatic symptom disorders, is only beginning to be explored in this rapidly evolving field.

7.1.3 Deep Brain Stimulation (DBS)

In DBS, unilateral or bilateral electrodes are placed in the brain using stereotaxic neurosurgical methods; these electrodes are then connected to a permanently implanted neurostimulator, which electrically stimulates that brain region [62]. Modifiable stimulus parameters include amplitude, frequency, pulse width, and electrode configuration [63]. Modulation of neuronal activity at the target site can affect patterns of brain activity within neural circuits and therefore has the potential to affect brain activity both "upstream" and "downstream" of the locus of electrode placement [63].

DBS for Depressive Disorders

The technique is widely used for the treatment of Parkinson disease, with electrodes implanted in the subthalamic nucleus or globus pallidus internus [62]. For depressive disorder, various parts of reward circuitry in the brain are targeted [64]. However, it remains an experimental technique for depressive disorder in both general adult and older adult populations [13].

DBS targets in depressive disorder have included the anterior gyrus cinguli (Brodmann area Cg25), the anterior limb of the internal capsule, the medial forebrain bundle, the nucleus accumbens, the habenula, and the thalamus [64]. Open data regarding stimulation of the anterior gyrus cinguli, the anterior limb of the internal capsule, and the nucleus accumbens have demonstrated short-term efficacy [64].

An open-label trial of subcallosal cingulate of DBS for treatment-resistant depressive disorder showed promising results [65]. During a period exceeding 2 years of chronic stimulation, response rates were 92%, and remission rates were 58%. This study included patients with bipolar depression and patients up to age 70 years. However, a subsequent randomized controlled trial of DBS in 30 subjects with treatment-resistant depressive disorder was conducted (mean age, 47.7 (22–68) years). Results were disappointing, with no significant differences in response or remission rates compared to the control group [66]. Given the failure of this randomized controlled trial to demonstrate efficacy of the technique, data supporting DBS are limited to open

trials and case reports. There are two case reports of the technique showing efficacy in older adults. One reported case involved a 64-year-old woman, with recurrent major depression since the age of 18. She responded to DBS (bilateral subcallosal gyrus) with remission for 5 months and then relapsed. Her DBS electrodes were turned off, and she then responded to nine sessions of bifrontal ECT. Remission post-ECT was then sustained with DBS for 6 months at the time of reporting [67]. The efficacy of DBS in this case appears confounded by the use of ECT, a modality known to be associated with efficacy. Another report of a positive treatment response to DBS involved a 66-year-old woman, with recurrent major depressive disorder since the age of 21 [62].

DBS for Neurocognitive Disorders

Exploratory work is ongoing regarding the use of DBS as a treatment for major neurocognitive disorder (dementia) [63]. Freund et al. published a single case report of stimulating the nucleus basalis of Meynert in a 71-year-old man with major neurocognitive disorder due to Parkinson disease, resulting in improvement in episodic memory, recognition, visuospatial abilities, processing speed, praxis, attention, concentration, alertness, drive, and spontaneity [68]. In a pilot study, Kuhn [69] reported bilateral low-frequency DBS of the nucleus basalis of Meynert in six patients with mild-to-moderate major neurocognitive disorder due to Alzheimer disease, with an average MMSE pretreatment score of 20.3 points. The study consisted of a 4-week sham-controlled phase and then an 11-month open-label follow-up period. The average age of the subjects was 69.5 years (+/− 7.7). Four out of the six patients were considered responders, based on stability of the ADAS-Cog over the 1-year study period. There are ongoing trials of DBS of the fornix and/or nucleus basalis of Meynert in major neurocognitive disorder due to Alzheimer disease, Parkinson disease, Lewy body disease, and Huntington disease. Sankar et al. [70] used DBS applied to the fornix in 6 patients with Alzheimer disease aged 51–69 years; in this study, hippocampal volume increases over 1 year were observed in 2 of 6 patients. This work, though interesting, remains experimental.

ECT and rTMS in the Presence of DBS Electrodes

For depressive and major or mild neurocognitive disorders, DBS remains investigational at present [40]. Psychiatrists could, however, find themselves confronted with the need to use another brain stimulation technique for a patient who has implanted DBS electrodes, either for psychiatric or neurologic disease. Several case reports exist demonstrating the safety of ECT in the presence of deep brain electrodes, for example, that of Puigdemont et al. [67]. In contrast, stimulation studies of rTMS in the presence of deep brain electrodes have demonstrated induced electrode currents that could result in tissue damage [71]. rTMS should not be applied to a patient with DBS electrodes in place.

7.2 Case Studies

The following case-based studies are reflective of the clinical use of rTMS in older patients with major depressive disorder, both straightforward and complex.

7.2.1 Case 1

Case 1 History

Mr. A. is a 72-year-old retired engineer with major depressive disorder with anxious distress. He was sent for consultation regarding the suitability of rTMS for his depressive disorder. His first episode occurred at the age of 68, and he responded well to treatment with sertraline as an outpatient. Following discontinuation of his medication 1 year later, he relapsed. When sertraline was restarted, he did not respond. He also failed an adequate trial of vortioxetine and was unable to tolerate venlafaxine or quetiapine due to side effects. He remains on sertraline 200 mg per day despite its relative lack of effect. He is on a waiting list for group cognitive-behavioral therapy, which starts in 9 months. His current depressive episode is chronic over the past 3 years, and he has continued to be treated as an outpatient. His symptoms include low mood, anhedonia, and decreased energy and concentration. He also has decreased appetite but pushes himself to eat, and his weight has remained stable at 160 lbs. (72.5 kg). He has no history of suicidal ideation or attempts and does not currently have active suicidal ideation, though he does sometimes think he would be better off dead. There is no history of hypomania, mania, or psychosis. He reports no issues with his memory, and there have been no falls. His medical history includes type 2 diabetes mellitus and osteoarthritis. He has no history of surgeries, no history of head trauma, and no implanted metallic hardware anywhere in his body.

In the context of ongoing depressed and anxious mood, his alcohol consumption has increased from an occasional beer on social occasions to two beers, three to four times per week. He is a nonsmoker and has no history of illicit drug use. Current medications include metformin 1000 mg twice a day and acetaminophen as needed. Recent medical workups including complete blood count with differential, electrolytes, renal and liver panels, thyroid-stimulating hormone, B_{12}, folate and ferritin levels are all within normal limits. His ECG is normal. Neuroimaging with CT scan revealed subcortical white matter periventricular changes.

On mental status examination, Mr. A. was well dressed and groomed and soft spoken. He appeared his stated age and described his mood as "down," while affect was congruent with a restricted range. There were no psychomotor abnormalities. Thought process was organized and coherent, and there was no evidence of psychosis or active suicidal ideation. There was fleeting passive suicidal ideation as described above. He was curious about the possible treatment of his depressive disorder with rTMS. Cognitive testing was within

normal limits, with Montreal Cognitive Assessment (MoCA) score of 29 out of 30 with one point lost for date. Insight was preserved and judgment was intact.

Case 1 Questions and Answers

Case 1 Questions

Question 1. Would this patient be a good candidate for rTMS?

Question 2. What are some clinical factors that might make Mr. A. less likely to respond to rTMS?

Question 3. Mr. A. developed depressive disorder for the first time later in life, at age 68. He also has white matter changes on neuroimaging. How do these factors affect his chances of responding to rTMS?

Question 4. If psychotic features were present, how would this have influenced the recommendation to try rTMS?

Question 5. How does the presence of significant alcohol use affect the proposed rTMS treatment?

Question 6. Mr. A. receives high-frequency stimulation to the left DLPFC, 5 days per week. However, after 4 weeks of treatment, he does not seem to be responding. Would you consider switching to ECT?

Case 1 Answers

Case 1 Answer 1 (Question 1—Would this patient be a good candidate for rTMS?)

This patient has a diagnosis of major depressive disorder, which is a primary indication for rTMS. It is considered first-line treatment for patients who have failed at least one trial of an antidepressant medication [36]. Reported response and remission rates in a 2014 meta-analysis by Berlim et al. were 29.3%, and 18.6%, respectively [14]. Although these rates are much lower than response and remission rates reported with ECT, they are still clinically significant, and rTMS is now accepted as an evidence-based treatment for depressive disorder [43].

Teaching Point
rTMS is considered a first-line treatment for patients who have failed at least one trial of an antidepressant medication.

Case 1 Answer 2 (Question 2—What are some clinical factors that might make Mr. A. less likely to respond to rTMS?)

Older age has been associated with poor response to rTMS, possibly due to age-related cortical atrophy. Because of this, he may require higher stimulus intensities as well as a longer course of treatment. He has also had several unsuccessful medication trials, at least two of which were of adequate dose and duration, and his illness therefore demonstrates a high degree of treatment resistance. Treatment resistance is associated with a lack of response to rTMS. Mr. A.'s current depressive episode has become chronic, with duration of 3 years. The longer the duration of a depressive episode in treatment-resistant depression patients, the less likely rTMS will be successful in treating the depressive episode [47]. The presence of white matter hyperintensities may also be associated with treatment resistance in general. The escalation in his alcohol use may also contribute to treatment resistance.

Teaching Point
Because treatment resistance and duration of depressive episode are associated with nonresponse, the best time to use rTMS is early in the course of depression, before treatment resistance is well established.

Case 1 Answer 3 (Question 3—Mr. A. developed depressive disorder for the first time later in life, at age 68. He also has white matter changes on neuroimaging. How do these factors affect his chances of responding to rTMS?)

Regardless of the age of onset of depressive disorder, current evidence suggests that with appropriate intensity and duration of treatment, older patients may respond as well as younger ones to rTMS [31]. Therefore, it would be reasonable to consider rTMS for an older adult with major depressive disorder with either early-onset or late-onset depressive disorder. White matter hyperintensities have been associated with treatment resistance in late-life depressive disorder in general. However, at least one study found that white matter hyperintensities did not have a demonstrable impact on treatment response to rTMS [42].

Teaching Point
Even with late-life onset of depressive disorder and the presence of white matter changes, older patients may respond to rTMS.

Case 1 Answer 4 (Question 4—If psychotic features were present, how would this have influenced the recommendation to try rTMS?)

Depressive disorder with psychotic features is a common presentation in the geriatric population. ECT remains the gold standard for the treatment of depressive disorder with psychotic features in older adults, as it is more effective than pharmacotherapy and has a faster onset of action. Pharmacotherapy with an antidepressant and an antipsychotic remains a reasonable alternative, when severity and urgency permit [33]. Among neurostimulation treatments, rTMS is less likely to be effective than ECT for psychotic depression [31]. A 2014 meta-analysis conducted by Ren et al. comparing ECT and rTMS also found that ECT was superior to rTMS for this presentation of depression [42].

Teaching Point
When neurostimulation is considered for depressive disorder with psychotic features, ECT remains the treatment of choice (See ► Chap. 6).

Case 1 Answer 5 (Question 5—How does the presence of significant alcohol use affect the proposed rTMS treatment?)

The escalation in his alcohol use may contribute to lack of response to treatment. In addition, there are some safety considerations regarding the use of rTMS in the context of substance use. One of the main risks associated with the use of rTMS is the induction of a seizure. In a state of acute withdrawal, alcohol has the potential to lower seizure threshold, thereby increasing the risk of seizures. Seizures with use of rTMS are rare and occur at a rate of about 1 in 30,000 treatment sessions [64]. However, the majority of rTMS-induced seizures have occurred in patients taking or withdrawing from medications or substances known to affect the seizure threshold including central nervous system depressants like benzodiazepines. Benzodiazepine and alcohol withdrawal lower seizure threshold and increase the risk of seizures in rTMS; other conditions with the potential to lower seizure threshold include epilepsy, brain lesions, and sleep deprivation. It would be prudent to ensure that a potential state of withdrawal is addressed and treated prior to initiating treatment with rTMS. This patient has heavy, but not daily, alcohol use. He should minimize his use of alcohol during rTMS treatment and avoid episodes of heavy use.

Teaching Point
In patients with conditions associated with lowering of seizure threshold, caution should be exercised regarding the possibility of seizures induced by rTMS. These conditions include brain disease, alcohol withdrawal, benzodiazepine withdrawal, and use of psychotropic medications associated with significant reductions in seizure threshold (e.g., clozapine).

Case 1 Answer 6 (Question 6—Mr. A. receives high-frequency stimulation to the left DLPFC, 5 days per week. However, after 4 weeks of treatment, he does not seem to be responding. Would you consider switching to ECT?)

There are several factors that may explain a lack of treatment response in rTMS. Older patients may require longer to respond to rTMS and to other treatments of depressive disorder. Age-related prefrontal cortical atrophy may also be a factor which might explain lack of response to rTMS. Higher treatment intensities and coil shapes which allow deeper penetration into the cortex may be necessary in this population. Research on appropriate coils and treatment protocols for older patients is ongoing.

Mr. A. might require a longer course of rTMS to determine if he is truly resistant to this treatment. If he has shown no response after 6 weeks, he is unlikely to respond. It could be appropriate to extend treatment beyond 6 weeks under limited circumstances, for example, if there were a partial improvement demonstrable on rating scales and no clear plateau of improvement. The use of rating scales can assist in assessing partial response and therefore facilitate decision-making. Some practitioners might consider switching to an alternate rTMS protocol (e.g., bilateral stimulation).

This patient has failed two adequate trials of antidepressants, and his episode has become chronic. These factors are associated with lack of response to rTMS. The best time to use rTMS may be early in the course of major depressive disorder, before treatment resistance is well established. It is possible that rTMS might have been effective earlier in Mr. A. illness but that at this point his degree of chronicity and treatment resistance make rTMS less likely to be effective.

Patients who do not respond to rTMS may still respond to ECT. Once a sufficiently long course of rTMS (6 weeks) was completed and the patient was deemed a nonresponder, it would be appropriate to consider ECT treatment for Mr. A. It is important to note, however, that the converse is not true. Patients who do not respond to ECT are unlikely to respond to rTMS [36]. Alternate pharmacotherapy trials including tricyclic antidepressants and various antidepressant augmentation strategies, as well as augmentation with psychotherapy (Mr. A. awaits starting cognitive-behavioral therapy), would also be appropriate approaches to management.

Teaching Points
- Older patients may require longer courses of rTMS and higher stimulus intensities (always within safety guidelines) to achieve response/remission.
- Failure to respond to rTMS does not preclude response to ECT. The converse, however, is not true; failure to respond to ECT predicts failure to respond to rTMS.
- The best time to use rTMS may be early in the course of major depression; e.g., after the first failed adequate trial of an antidepressant, before treatment resistance and chronicity are well established.

Case 1 Analysis Although rTMS is associated with lower response and remission rates for depressive disorder than is ECT, rTMS is considered an evidence-based treatment for depressive disorder and is considered first-line treatment for patients who have failed at least one trial of an antidepressant medication. In the case of an older man such as Mr. A., certain factors such as age-related prefrontal cortical atrophy, long duration of depressive disorder, as well as treatment resistance need to be taken into account when considering treatment with rTMS. Mr. A. had not responded to two antidepressant trials, so has a significant degree of treatment resistance. There were no acute psychiatric concerns such as psychosis, acute suicide risk, or inanition, which would have warranted more definitive treatment with a robust modality such as ECT.

He was motivated to pursue rTMS but had to be informed of the relatively limited efficacy data, including the 29.3% response rate and 18.6% remission rate. The trial of rTMS was reasonable, as long as he was able to make an informed choice among the alternatives of pharmacotherapy, psychotherapy, and other forms of brain stimulation such as ECT. A complete review of his medical history revealed no major concern that would preclude the use of rTMS. His heavy use of alcohol had to be discussed and managed given the risk of lower seizure threshold associated with withdrawal. Given his age, he was likely to require a longer treatment course with rTMS (e.g., 4–6 weeks).

Although the choice of rTMS was reasonable and to some extent guided by patient preference, he did not respond in 4 weeks. He might have responded to a longer course (up to 6 weeks), but the fact that he did not show even a partial response at 4 weeks makes that possibility less likely. The use of a structured depression rating scale might have facilitated assessment of a partial response and might have helped with clinical decision-making.

Prolonging the treatment course, switching antidepressants, trying alternate antidepressant augmentation strategies, altering the rTMS treatment protocol, adding psychotherapy, and considering ECT would all be reasonable as part of an approach after a failure to respond to rTMS.

7.2.2 Case 2

Case 2 History

Mrs. B. is a 66-year-old social worker with history of recurrent major depressive disorder. She presents with symptoms of low mood and anhedonia. She no longer exercises or reads for pleasure as she did previously. She has decreased energy and fatigue. She feels guilty about being a burden to her family and has intermittent passive suicidal ideation. She has initial insomnia taking up to about 2 hours to fall asleep. On average, she sleeps about 5–6 hours each night and spends much of her weekends in bed. Her appetite is unchanged, and she has not lost weight. Her concentration is poor, and she has significant concerns about her memory. She is still able to function at work. There are no symptoms of anxiety, and she has no history of hypomania, mania, or psychosis.

Her first depressive episode occurred at the age of 30 and was treated successfully with desipramine 100 mg daily. She had a second episode at the age 50; she responded to fluoxetine 60 mg daily, which she took for approximately 3 years. Her most recent episode began at age 63. This time, she was unable to tolerate any selective serotonin reuptake inhibitor or serotonin norepinephrine reuptake inhibitor due to nausea and ultimately settled for a partial response on bupropion 150 mg daily. She was unable to increase the dose because of insomnia and elected to stay on the bupropion at its current dose despite its limited efficacy. The addition of cognitive-behavioral therapy has helped her to cope with her illness, but she remains symptomatic and functionally impaired. Mrs. B. scores 35 (consistent with severe depression) on the Montgomery-Asberg Depression Rating Scale (MADRS). On cognitive testing using the MoCA, she scored 27 out of 30, with one point each lost in Trails B, delayed recall, and date.

She is a nonsmoker and consumes about two glasses of wine per week. There is no history of illicit drug use. Her past medical history is significant for hypertension, osteoporosis, and postherpetic neuralgia in her chest. Her medications include bupropion 150 mg qAM, clonazepam 0.75 mg bid, pregabalin 25 mg tid, raloxifene 60 mg qAM, and eprosartan 600 mg qAM.

Her mother had major depressive disorder with multiple episodes. Her grandmother had a neurocognitive disorder with onset in her 80s. She is not certain but thinks that her grandmother might have had a seizure in the later stages of her neurocognitive disorder.

Case 2 Questions and Answers

Case 2 Questions

Question 1. Mrs. B. has a possible family history of seizure. How would this influence your decision to give her rTMS treatment?

Question 2. Mrs. B. is currently taking clonazepam, pregabalin, and bupropion. How might these anticonvulsant medications influence her rTMS treatment?

Question 3. What impact is rTMS likely to have on Mrs. B.'s cognitive function?

Question 4. What steps would you consider if Mrs. B. relapses?

Case 2 Answers

Case 2 Answer 1 (Question 1—Mrs. B. has a possible family history of seizure. How would this influence your decision to give her rTMS treatment?)

One of the main risks associated with the use of rTMS is the induction of a seizure. Seizures with use of rTMS are rare and occur at a rate of about 1 in 30,000 treatment sessions [64]. A personal history of epilepsy, or a history of seizure in a first-degree relative (e.g., parent, sibling, child) although not an absolute contraindication, is associate with increased risk of seizure. The family history in this case is not in a first-degree relative and may have been due to a specific pathological condition (neurocognitive disorder) which the patient does not have. Therefore, in this case the positive family history would not be considered to significantly increase her risk of having a seizure from rTMS. The patient herself does not have a medical condition which increases the risk of seizure during rTMS.

All patients who receive rTMS should undergo screening for conditions associated with increased seizure risk. The pre-rTMS evaluation should pay careful attention to the presence of any medications which alter seizure threshold and to any medical conditions which increase the likelihood of a seizure (e.g., a history of traumatic brain injury or epilepsy). This

information can then be used to provide the patient with a more accurate assessment of risks and benefits. Of note, even in patients with epilepsy, the incidence of seizure was relatively low (1.4%) [8].

Teaching Point
During the pre-rTMS evaluation, special attention should be paid to factors which increase the likelihood of seizures, such as a family history of seizures, the presence of focal brain disease, and the use of medications which lower seizure threshold.

Case 2 Answer 2 (Question 2—Mrs. B. is currently taking clonazepam, pregabalin, and bupropion. How might these anticonvulsant medications influence her rTMS treatment?)

rTMS therapy can be administered in the presence of concurrent antidepressant or other psychotropic medications [64]. There are currently no data from controlled trials supporting the use of medications with TMS. There is also no evidence of an increased risk of adverse events by combining medications with TMS.

With benzodiazepine and anticonvulsant medications, care should be taken to avoid withdrawal from these medications during rTMS, as this would increase the risk of a seizure. Keeping the dosage of these medications stable during rTMS would be prudent. A significant change in the patient's medications during the course of rTMS treatment should prompt consideration of reassessment of the patient's motor threshold to ensure that there are no significant changes in this parameter.

Bupropion does lower seizure threshold moderately, but she is on a relatively low dose, and her depressive disorder has had a partial response to this medication, which is currently at its maximum tolerable dose for her. Keeping the dosage of this medication stable during rTMS treatment again seems like the most prudent course. Some data suggests that starting a new antidepressant at the time of rTMS initiation can improve response and remission rates [36]. Consideration could therefore be given to changing her bupropion to another agent she has not previously tried. However, given her history, medication tolerability of alternative agents may be an issue.

Teaching Point
rTMS therapy can be administered with or without concurrent antidepressant or other psychotropic medications. Caution should be exercised if medications which lower the seizure threshold are used or if there is potential to withdraw from medications with anticonvulsant properties.

Case 2 Answer 3 (Question 3—What impact is rTMS likely to have on Mrs. B.'s cognitive function?)

Mrs. B. has various factors that place her at risk of developing a major neurocognitive disorder, including age, history of depressive disorder, one vascular risk factor (hypertension), as well as her family history of major neurocognitive disorder. Given the multiple risk factors as well as ongoing treatment with brain stimulation, this case would warrant baseline and follow-up cognitive assessments. rTMS has not been shown to impair cognition in any domain [31]. If her depressive disorder improves, her cognition will likely improve as well. Some studies have shown improvement in cognition with rTMS, independent of response to depression [55]. This has, however, not been a universal finding and remains undetermined.

Teaching Point
rTMS does not impair cognition.

Case 2 (Continued)

The patient received 6 weeks of high-frequency stimulation to the left DLPFC, five times per week. Follow-up of MADRS scores during treatment with rTMS reveal the following scores. Her MADRS scores dropped to 31 (consistent with moderate depression) by week 2 and then to 18 (mild depression) by week 4 of treatment. At the end of her 6-week course of treatment, her scores dropped further to 9. Her gains were maintained over time with no changes to her medications, and 6 weeks after her last treatment, she remained with remission with a MADRS score of 4. MoCA score was improved at 29 out of 30.

Case 2 Answer 4 (Question 4—What steps would you consider if Mrs. B. relapses?)

Mrs. B. responded well to rTMS and achieved remission. Currently available data suggests that if rTMS responders relapse, they can regain their previous improvements by reintroducing rTMS [64]. The duration of effect appears to be on the order of 4–6 months in general. Patients who relapse frequently can be considered for maintenance rTMS. Expert consensus recommend maintenance treatment at a frequency between one session at a time either monthly, biweekly, or weekly or based on patient's response.

Mrs. B. has a history of response to desipramine. If she relapses quickly or frequently after rTMS, a trial of desipramine could be considered. Desipramine lowers the seizure threshold, so if it were to be reintroduced, the slightly increased risk of seizures would have to be discussed with Mrs. B. if she were continuing with simultaneous rTMS. It might also be prudent to redetermine her motor threshold. She was able to tolerate desipramine at age 30, but it is also possible that she would have more difficulty tolerating this tricyclic antidepressant at her current age. Older patients are more vulnerable to the side effects of tricyclic antidepressants, e.g., dry mouth, constipation, orthostatic hypotension, and anticholinergic effects on cognition, including risk of delirium.

Teaching Point
A return to rTMS will usually be effective when patients relapse after having responded. For patients who relapse repeatedly, maintenance rTMS can be helpful.

Case 2 Analysis Mrs. B. has a history of recurrent major depressive disorder, and her current episode has become chronic, as she has been unable to tolerate adequate pharmacotherapy. rTMS was considered given the primary diagnosis and absence of contraindications; the family history of seizure was considered but deemed to be insignificant. Caution was exercised regarding her medications, both in limiting bupropion to a relatively low dose and in avoiding withdrawal of clonazepam and pregabalin. For Mrs. B., rTMS proved to have significant impact on her depressive symptoms as manifested by decrease in her MADRS scores. Her improvement was maintained 6 weeks after her last treatment, and her cognition had improved. She could expect ongoing benefit for 4–6 months on average, but if she were to relapse, a return to rTMS would likely be effective. If she were to relapse multiple times, maintenance treatment could be considered at a frequency of once per week and once per month according to her symptoms.

7.3 Key Points: Somatic Therapies (rTMS and DBS)

- rTMS shows efficacy in the treatment of major depressive disorder, with approximate response rates of 30% and remission rates of 20% in the general adult population.
- rTMS was initially thought to be less effective in older adults. However, the evidence suggests that older adults may respond as well as younger adults with higher intensity of stimulation and longer treatment courses.
- rTMS can be considered as an option for patients who have failed at least one trial of an antidepressant medication.
- Treatment resistance and duration of depressive episodes are associated with a lack of response to rTMS.
- The age of onset of depressive disorder and the presence of white matter changes on neuroimaging do not influence response to rTMS.
- ECT is superior to rTMS for depressive disorder with psychotic features.
- Patients who do not respond to rTMS may respond to ECT, but patients who fail to respond to ECT are unlikely to respond to rTMS.
- The main serious side effect of rTMS is induction of a seizure.
- The presence of metallic hardware or devices close to the coil is the only absolute contraindication to rTMS.
- DBS remains an investigational treatment for depression. While early open trials were promising, subsequent randomized controlled trials were negative. Exploration of alternate targets and of its use in other disorders is ongoing.

7.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following statements about somatic therapies is true?

A. rTMS is the treatment of choice for depression with psychotic features.
B. ECT is contraindicated in a patient who has DBS electrodes in place.
C. rTMS has not been demonstrated to impair cognition in any domain.
D. The most common side effect associated with rTMS is induction of a seizure.

Answer: C

ECT remains the gold standard most effective treatment for depression with psychotic features. rTMS is less effective than ECT in the treatment of major depressive disorder, particularly with psychotic or melancholic features, or treatment-resistant depressive disorder (which makes statement A untrue). Several case reports exist demonstrating the safety of ECT in the presence of deep brain electrodes (statement B is untrue). In contrast, stimulation studies of rTMS in the presence of deep brain electrodes have demonstrated induced electrode currents that could result in tissue damage. Seizures with rTMS are rare and occur at a rate of about 1 in 30,000 treatment sessions (statement D is untrue). Most common side effects associated with rTMS treatment are mild headache (10%) and discomfort at the site of stimulation (6%). rTMS has not been demonstrated to impair cognition in any domain. Most studies have found rTMS to have no effect on cognition or a possible independent effect of stimulation of the left DLPFC on cognition (which makes statement C true).

MCQ 2. Which of the following is *not* an rTMS coil?

A. Figure-8
B. Double-cone
C. H-shaped
D. FEAST

Answer: D

Various coils for use in treatment with rTMS exist and include the figure-8 coil (answer A) which is the most common coil, consisting of two round coils placed side by side to form the shape of the numeral 8. Another coil, a double-cone coil (answer B), is shaped to accommodate the curvature of the skull. A third coil, the H-shaped coil (answer C), fits around the head in a helmet-like configuration and produces a focal magnetic field which may penetrate slightly more deeply into the brain than the figure-8 coil; the clinical impact of this is as yet unclear. Currently, there is no rTMS FEAST coil (answer D is correct). FEAST stands for focal electrically administered seizure therapy, an investigational brain stimulation treatment.

MCQ 3. Which of the following is a proposed mechanism for the failure of early rTMS studies to demonstrate efficacy in older depressed patients?

A. Prefrontal cortical atrophy
B. Concomitant polypharmacy
C. Subcortical white matter changes
D. Lower seizure thresholds

Answer: A

Magnetic field strength falls off quickly over distance from the stimulus. If the DLPFC has atrophied and is thus relatively more distant from the coil on the scalp, it may be difficult to stimulate the area adequately (answer A is correct). Concomitant medications and subcortical white matter changes are not thought to be relevant to treatment response (answer B and C). Older patients have higher seizure thresholds than younger patients (answer D).

MCQ 4. All of the following are contraindications to rTMS *except*:

A. Seizure disorder
B. Metal coil in central nervous system
C. Subcortical white matter changes
D. Benzodiazepine withdrawal

Answer: C

Disorders with the potential to lower seizure threshold and are associated with increased risk with high-frequency rTMS include epilepsy (answer A), brain lesions (e.g., vascular, traumatic, infectious, metabolic, tumors), sleep deprivation, heavy alcohol use, and taper of medications or substances that are associated with increased risk of seizures such as benzodiazepines (answer D). There is only one absolute contraindication to rTMS, and this is the presence of metallic hardware (answer B) in close contact with the coil used to administer the stimulus. Other types of hardware may also include cochlear implants, medication pumps, internal pulse generators, or any other ferromagnetic implants. These devices may be at risk of malfunction due to the nature of the magnetic pulses generated by the coil. Subcortical white matter changes do not appear to have a demonstrable impact on treatment with rTMS (answer C is correct).

MCQ 5. Following treatment of depression with rTMS, what is the average mean time to relapse?

A. 1 month
B. 4 months
C. 14 months
D. 4 years

Answer: B

In the general adult population, the duration of the antidepressant effect in rTMS responders may be around 4–6 months with the mean time to relapse being on average 164 days (+/− 4 days).

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Psychotherapy in Late Life

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8.1 Background

8.1.1 Generalities

» . . . I am convinced that no one therapy has a monopoly or truth for human experience. The essence of therapy[1] is the personal encounter between the client and therapist (. . .) I see the therapeutic encounter as an opportunity for clients to explore their experiences, learn about themselves, and learn how to cope in a safe place with someone who tries to understand them, who meets them as another human being, and who has struggled to cope and make sense of life [1].

During the French Revolution, Philippe Pinel pointed out the lack of knowledge regarding proper treatment of the psychiatrically ill. "One of the fundamental principles of conduct one must adopt toward the insane is an intelligent mixture of affability and firmness" [2]. With such a philosophy, Pinel was establishing the principles of individual psychotherapy upon which Sigmund Freud would build more than a century later [2]. The Enlightenment era that ensued shaped the development of modern psychiatry; its key influence emphasized the dignity of each human being and the importance of humanism. As a result, early psychiatrists attempted to develop therapeutic techniques that included personalizing the care, using non-intrusive and compassionate approaches, appealing to reason when possible, and giving the patient some responsibility for improving symptoms and behavior [3].

This still constitutes the standard of care for clinicians today, not only psychiatrists but all physicians, nurses, and psychotherapists. The gifts of modern science and the philosophy of the Enlightenment to the specialty of psychiatry included stressing the importance of careful observation in order to understand disease, mechanisms, and progression. Other significant legacies are an emphasis on the dignity of the individual, the value of "moral treatment,"[2] and the integration of the "mind," "spirit," and "brain" rather than a dualistic understanding [3]. It is interesting and reassuring to note that such core values still seem to have their place in psychotherapy, although they might have made their way through our collective unconscious under a different name sometimes: the "not-knowing stance" necessary to observe with high level of objectivity, a patient-centered approach, trauma-informed care, and the biopsychosocial model (see Table 8.1).

Table 8.1 Core values in psychotherapy

Enlightenment era (eighteenth century)	Modern (twenty-first century) psychotherapy
Careful observation to determine pathophysiology	Being "curious and interested," "not-knowing stance"
Dignity	Patient-centered care
Moral, nonintrusive treatment	Trauma-informed care
Integration of the mind, spirit, and brain	Integrative care, biopsychosocial conceptualizations of illness and treatments

Learning and personal growth can take place throughout the life span, and advanced age should not be a deterrent for clinicians in initiating a psychotherapeutic journey with geriatric patients [4]. In fact, many older adults express a preference for psychological over pharmacological treatments [5, 6]. Moreover, the geriatric population faces specific challenges, especially upon relocating to long-term care facilities, including difficulty in establishing meaningful interpersonal relationships with other residents and staff members, loss of identity and purpose in life, sadness and boredom, and lack of social support [7]. Suicide is largely a geriatric concern (see ▶ Chap. 10), with the highest rate of suicide completion in depressed older white males, particularly those who have been recently widowed or who use alcohol excessively. Hence, the centrality of the interactive nature of the psychotherapeutic work becomes a tremendously relevant factor in tackling those core issues.

Also, given the impact of side effects of medications in an aging brain and body and the risk of drug interactions with other classes of medications, such a preference for psychotherapy should be supported. When considering older patients, the open-minded therapist believes in an approach that does not generalize or distinguish on the basis of age. Discovering the relevant developmental phase for each individual (Erik Erikson listed eight stages of psychosocial crisis) can be very helpful. Even though old age is usually associated with "ego integrity versus despair," other phases may help more with therapy planning if they are still incomplete. We can assist each patient in determining at which developmental phase they are currently stuck, creating a more acceptable plan for therapy (see ▶ Chap. 25). Clinicians should accept that patients will do what they are able to do. Some older adults do better than the young and others not so well, but so what? When we want to do our best, we adapt and do our best. Plus, clinicians should take every opportunity to be psychotherapeutic, bringing each patient further onto the path of self-knowledge and healing. Sometimes, the intervention is just about planting a thoughtful seed even during brief encounters.

Nonetheless, this chapter will be an overview of the various approaches and will detail which psychotherapies were studied specifically with an older population. Reminiscence therapy has been specifically developed for older populations. Cognitive behavioral therapy (CBT) and interpersonal therapy (IPT) have been developed for depressive disorders. CBT has also been developed for anxiety disorders and dialectical

1 The words "therapy" and "psychotherapy" are considered equivalent in the context of this chapter (unless stated otherwise); hence, both will be used interchangeably. The same applies to "therapist" and "psychotherapist."

2 Up until the French Revolution (late 1700s), psychiatrically ill persons were treated as criminals, shuttered away in dungeons, and chained to their cells in abominable conditions. Philippe Pinel, known to many as the first to remove chains from the "insane," laid the groundwork for humanitarian treatment ("traitement moral"). His publications assured him the honorific title, "father of psychiatry" [2].

behavioral therapy (DBT) for personality disorders, which have been successfully modified for older patients. Both CBT and DBT can be learned, and because they have been manualized, there is a potential for greater consistency in clinical practice. Furthermore, stronger statistics support their application. But we are aware that this text is also only an overview; it does not render justice to over a century of extensive work by all the founders and clinicians of different types of psychotherapy who should be better placed to speak of their own approaches. To fully appreciate each original author's specific therapy, we invite the reader to refer to the formative research and writings.

However, it is important to keep in mind that even if evidence is lacking for a specific type of psychotherapy, it can remain valuable and worth trying with an older adult based on clinical judgment, the patient's goals, and mutual agreement. After all, each therapist's own set of skills is a unique tool that can catalyze the patient's desire to change or feel better; for specific approaches to be effective and meaningful, they should incorporate such assets and embrace the use of creativity.

The concept of psychotherapy has evolved over the past decades and encompasses a highly diverse arsenal of interventions to the point that finding a universally accepted unifying definition can be challenging. For therapists working with older patients, another one of their missions will be to help their patients identify less with their aging bodies and our culture's view of attractiveness, shifting instead to a paradigm that values life experience and the cultivation of wisdom and works on redefining personal goals [1].

Older adults constitute a heterogeneous group, and yet many have common features. Because of the process of psychotherapy itself, sometimes involving tangible activities (e.g., homework for CBT) and in other cases not so tangible elements (e.g., intuitive interventions, nonverbal and somewhat unconscious interactions in psychodynamic therapy), it might be hard to pinpoint what exactly worked or made it successful. There is a significant body of research that finds common effective factors to be at the root of successful outcome of psychotherapy (see Table 8.2) [8]. Most comparisons of different therapies find them more alike than different. Trust is a fundamental element; patients make rapid judgments about whether they can trust their therapist. The initial encounter is critical based on the observation that more patients prematurely terminate from therapy after the first session than at any other point. Laska et al. [9] found that 11.5% of success in psychotherapy is accounted for by collaboration and common goal consensus, and 9% is due to empathy, 7.5% to therapeutic alliance, 6.3% to positive regard and affirmation, 5.7% to congruence and genuineness, and 5% to other therapist factors. They believe that only 1% of outcome success is attributable to treatment method per se. Alliance is the most researched common factor [9]. It can be defined as "the degree to which the therapy dyad is engaged in collaborative, purposive work." Empathy is a complex process by which an individual can be affected by and share the emotional state of another, assess the reasons for another's state, and identify with the other by adopting his or her perspective [8]. Related constructs are positive regard/affirmation and congruence/genuineness.

Table 8.2 Examples of common factors in psychotherapy

Patient factors	Therapist factors	Relationship factors (factors common to patient and therapist)
Motivation/ desire to change cognitive/behavioral/emotional patterns	Empathy/ respectful listening Positive regard/ affirmation	Common goal Therapeutic alliance
Facing and exposure	Congruence/ genuineness	Expectation of treatment effectiveness
Mastery and control	Confronting Consistency Availability Flexibility and open-mindedness	Belief in the internal locus of control Appropriate silences for reflection

These factors are more than a set of therapeutic elements that are common to most or all psychotherapies. They collectively shape a theoretical model about the mechanisms of change in psychotherapy [8]. Interestingly, experience or expertise is not essential; that is to say, a positive outcome is possible even when working with a beginning therapist.

While no therapy models are seen as much more effective than others, there is no evidence of harmful results from using already well-learned therapies that incorporate the common factors described previously. To adapt to specific needs or limitations of older patients, the most valuable therapist will be flexible, eclectic, and adjusting to frequent changes in situation or medical status. He or she will use approaches that are the most helpful at any given moment. Integrative therapists have the ability to combine various approaches, e.g., to bring a gestalt perspective to CBT and/or a cognitive perspective to gestalt therapy [10]. All therapies with structure, given by empathic and caring therapists, and which facilitate the patient's engagement in behaviors that are salubrious, have approximately equal effects [8]. Conversely, there is evidence that rigid adherence to a therapy protocol can attenuate the alliance and increase resistance to the treatment, whereas flexibility in adherence is related to better outcomes. Studies have shown that effective therapists are able to form stronger alliances across a range of patients, have a greater level of facilitative interpersonal skills, express more professional self-doubt, and engage in more time outside of the actual therapy practicing various therapy skills [8].

One of the outcomes of a process where many common factors are actualized is attachment. Attachment is now well accepted as beneficial at all ages [11]. When attachment is deficient in childhood, there are greater challenges, but it is never too late to address and work on them. Hence, the patient's connection with a therapist, supportive friendships (that flourish when fairness skills are high enough), and participation in good groups are effective therapies.

Teaching Point

Common or nonspecific factors in psychotherapy mean that the main elements (such as empathy and working toward a common goal) contributing to a therapeutic success are often found in most of the various approaches. The inherent qualities and skills of the therapist and the commitment of both patient and therapist are more important than the technical skills.

The various overlaps and internal variations of some forms of therapies make the process of classification daunting and arbitrary at best (see Fig. 8.1a, b). Do we have another indication that psychotherapies might have more similarities than differences? After all, the therapy can be a complex interplay of subjective, multilayered, overlapping elements. In any case, it is important to keep in mind that just like languages, medical treatments or educational methods, psychotherapies are likely to change to adapt to the specific cohorts of people that also evolve throughout time. Just like each person's development, the process of co-creation between therapist and patient is inherently dynamic and unique.

In a case study, Rothe suggested that "impending death may force the individual to undergo a hurried and comprehensive process of self-analysis and to engage in urgent corrective actions" [12]. Realizing that urgency may be counterproductive allows more deliberate and accurate planning and negotiation of therapy.

Psychotherapy is often overlooked as a treatment modality despite being an effective treatment method for a number of psychiatric disorders seen in older adults. Therapy especially helps with many stressors including family, relationship, and health changes and even the role transitions involved in moving to long-term care settings [13]. Unfortunately, there is a paucity of publicly funded psychotherapy services for older adults. As well, some medical practitioners may be reluctant to refer geriatric patients for psychotherapy [14]. Because of

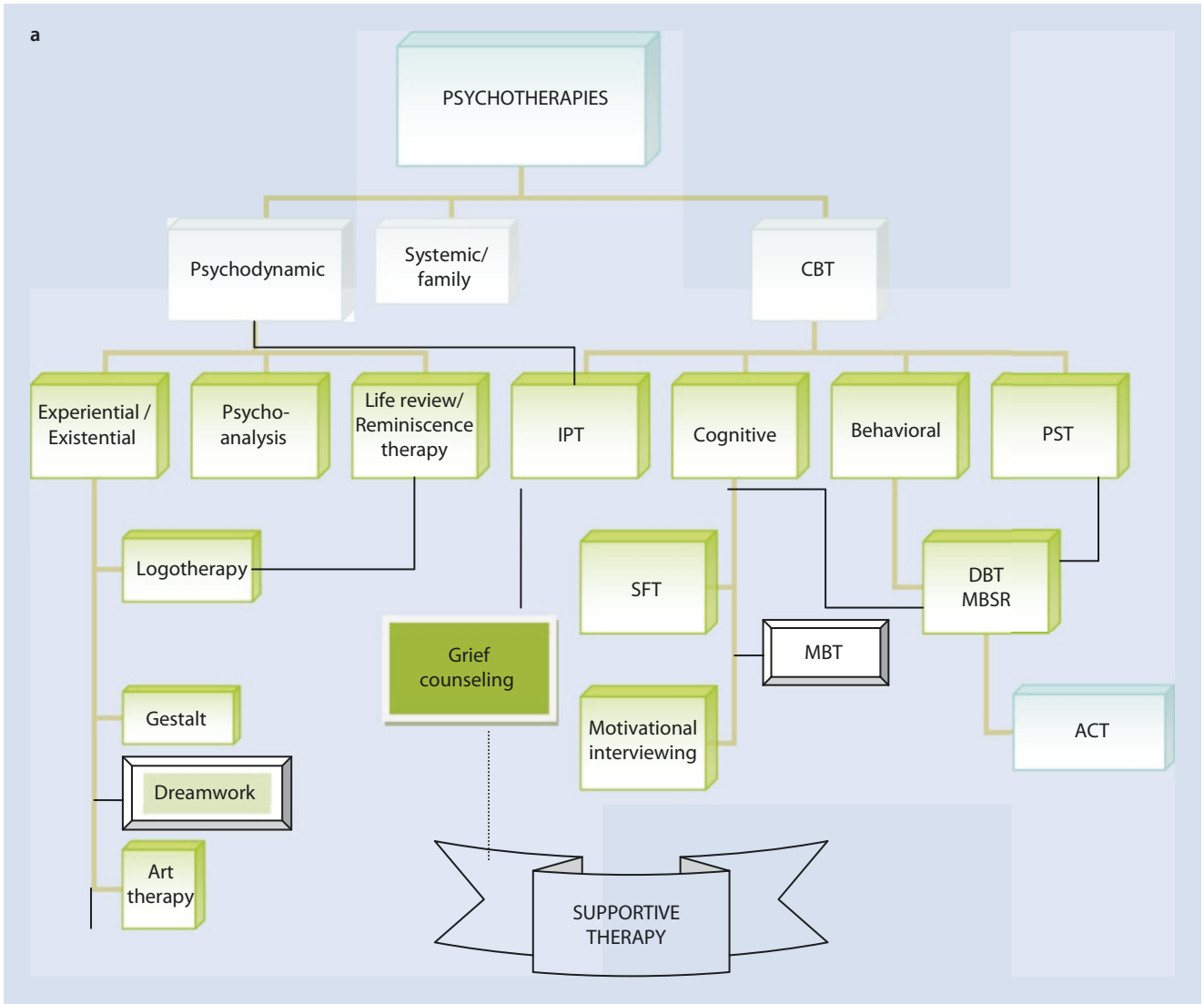

Fig. 8.1 a Types of psychotherapy

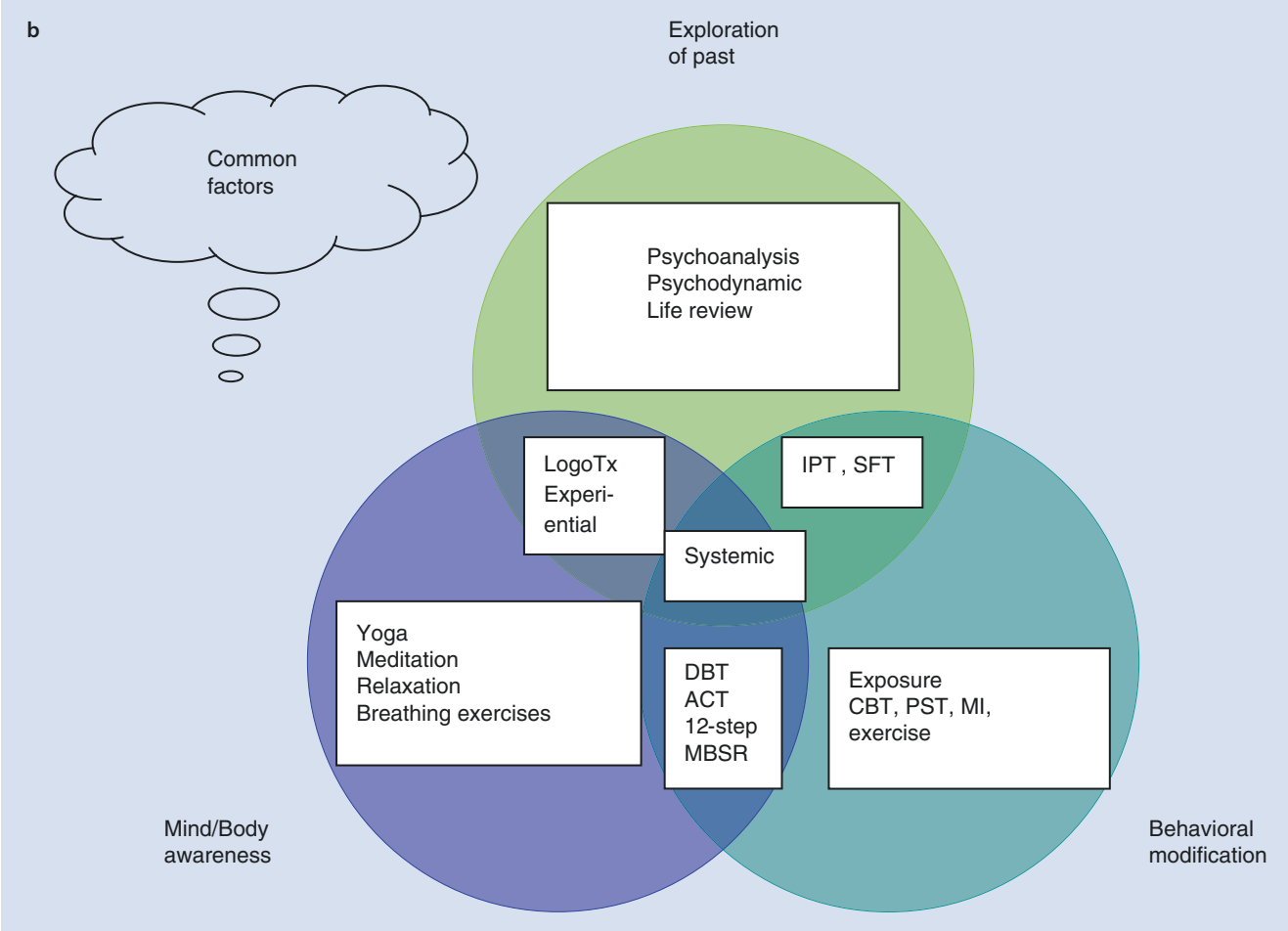

Fig. 8.1 (continued) **b** Overlap of therapeutic approaches. *ACT* Acceptance and Commitment therapy, *CBT* Cognitive-behavioral therapy, *DBT* Dialectical-behavioral therapy, *IPT* Interpersonal therapy, *LogoTx* Logotherapy and existential analysis, *MBSR* Mindfulness-based stress reduction, *MBT* Mentalization-based therapy, *MI* Motivational interviewing, *PST* Problem-solving therapy, *SFT* Schema-focused therapy

the cost and limited availability of psychotherapy in certain settings, we suggest assessing a patient's "readiness" for change in psychotherapy. The first step is for both the therapist and the patient to recognize and accept that a problem serious enough to justify the work and cost of psychotherapy exists. It is a choice that an informed individual makes rather than a prescription that another believes will be corrective therapy.

Therapy is ideal when it is sought by a person who is ready for it. The therapist does the negotiating with the patient at the earliest part of therapy. When there is no negotiation but therapy is presented as "take it or leave it," the risk of "leaving it" (not really being "onboard" for the project, etc. even as clear defiance) is much higher. The negotiations are part of the respect building between parties. For agencies that can provide funded therapy, triage principles are often practical and needed. Some cases are trivial, and others are more difficult that almost no amount of resources could be effective. Efficiencies like group therapy can also provide equal or better results for some patients with common problems. There are twice as many women as men in the age group of 65–85 years [15]. This fact can put women at higher risk of isolation, which can lead to a higher prevalence of depressive symptoms [15]. Psychotherapeutic interventions such as groups often help increase socialization and ability to cope with losses (see Table 8.3). Being in a group with others who experience similar problems helps correct self-esteem issues by establishing a better perspective. A poorly developed sense of self will make the patients more fragile and sensitive to losses. On the other hand, a healthy sense of self or "flexible narcissism" (developed through mirroring, idealization [16], good-enough parenting, and some early experiences of frustration with validation during childhood and in group therapy) helps a person to process losses more adaptively.

Age can make one more resilient to stressors [15]. The frequent age difference between the patient and the therapist may lead the patient to relate to the therapist as a son or daughter, a phenomenon called reverse transference [15]. Romantic transference can be a source of humiliation for the patient. Conversely, the therapist's fear of aging and emotional memories of parents and grandparents are another common area of interference [15]. Careful attention to the realities of therapy rather than friendship is extremely important for beginning therapists. Being objective requires healthy boundaries that recognize that the bulk of hard work

Table 8.3 Therapeutic factors associated with group therapy and potential advantages for older adults over individual therapy

Therapeutic factor	Group therapy advantages
Instillation of hope	Seeing progress in others and being inspired by them
Universality	An experience of "welcome to the human race" by sharing problems in common with others
Imparting information	Opportunity to share information with others in the group, develop a better perspective or provide helpful suggestions, such as "Did you know…?" and "Why don't you…?"
Altruism	An experience of the benefits of receiving through giving to others, helpful in appreciating that when their loved ones help them, they might also find it gratifying, and not necessarily a burden
Developing socializing techniques	Expressing accurate empathy to others in the group; foster self-efficacy
Role modeling	Imitation as a form of praise of themselves or of others; self-esteem restoration
Recapitulation of primary family	Re-experiencing their families of origin, but with improvements, and where interpersonal growth is permitted
Group cohesiveness	The group's collective sense of togetherness, sense of belonging
Existential factors	A notion that we are ultimately alone, that life is not always fair, and that we need to take personal responsibility, regardless of age or stage in life
Catharsis	An opportunity to vent to each other, process difficult emotions, and overcome impasses

really does belong to the patient, and when therapists take too much responsibility for the outcome, blurred boundaries result in ineffective therapy.

Although some believe that short-term psychoanalytic therapy and cognitive psychotherapy are less suitable for older adults because they make considerable demands of the individual's capacity for introspection or abstract thinking, their features are important and contribute to effectiveness in mentalizing, or theory of mind. There is good evidence supporting the new therapy of mentalizing [17]. Mentalizing includes the common effective factors listed previously, and it focuses on learning to think about thinking, one's own thinking and that of others, as a focus for finding fairness and consensus between therapist and patient.

As a practical approach for those wishing to provide effective psychotherapy who have not had extensive training, we suggest that the most powerful component of therapy is the relationship one develops with the patient. Various authors believe that such a relationship as lived rather than analyzed is the primary therapeutic intervention [11]. We believe that this is best accomplished through *being* rather than *doing*. There is a rich heritage for this idea in eastern philosophy (Buddhist especially), and mindfulness emphasizes it as an overall goal. Being in the moment is a constant goal for meditation. Mindfulness has been developed and widely accepted therapy in the world as a foundation for emotion management and well-being. In our daily life, it means being aware, each moment, of what we are doing as we are doing it [18], as opposed to being on automatic pilot.

Participating in psychotherapy appears to be a form of remoralization [8]. From a philosophical perspective, since older adults are a vulnerable population and are often victims of oppression or abuse, and also due to ageism, one could conceptualize the framework of therapy as one enhancing social justice [19]. All patients possess inner strengths, and it is the therapist's role to invite them to unearth such riches. Seeing our patients as capable beings (and also teachers to the therapist interested in the breadth of human experience) rebalances perspective and is thus empowering.

The list of specific therapies below is not for practitioners to follow. At best, it suggests techniques and concepts that we could incorporate leading to creative eclectic therapies of our own. Those who have been trained (or choose to be) in any of the specific therapies already have or will gain a solid framework to meet the patients where they are. In sharing that with patients, they are meeting one of the most important components of common factors theory.

Table 8.4 Procedural adaptations during therapy for older adults

Parameters of the encounter	Procedural adaptations
Room	Comfort; adjust light, temperature, ventilation
Materials	Larger font
Understanding	Invite question; ask patient to repeat recommendations
Duration and pace of sessions	Adjust based on the patient's limitations
Psychoeducation/ memory aids	Audio/videotape sessions; provide handouts
Extra support	Use an informant (caretaker or friend) as needed

8.1.2 Procedural Adaptations

Given the higher incidence of confounding factors in older populations (e.g., declines in sensory functions and speed of processing), certain modifications to standard therapy procedures are advisable [4, 6]. The following elements are summarized in Table 8.4:

- Find a room that is quiet, well-ventilated, and well-lit.
- Give written materials to the patient; fonts for written material should be larger.
- Memory aids (handouts) can be very helpful.

- Psychoeducation is an integral part of almost all modalities and should be reiterated as needed.
- Ask the patient to repeat the recommendations and invite questions.
- Schedule sessions at the most optimal time, taking into account decreased mobility, and other medical treatments.
- Slow the pace of therapy or increase length of sessions.
- Audio or videotape sessions.

8.1.3 Types of Psychotherapies

In the context of emphasizing the importance of psychotherapy for mild depression in older patients, the World Health Organization defines four main psychotherapeutic treatment groups: psychodynamic therapy, interpersonal therapy (IPT), supportive counseling (Rogerian person-centered therapy), and cognitive behavioral therapy (CBT) [20]. This textbook chapter will organize the main psychotherapies based on a similar structure and listing additional variants in certain categories (see ◘ Fig. 8.1a). While the following approaches described have been categorized based on their philosophy or focus of treatment, it is important to keep in mind that they may be used in combination, or two approaches can overlap (see ◘ Fig. 8.1b). For instance, schema-focused therapy includes elements of CBT and psychodynamic therapy. Also, it might be challenging to make the distinction between technique and therapy (e.g., CBT can be delivered as bibliotherapy).

Supportive Therapy

This therapy constitutes the fabric, the common denominator of all approaches (see ◘ Fig. 8.1a). It includes nonspecific factors (see ◘ Table 8.2). Providing a safe environment, warmth, empathy, and hope is key component of this approach, like the "oxygen" of the therapeutic dyad [4]. The encouragement of an internal locus of control is another factor common to all psychotherapies.

It is important to use positive supportive statements (e.g., genuinely felt compliments when appropriate) [21]. On a nonverbal level, a handshake or a tap on the shoulder at the beginning and/or at the end of the session as well as physical assistance when the patient is frail can represent a nice reassuring gesture, a gentle emotional holding to facilitate the connection if there is some sensory impairment. Grief support counseling is a subset of this approach and should be available early on. Recovery from grief means "discovering and completing" the unfinished emotions or elements regarding the unique lost relationship [22]. Contradictory emotions will be looked at and eventually integrated in a whole perspective of what has been and can include giving up the hope for a better or different yesterday. For some people it is accomplished through a process of forgiveness, but it is important to start with each person's own definition, misconceptions, or resistance elements toward this often vague concept. A patient at one of the author's community clinic aptly wrote during a creative writing session: "Forgiving is a word for those who don't have to use it."

Behavioral Therapies

These interventions share the theoretical assumption that human behavior is learned. They can employ strategies such as (1) changing how people process information from their environment (e.g., cognitive restructuring), (2) skill building (e.g., problem-solving, communication skills), and (3) mood regulation skills (e.g., mindfulness exercises, behavioral activation). Behavioral therapy tends to focus primarily on skill building and assumes that changes in information processing are achieved via increased positive experiences with new behavior.

Mindful Awareness

Kabat-Zinn's operational working definition of mindfulness is "the awareness that emerges through paying attention on purpose, in the present moment, and non-judgmentally to things as they are" [23]. Mindful awareness means attending to the richness of our here-and-now experiences and is a form of intrapersonal attunement [18]. In *The Mindful Brain*, Daniel Siegel describes admirably mindful awareness as the following: "The role of mindful awareness is to enable the mind to "discern" the nature of the mind itself, awakening the person to the insights that preconceived ideas and emotional reactions are embedded in thinking and reflexive responses that create internal distress. With such disidentification of thoughts and emotions, by realizing that these mental activities are not the same as "self," nor are they permanent, the individual can then enable them to arise and burst like bubbles in a pot of boiling water" [18].

Wallin wrote that "mindfulness (like mentalizing) can allow us to be present for our experience, rather than submerged by or dissociated from it" [11]. It is a form of experience that seems to promote neural plasticity. It activates different areas of the brain, e.g., some that might be malfunctioning when there is cognitive impairment from depressive disorders, posttraumatic stress disorder, or attention deficit hyperactivity disorder. Immune response, stress reactivity, and general well-being are also improved with mindfulness. Additionally, mindfulness-based stress reduction (MBSR) can help reduce the subjective state of suffering and accelerate healing for chronic medical conditions. Interpersonal relationships, which have been shown to promote emotional longevity, are also enhanced by its practice. Via cognitive therapy, mindfulness can prevent relapse of depressive disorder. ◘ Table 8.5 lists some symptoms that mindfulness could alleviate.

Studies have shown that specific applications of mindful awareness improve the capacity to regulate emotions and reduce negative mindsets [11]. It helps in transitioning from one activity to the other in our busy, fast-paced existence. Therefore, a psychotherapeutic session (individual or group) often starts with such a practice.

Mindfulness practices are therefore the foundations of many psychotherapy models. It may result in outcomes such as patience, non-reactivity, self-compassion, and wisdom [18]. Mindful awareness can promote love for oneself. But mindfulness is not "self-indulgent"; in fact, it is a set of skills that enhances the capacity for caring relationships with others. By becoming one's best friend, we are more apt to care for others.

Table 8.5 Indications for mindfulness practices

Clinical problems
Depressive disorders
Anxiety disorders (panic disorders, agoraphobia)
Eating disorders
Posttraumatic stress disorder
Obsessive-compulsive disorder
Beginning of each therapy session
Prior to an anxiety-provoking procedure (e.g., surgery, CT scan for a patient with claustrophobia)

Religious practices such as prayers, as long as they are not socially oppressive, should be encouraged whenever they provide relief from distressing emotions, since they act similarly to mindfulness practices. Many forms of prayer in different traditions require that the individuals pause and participate in an intentional process of connecting with a state of mind or entity outside the day-to-day way of being [18]. Prayer and religious affiliation in general have been demonstrated to be associated with increased longevity and well-being.

Cognitive Behavioral Therapy (CBT)

Aaron Beck, a psychoanalytically trained therapist who wanted to implement simple effective therapies, developed the CBT. CBT focuses on dysfunctional beliefs and aims to correct the underlying dysfunctional beliefs that maintain depressive symptoms (see Table 8.6). Our thoughts influence our behaviors, which influence our mood (and vice versa), and these three areas interplay and impact one another.

As clinically indicated, such a therapy can focus on either the cognitive component (inaccurate assumptions or dysfunctional thought patterns, by challenging them or using Socratic reasoning) or on the behavioral component (by developing more adaptive behaviors) or both. Behavioral techniques include monitoring behaviors and affect patterns, assigning pleasant events, controlling or avoiding depression-eliciting stimuli, and limiting worry and depressive ruminations with time limits, behavioral exposure, and skills training (through relaxation, problem-solving, and interpersonal skills). Socratic questioning is used in psychotherapy as a cognitive restructuring technique, the purpose being to help uncover the assumptions and evidence behind distressing thoughts through a dialectical perspective. Table 8.7 gives examples of Socratic questions in cognitive therapy to deal with automatic thoughts (i.e., *fleeting*, *primitive*, *telegraphic thoughts at the deepest level of conscious thought that we feel to be true* and *situation-specific thoughts)* that distress the patient. Careful use of Socratic questioning enables a therapist to challenge recurring or isolated instances of a person's illogical or maladaptive thinking while maintaining an open position that respects the internal logic to even the most seemingly illogical thoughts. Ultimately, the goal is to teach the patient a new rational way of approaching reality, in the hope that he or she will use such tools in the future and will prevent the emergence of dysfunctional thoughts and resulting unpleasant emotions.

Table 8.6 List of common cognitive distortions used among older adults

Dysfunctional cognitive patterns	Clinical manifestations and associated script
Black and white thinking	Depression: "If I'm not a success, I am a total failure." Anxiety: "If my blood pressure is higher than 140, I'll die."
Discounting the positive	Depression: "Nothing works, what is the point in trying another medication/therapy?" Anxiety: "I'm doomed, I panic upon meeting new people about 90% of the time."
Should statements	Depression: "I should go to this funeral, my religion says so, but I feel guilty because I am tired and I don't feel like it." Anxiety: "I should go to this funeral otherwise my family will stop talking to me and I'm afraid of being rejected."
Catastrophizing	Depression: "If I fall and need help, no one will be there to help me because I am worthless." Anxiety: "If I'm late for the appointment with the doctor, it will be a disaster."
Jumping to conclusions	Depression: "She didn't come visit me, therefore she hates me, everyone does." Anxiety: "The doctor didn't get back to me with the results, it must mean I will die soon and he's afraid to tell me."

These therapies conceptualize depression as the result of an inability to cope with life stressors, poor affect regulation skills, social isolation, and difficulty in solving problems [24]. There is sufficient evidence in the literature to support the use of CBT in the treatment of major depression and generalized anxiety disorder in the older adults [14]. Areán and Cook [25] reviewed data on the acute and long-term effects of CBT, IPT, brief dynamic therapy, and combined antidepressant medication and psychotherapy. In their literature review of psychotherapies for late-life depression, they found that CBT and most other modalities were efficacious and necessitated minor adaptations [25]. Patients who respond to CBT tend to maintain the treatment gains up to 2 years [25]. In the same review, two other studies showed that CBT delivered as bibliotherapy was more efficacious in treating mild-to-moderate depressive symptoms in older adults than attention control and no treatment. Treatment gains persisted for 2–3 years after psychotherapy ended. Based on five trials from a Cochrane study [20], cognitive behavioral therapies were more effective than controls. Three trials examined cognitive bibliotherapy compared with waiting list control. A highly significant difference between groups was found in favor of cognitive bibliotherapy.

Table 8.7 Examples of Socratic questioning

Cognitive restructuring principles	Inquiry	Clinical applications (e.g., tensions with adult daughter)
Revealing the issue	"What evidence supports this idea? And what evidence is against its being true?"	"Why do you think your daughter would be angry with you? What are the elements of your relationship that do not support
Conceiving reasonable alternatives	"What might be another explanation or viewpoint of the situation? Why else did it happen?"	"If she is indeed angry, could it be that something else has happened that has nothing to do with you?" "Other than resentment toward you, what are other factors that could explain why your daughter has not called you in a week? Could it be that she is busy with other obligations?"
Examining various potential consequences	"What are worst, best, bearable and most realistic outcomes?"	"What is the worst that could happen if she is currently upset with you? Is there anything positive that could come out of this conflict?"
Evaluate those consequences	"What is the effect of thinking or believing this? What could be the effect of thinking differently and no longer holding onto this belief?"	"How does thinking about the worst scenario affecting your mood? What would it change if your explanation were different?"
Distancing	"Imagine a specific friend/family member in the same situation or if they viewed the situation this way, what would I tell them?"	"Imagine your neighbor in a similar situation with his son, what would be most helpful to tell her/him?"

CBT along with cognitive therapy and brief dynamic therapy has positive effects 1 and 2 years after treatment [24]. There is proven efficacy of CBT and brief psychodynamic therapy for anxiety and depressive disorders. CBT and schema-focused therapy (see ▶ section Schema-Focused Cognitive Therapy) in particular can be useful for older adults [26].

Dialectical Behavioral Therapy (DBT)

DBT groups teach specific skills to increase mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance. The modification for older adults targets cognitive/behavioral rigidity and emotional constriction. DBT plus medication showed a faster reduction in depressive symptoms when compared with medication alone [6].

Mindfulness or stress reduction-based techniques are among the modalities to achieve better emotional regulation. The main characteristics of mindfulness include (1) observing, noticing, and bringing awareness; (2) describing, labeling, and noting; and (3) participating, all of which are done (a) nonjudgmentally with acceptance, (b) in the present moment, and (c) effectively.

Social Problem-Solving Therapy (PST)

It is based on a model in which ineffective coping under stress is hypothesized to lead to a breakdown of problem-solving abilities and subsequent depression. It mainly addresses:

- Problem details
- Present goals
- Multiple solutions
- Specific solution advantages
- Assessment of the final solution in context

PST is more effective than reminiscence therapy or waiting list [25]. It can be delivered in a limited amount of time; therefore, it is suitable in primary care settings. PST was associated with significantly greater improvements in depressive symptoms compared with reminiscence therapy.

Motivational Interviewing

Motivational interviewing is a method that works on facilitating and engaging intrinsic motivation within the patient in order to change behavior. Motivational interviewing is a goal-oriented, patient-centered counseling style for eliciting behavior change by helping patients to explore and resolve ambivalence. For instance, one approach is to invite the patient to make an exhaustive list of all the pros and then the cons of a destructive behavior. One of its indications is substance-related disorders.

Interpersonal Therapy (IPT)

IPT is a short-term (12–16 sessions), manual-based treatment that was developed for treating depression in the early 1980s [13]. The treatment was derived empirically, primarily from the field of social psychology. It consists of elements of psychodynamically oriented therapies (exploration, clarification of affect) and CBT (behavior change techniques, reality testing of perceptions) that are used to address four areas of conflict: (i) unresolved grief/loss, (ii) role transitions, (iii) interpersonal role disputes, and (iv) interpersonal deficits. These four areas, especially grief/loss (e.g., bereavement, loss of function or good health) and role transitions (e.g., retirement), can all be addressed in an older population (see Table 8.8).

The IPT approach is consistent with the biopsychosocial model of disease and is fully compatible with the concomitant use of psychotropic medication. In fact, considerable effort is spent educating patients about the biopsychosocial model of depressive disorder. Interpersonal relationships are seen as the stage upon which depressive disorder is expressed. All

Table 8.8 The four major problem areas in interpersonal therapy

Major problem	Senior specific example
Grief	Death of spouse/friend/family member; loss of bodily functions
Role transition	Retirement, adjusting to medical disability, ceasing to drive, self-image issues
Role disputes	Caregiver role disagreements, conflict between partners, disputes with adult children
Interpersonal deficits	Difficulty reaching out for or accepting help, social isolation

important relationships are systematically explored with regard to the degree of attachment they contain for the identified patient that may indicate a causal factor in the development of a depressive disorder (such as a role dispute). This short-term treatment makes no attempt to alter personality and focuses on current problems. The therapist is a benevolent facilitator without inviting a deepened transferential relationship.

Older patients are more apt to be forthcoming and more eager to work toward goals in treatment [16]. The conversational style inviting the patient to tell his or her story should be comfortable and helpful. Family members often misconstrue or misattribute problem behaviors to volitional acts of defiance, when they actually are features of executive dysfunction, the least understood aspect of cognitive impairment (ci). The therapy can be adjusted for these patients (IPT-ci) and the approach includes (1) reminding the patient of abilities that remain intact that could be further developed to help compensate for the lost abilities and (2) helping the patient to foster new attachments commensurate with his or her current abilities and, when necessary, helping the patient accept increased dependency on others. It is important to adapt the interventions, especially since deficits in executive functions are associated with a poor and unstable response to antidepressant medication [24].

In one study, IPT was found to be more effective in moderate-to-severe depression [27]. Another study by Reynolds and examined by Mackin [24] found that older patients with recurrent major depressive disorder can be successfully treated with a combination of antidepressant therapy and IPT, and that older patients respond as well, albeit more slowly, as middle-aged patients. IPT may be most effective as a maintenance treatment when combined with an antidepressant medication for more severely depressed older adults [25].

Teaching Point

IPT is another psychotherapy that is suitable for primary care settings. With the anticipated worldwide shortage of psychiatrists in the foreseeable future, such an advantage becomes an important consideration. The basic principles can be taught to a variety of clinicians.

Psychoanalytically-Oriented Therapies

Psychodynamic Psychotherapy

Relationships in early life form the basis of attachment and are internalized, assisting the formation of a sense of self. One model holds that much psychopathology is theorized as being related to arrests in the development of the self. It reframes current interpersonal and emotional experiences in the context of past events. During therapy, patients are encouraged to develop insight into past experiences and how these experiences influence their current relationships [13].

Empathic listening, exploratory inquiry, and interpretation and clarification of unconscious determinants are essential parts of that approach (see Background ▶ Sect. 1.1 on common factors theory). Short-term psychodynamic psychotherapy is effective in treating depressive disorders in samples for older adults. This treatment is typically described as lasting less than 40 sessions [28].

Intensive short-term dynamic psychotherapy as developed by Habib Davanloo is an intensive emotion-focused psychodynamic therapy with an explicit focus on handling resistance in treatment, e.g., in somatic symptom conditions and depressive, anxiety, and personality disorders arising from adverse childhood experiences [29]. (See ▶ Chap. 14.) Problems arising from exposure to family dysfunction while growing up are suggested to be by-products of strong unprocessed emotions coupled with deficits in capacity to regulate emotions. The goal of this psychotherapy is to understand and cope better with these feelings.

Life Review and Reminiscence Psychotherapy

These approaches are akin to the positive version of Socrates' fundamental belief implying that the only life worth living is the examined life. These approaches are derived from Eriksonian developmental theory and were specifically developed for older adults. They are both based on the patient re-experiencing personal memories and significant life experiences. They are entirely patient centered, as each person knows best about her or his own life. They both assist older people in experiencing their personal value and self-identity. Reminiscence therapy uses the recall of past events, feelings, and thoughts to facilitate pleasure, better quality of life, and better adjustment. It is valuable because it can be conducted during daily activities such as mealtime and walking around a facility. There does not seem to be reported adverse events to reminiscence therapy, and it can alleviate feelings of loneliness, anxiety, and depression [7].

Life review therapy is an advanced type of reminiscence, exploring problems through narration. The life story is an internalized and evolving myth of the self, which provides unity and purpose in the individual's life [30]. It is an especially relevant process for older adults as they face their last opportunity to sum up their life and its meaning. Erikson emphasized that studying one's life story enhances the individual's sense of integrity, gratitude, and acceptance. It can help the patient overcome unresolved conflicts. In life review, individuals are encouraged to acknowledge past conflicts and to consider their meaning in their life as a whole. It is more structured and focused on both positive and negative life events. The life story reflects what a

Table 8.9 Aspects that can be positively impacted by reminiscence therapy in the institutionalized older adults

Positive outcomes of reminiscence therapy	Comprehension skills
	Self-esteem
	Self-integration
	Coping skills
	Satisfaction with life
	Functional activities
	Social functions
	Feeling of belonging
	Security
	Health
	Pleasure
	Well-being
	Prevention of behavioral problems

person leaves behind and how he or she wants to be remembered. Reviewing and writing one's life story appears to be therapeutic [1]. People writing their memoirs also mention the significant advantage of keeping their linguistic skills alive.

Additionally, in a group of patients with major or mild neurocognitive disorders (Alzheimer disease or other neurocognitive disorders), it was found that a cognitive rehabilitation model (using strategies such as remembering names) produced significant improvements on goal performance and satisfaction [14]. Studies show that reminiscence therapy has a positive effect on older adults' psychological and subjective well-being. Self-esteem, satisfaction, and meaning are all measures that were improved by such interventions, while anxiety and depressive symptoms decreased [30]. These attributes could even prevent depressive disorders in late life [30]. The positive effects persisted when measured at 1 and 3 years post-therapy [31]. (See Table 8.9 for the aspects that can be improved by reminiscence therapy [30, 31].)

Life review therapy uses the normal reminiscing of aging to deepen the person's self-knowledge often with exercises such as photograph scrapbook review, memoir writing, and pilgrimages to childhood sites [30]. For instance, one method to facilitate the emergence of positive memories is the use of narration and creative writing, stimulated by a specific prompt such as "describe your best childhood friend" or "describe a joyful family celebration."

Areán and Cook [25] say that reminiscence psychotherapy may be useful for treating depressive disorders in confused or older adults with early major neurocognitive disorder living in residential facilities. However, unfocused reminiscing may not be suitable for persons who have trauma histories, such as Holocaust survivors [15]. Reminiscence psychotherapy focuses more on positive memories in group settings to improve self-esteem and social cohesiveness; people choose to tell the stories that help them present themselves [30]. Also, involving others in our life stories allows for new perspectives.

Teaching Point

Therapeutic interventions centered on creating life review and reminiscing have a positive effect on well-being, self-esteem, sense of meaning, and life satisfaction. They also reduced depression and anxiety symptoms. Studies support the effectiveness of life review as an early intervention that prevents depression in late life [30]. In summary, CBT, reminiscence therapy, DBT, and the combination of medication and IPT are acutely efficacious in treating major depression in ambulatory older adults [24].

8.1.4 Experiential Psychotherapies

This form of therapy encourages people to identify and address hidden or subconscious issues through experiences such as role-playing, guided imagery, the use of prompts, and a range of other activities. It represents a safe way of experiencing painful emotions and releases them through not only words but also movement. Experiential psychotherapy is the treatment of choice for emotional trauma. It allows trauma survivors to access their emotions; integrate the mind, body, and spirit; and reconnect with their authentic selves. (See ► Chap. 14.)

Art Therapy

Art therapy by using various media (e.g., painting, dancing, writing, music) is a good example of providing direct, experiential, "hands-on" exposure. Music has been shown to help adults with major neurocognitive disorders. Art therapy might also facilitate some transgenerational connections to ancestors and optimize life review or reminiscence approaches. For instance, it could be therapeutic for baby boomers to be inspired by people who raised them and were used to make the best out of scraps of materials while sewing quilts or building wooden houses, viewing them under a new light, such as resilience through creative frugality. The ability to mentalize is correlated with an interest in art, maybe because high levels of mentalization are associated with a sense of internal freedom to explore thoughts, feelings, desires, and experiences [17].

Teaching Point

Art therapy is a valuable modality as it engages the senses and can help people who have suffered trauma and are often alienated from their bodies (see ► Chap. 14).

Logotherapy and Existential Analysis

Logotherapy and existential analysis, developed based on Viktor Frankl's conception of meaning of life (Frankl was a neuropsychiatrist imprisoned in the Nazi concentration camps), form a type of analysis that strives to find meaning in one's life, because life has meaning under all circumstances

[32]. Meaning is not invented but, rather, "detected." There are three fundamental characteristics of human existence which converge to define the human person (i.e., spirituality, freedom, and responsibility).

Gestalt Therapy

The German word "gestalt" means "form or shape." It is an existential/experiential form of psychotherapy that emphasizes personal responsibility and that focuses upon the individual's experience in the present moment, the therapist-patient relationship, the environmental and social contexts of a person's life, and the self-regulating adjustments the patient makes as a result of his/her overall situation.

Dreamwork

Dreamwork differs from classical dream interpretation in that the aim is to explore the various images and emotions that a dream presents and evokes while not attempting to come up with a single unique dream meaning. In this way, the dream remains "alive," whereas if it has been assigned a specific meaning, it is "finished." Dreamworkers take the position that a dream may have a variety of meanings depending on the levels (e.g., subjective, objective) that are being explored. Mature mentalizers have a specific interest in dreams and internal worlds of other people [17].

8.1.5 Corporal Mediation Therapies

These modalities catalyze the body-mind integration. Also, some are based on the premise that "the body keeps the score." (See ▶ Chap. 14.) That is to say, traumatic experiences that occur at a preverbal stage will not be encoded in the declarative memory system but rather in somatic, nonverbal memory. Therefore, relying solely on other well-known therapies that tend to use exclusively language (e.g., cognitive, psychodynamic modalities) will be insufficient. More generally, emotions are connected to the body and often have somatic manifestations. Moreover, because of the physical nature of the primary attachment relationship between the infant and caretaking figures and because it is the setting to learn affect regulation, an attachment-oriented treatment must have a focus on the somatic self [11].

Relaxation and Awareness Techniques

Deep breathing, autogenic and progressive relaxation [4], meditation, and yoga are used to increase self-awareness and induce relaxation to cope with difficult emotions. Tai chi is a gentle exercise, well suited for people with various physical capabilities, especially older adults.

Eye Movement Desensitization and Reprocessing (EMDR)

There is no empirical research on the efficacy of EMDR treatment in older adults. It was developed for the treatment of posttraumatic stress disorder (see ▶ Chap. 14). It is a relatively straightforward method, easy to use, especially when cognitive functioning is suboptimal. Some say that its effectiveness stems from the common factors of therapy.

Brainspotting

Brainspotting is a relatively new type of therapy developed by David Grand and designed to help people access, process, and overcome trauma, negative emotions, and pain, including psychologically induced physical pain [33].

8.1.6 Systemic Family Therapy

This type of psychotherapy invites us to think of the person in relationship with a complex environment or system. A system is a combination of elements that coordinates to lead to a result or to compose a whole. It is also a mode of organization with rules and traditions (e.g., language, politics). Families and treatment teams are also organized in a specific way and constitute systems. Systems are capable of self-regulation and use feedback to maintain homeostasis. At the root of the establishment of the smallest family system (a system composed of two people such as parent-child or patient-therapist) lies attachment or what Stern described as the intersubjective experience or sharing of psychic landscapes [34]. Emotional attunement is a fundamental element for the development of secure attachment.

During the 1950s, some clinicians had noticed that the improvement of a patient with a psychiatric disorder triggered the emergence of symptoms in a family member. Also, most psychiatrists and psychiatric nurses would agree on how powerful the reality of splitting can be on an inpatient unit team caring for a patient with borderline personality disorder.

The role of the environment is examined from a circular perspective taking into account the reciprocal influences between the subject and his or her context. For instance, there is a group conception of psychiatric illness in more traditional societies [35]. Also, family therapists consider the symptom like an adaptation strategy of the system to maintain homeostasis more than a weakness, and we have to work as coaches or catalysts for the family who must find its own solutions. According to Minuchin [36], the symptom organizes how each family member positions himself or herself regarding the identified patient. It organizes the scenario or drama of the family structure that the therapist will try to destabilize to allow the disappearance of the symptom [36].

With older patients, psychotherapy may involve multigenerational issues, because families are often very involved in the older patient's everyday life in a way that is distinct from younger patients. Moreover, in our aging population, many systems (e.g., family, living environment, team of care) can intersect, and some clinical impasses can be addressed from a contextual or systemic framework (see ◘ Table 8.10).

In the emergency department, we have to consider the various contexts, e.g., reason for consultation, current support network, and fears related to the hospital environment.

Table 8.10 Geriatric applications of systemic/family therapy

Settings	Clinical problems
Home care	Poor medication adherence
Humanizing the care of the dying	Chronic illnesses
Hospitalization	Decreased mobility
Transfer to a long-term care facility	Neurocognitive disorders

Being sensitive to the patient's situation and her/his environment can allow the solution to emerge. Context shapes us, and symptoms are often context dependent.

Teaching Point
When hospitalization is necessary, separation can reactivate some defenses. It is important to meet with the family system early on to explore the potential barriers to care and come up with a solution in the patient's best interest while being acceptable to the other members of the family.

Often, psychotherapy with more debilitated patients becomes a combination of individual and family therapy [15]. With cognitively impaired patients, the active involvement of family members is essential.

A structural approach is used to modify the relational structure by intervening in the present. A solution-oriented approach modifies the present rather than explores the past (which will manifest itself in the present). Structural family therapy is a strength-based, outcome-oriented treatment modality following ecosystemic principles, as outlined below:

- Context organizes us. Our behaviors are a function of our relations with others. The structural family therapist focuses on what is taking place among people, rather than on individual psyches.
- The family is the primary context, the "matrix of identity" where we develop ourselves as we interact with spouses, parents, children, and other family members. The family is in constant transformation, adapting to an ever-changing social environment. For instance, sudden changes in an older adult's health status will force the family members involved in his or her care to adapt and redefine certain roles or transactions.
- The family's structure consists of recurrent patterns of interaction that its members develop over time, as they accommodate to each other. For instance, the oldest adult child might be polarized in the responsible role, or have the role of a mediator when there is conflict, while another sibling could be labeled as the loyal one. In an older couple where there is a clear division of labor (only one can drive, the other cooks) and when one can no longer accomplish the assigned tasks due to illness or death, it creates a disequilibrium and symptoms and forces adjustment from all parts of the system.
- A well-functioning family is not defined by the absence of stress or conflict but by how effectively it handles them as it responds to the developing needs of its members and the changing conditions in its environment (e.g., how the spouse and children of an older patient adapt to the patient's prolonged hospitalization).
- The job of the structural family therapist is to locate and mobilize underutilized strengths, helping the family outgrow constraining patterns of interaction that impede the actualization of its own resources.

Subtypes of systemic therapies are marital/couples counseling, family therapy (usually consists of at least two generations sharing aspects of life and it can be in any configuration), and psychodrama. The required therapeutic attitudes and skills include flexibility, direction, non-blaming, and being more a coach than an expert (i.e., letting families find their own solutions). Ausloos [37] once wrote: "A family poses only problems it can resolve." Also, he emphasized the importance of circularization of the information: the information must come from the family and go back to it to unblock and activate the process. It is about making the members discover "things they didn't know they knew" [37] about their family.

8.1.7 Combination (or Second- and Third-Generation) Therapies

Schema-Focused Cognitive Therapy

This is an integrative approach to treatment that combines the best aspects of CBT, experiential, IPT, and psychoanalytic therapies into one unified model. It was introduced by Jeffrey Young as an effort to move back toward psychoanalytic concepts. It targets the long-standing patterns or themes in thinking, feeling, and behaving/coping (e.g., schemas, "schemes," or "life traps") that have been maladaptive in the person's life [38]. For instance, some schemas that older adults could identify with are social isolation, dependence, and vulnerability to illness (see Table 8.11).

Schema-focused cognitive therapy consists of three phases: (1) assessment phase, during which schemas are identified; (2) emotional awareness and experiential phase, wherein patients get in touch with these schemas and learn how to spot them when they are operating in their day-to-day life; and (3) behavioral change stage, during which the patient is actively involved in replacing negative, habitual thoughts and behaviors with new, healthy cognitive and behavioral options. Common factors remain ubiquitous; in their article, Cousineau and Young emphasize the importance of respect and authenticity during the therapy [38].

Table 8.11 Examples of cognitive schemas or themes common in older patients

Schemas	Examples
Low self-efficacy/ dependence	"I can't do anything by myself, I need others to care for me."
Social isolation	"Getting old means losing everyone I love; I might as well get used in being by myself. What is the point in gathering with others?"
Vulnerability to illness	"I am old and frail; I can't leave the house otherwise I will have a pneumonia."
Reactivation of abandonment issues	"My children and grandchildren are rejecting me, just like my parents abandoned me."
Survivor guilt	"I don't know why I survived the Holocaust, when I know such good people who died during the war... Why am I the one to stay?"
Entitlement	"I always had the best, nothing less. I am of superior quality; therefore, I deserve the best doctor and treatment."

Acceptance and Commitment Therapy

Acceptance and commitment therapy is derived from DBT and helps focusing on the remaining resources, which is especially important with older adults when the cumulative losses make it challenging to see and acknowledge the intact abilities, hence maintaining a positive perspective. Acceptance and commitment therapy teaches mindfulness skills to help individuals live and behave in ways consistent with their personal values (commitment) while developing psychological flexibility (acceptance). In this context, mindfulness consists of a collection of processes that function to undermine the dominance of verbal networks and include [39]:

- Acceptance
- Defusion or stepping back from the negative impact of thoughts and beliefs
- Contact in the present moment
- Transcendent sense of self

Teaching Point

Defusion is the separation of an emotion-provoking stimulus (also called "trigger") (see ► Chap. 14) from the unwanted emotional response as part of a therapeutic process.

Improved well-being was found among older adults with higher psychological acceptance [5]. The findings from a study by Davidson et al. [5] indicated that symptoms of depression in older adults living in long-term care homes improved significantly during the course of a 6-week intervention with acceptance and commitment therapy compared to a wait-list control. The treatment was developed based on the following core processes:

- Determining core values
- Acceptance of current circumstances and internal experiences
- Defusion from thoughts and feelings (achieving psychological distance from these experiences)
- Being present in the moment
- Engaging in committed action

Mentalization-Based Therapy

Mentalizing is the process by which we make sense of each other and ourselves in terms of subjective states and mental processes [17]. It is intuitive and easy to learn at the basic levels needed for good results. Mentalizing is a profoundly social phenomenon. As human beings, we generally and automatically form beliefs about the mental states of others, and our own mental states are strongly influenced by these beliefs. But human beings can temporarily lose awareness that others have minds, especially when under high stress. Even a therapist, when working with a non-mentalizing patient, is constantly at risk of losing his or her own capacity to mentalize. Mentalization-based therapy for patients with borderline personality disorder was founded on the specific theoretical basis that frequent loss of mentalizing is the underlying pathology that gives rise to the characteristic symptoms (e.g., dysfunction in self-regulation, impulse control, and interpersonal relationships). The incorporation of mentalization in treatment of severe personality disorders (see ► Chap. 25) does require more training and experience.

Secure attachment lays the groundwork for mature mentalizing later in life [17]. Therefore, mentalizing deficits can be addressed during therapy, where a trusting relationship with a professional can unfold. The patient will eventually feel "felt" by the therapist [11]. The process of identification is another important mechanism that develops the patient's mentalizing skills; the therapist's ability to use his or her mind and to demonstrate a change of mind when presented with alternative views is internalized by the patient [17]. The therapist's own ability to embody self-awareness will provide powerful modeling and contribute to the transformative relationship taking place in therapy.

Mentalizing specifies "curious and interested" as its mindset, the humility or "not-knowing stance" described by Bateman and Fonagy [17, 40]. Mentalizing uses mindfulness as a foundational concept and expands it to past and future as well as the minds of others. Most other therapies emphasize practices, procedures, and protocols that are more *doing* than *being*. There are certainly *being* aspects that become common to all therapists with experience and growing wisdom.

Being curious and interested (real knowing) along with acceptance (not necessarily in agreement) seems to be an extremely important component of success in psychotherapy. It is the foundation for collaboration between patient and therapist and a practical definition for love. Consistent with "two (or more in the case of groups) heads are better than one," categorically working on options is better accomplished when different opinions can interact and support each choice. The other components of effective therapy are the choices that can be worked out fairly. Fairness, or iterative collaboration, is a

core value in the healthiest solutions. It is the goal of therapy with personality disorders. Effective psychotherapy with those who experience personality disorders really is fairness training. Mentalizing is, in essence, the work of a fairness process.

Mentalization-based therapy was developed as a research-based treatment to be quickly learned and easily implemented by mental health professionals of various professional disciplines. The results from a recent study [40] suggest that mentalization-based therapy is an effective treatment for patients with borderline personality disorder and comorbid antisocial personality disorder. More specifically, patients treated with mentalization-based therapy showed a significantly greater reduction in anger, hostility, and paranoia. The frequency of self-harm episodes was also lower. Bateman and Fonagy state that mentalization-based therapy is designed to avoid possible harmful effects of overzealous, clumsy transference interpretations delivered without the balancing statements by expert practitioners [17].

Teaching Point

Mentalization is a foundational element of the psychotherapeutic process that should permeate the relationship. The therapist should not only model the need for becoming aware of one's own emotions or thoughts in daily life in general but should himself/herself be aware of what he/she is doing as he/she is doing it also in therapy, by asking "what am I doing" in this chair or "what is it like for me now" while with the patient. The therapist's role is to help the patient establish a secure base where his/her past attachment patterns can be deconstructed to develop new, healthier ones in the present [11].

8.1.8 Psychotherapy Formats

Group Therapy

Certain group interventions, particularly CBT, appear promising for use with depressed older adults. It is a great format to counteract certain negative experiences stemming from loneliness and grief. Also, it may offer significant advantages to older people including being less expensive than individual treatment, and the social network provided by group therapy presents potentially superior therapeutic benefits for a cohort dealing with various losses (see ◘ Table 8.3). The core of 12-step programs is usually delivered in a group setting. The addition of group therapy to individual sessions dramatically expands the contexts in which processes (such as mentalizing) can take place [17].

Book Therapy

Bibliotherapy is an expressive format of therapy that involves the reading of specific texts with the purpose of healing. Various therapies (such as CBT) use it as a delivery modality. It uses an individual's relationship to the content of books and poetry and other written words as therapy. It consists of promoting skills acquisition via selected readings, not only self-help books. In fact, reading fiction seems to be correlated with the development of empathy. *Bibliotherapy* is often combined with writing therapy. This can be used as an adjunct to other forms of therapy. Among its advantages, the material is processed at the patient's pace, self-administered (which can decrease fear of stigmatization) and a good option for those with decreased mobility. The author (in the case of self-help book) serves as "therapist" [4]. In other genres, the fictional hero can represent a comforting and inspiring figure.

8.1.9 Other Forms of Therapy

The literature abounds in types of therapies (easily over a hundred of psychotherapies), some being more integrated in our balanced way to live and having incontestable benefits (such as "play therapy," "pet therapy," certain martial arts, or "wilderness therapy") and others sounding more vague, not to say questionable (e.g., "psychedelic," "nude," "primal," "attack"). Some of them are simply variants of well-established approaches. Others seem to have synonyms (Jungian versus depth psychology). With those approaching the end of life, based on religious beliefs, pastoral counseling should be considered as a form of therapy. A religious counselor can guide a healthy negotiation of stages associated with end-of-life care through a personal inventory and working on more spiritual notions, e.g., transcendence and forgiveness.

8.1.10 Special Considerations

On Becoming an Older Therapist

There are significant advantages for older therapists. The experience with an exposure to a whole life span of developmental challenges nourishes the interactions with a person struggling in life. Some say that their clinical experience stretched their tolerance for affect. But the unconscious life continues and one should still stay vigilant about blind spots. The advanced age of the therapist also introduces the likelihood of new countertransferential aspects if the therapist gets ill. It becomes crucial to remain aware of limitations that make the therapeutic encounter ineffective. Some older therapists may be hesitant about starting a therapeutic process with someone who has intense anxiety about separations [9]. The key lies in maintaining self-awareness. And the integration of mindfulness approaches as we practice side by side with our patients enhances that precious tool.

On Accompanying a Patient with a Terminal Illness

A therapist accompanying a patient during the course of an incurable, progressive illness might experience helplessness feelings. (See ▶ Chap. 33.) At that point, it might be appropriate to view oneself as a receiver of the patient's personal words of wisdom when the patient is now forced into a last stage of life where review of one's personal trajectory becomes

indicated to develop a global perspective, which allows self-compassion and serenity to emerge. The guiding figure that the therapist initially represented becomes the learner, and the patient can find ultimate joy and empowerment in modeling how to die and how to say goodbye and, in a way, thank you. Such a role reversal allows for a dynamic of gratitude initiated by the patient to occur. At a termination session with one of the authors who was a resident then, a patient, offering a goodbye present, said: "It takes humility to accept a gift."

Teaching Points

The core principles of the therapies with older adults are similar to those of younger adults [16]. Certain issues unique to the older adults include cognitive limitations, medical comorbidities, and transference/countertransference related to the disparity of the ages between the patient and the therapist. Common factors such as empathy, alliance, and affirmation are aspects of therapy that predict outcome and seem to differentiate more effective therapists from less effective ones. Psychotherapy is a valuable framework for older patients since it provides a support to deal with various changes while at the same time being an ultimate opportunity to address past attachment patterns causing current distress. The new attachment relationship becomes a co-construction between patient and therapist, and their exchanges are meant to lead to the transformation of the person.

8.2 Case Studies

The following two cases illustrate the progression of psychotherapeutic encounters with older adults and facilitate the assimilation of psychotherapy principles at any training level.

8.2.1 Case 1

Case 1 History

Ms. L. was a 65-year-old woman who was transferred to you from a psychiatrist colleague who recently left the practice. Ms. L. stated that she was diagnosed as "bipolar" in the past. During your initial encounter, her main concerns were her difficulty with breathing and chest pain when she was stressed (a significant trigger was her daughter's substance use problems). She had episodes when she became "panicked," and she no longer could leave the house or drive. She had been stable on her treatment regimen except when she had those "anxiety attacks." "Then nothing works." She admitted that she had increased her alcohol intake at night to help with her sleep lately. She also used to do that when she was with her ex-husband who was abusive to her. She was an active smoker and had smoked for over 40 years. She had not used other substances.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What is your next step in assessing this patient?

Question 2. (a) What is your first step in clarifying her diagnosis? (b) Based on your diagnostic hypotheses, which psychotherapeutic approaches would you recommend at this stage?

Question 3. What will be your new approach with this patient?

Case 1 Answers

Case 1 Answer 1 (Question 1—What is your next step in assessing this patient?) Clinicians should review the following items:

A1.1. *Medication review, for safety purposes.* This is especially important in the case of sedatives like benzodiazepines, because of addictive/lethal potential, risk of falls, and risk of exacerbation of depressive disorder and cognitive impairment, all of which consequences would affect treatment. Moreover, prescribed sedatives could have additive effect with alcohol use; in this view, a potential substance-related disorder that is not disclosed to the therapist because of fear of being judged when therapeutic alliance is not yet formed could have fatal consequences.

A1.2. *Review of psychiatric history.* Clinicians, even those who are essentially therapists, need to clarify the context of a bipolar disorder diagnosis, since it is often overdiagnosed. Clinicians also need to clarify the chronology (first episode), how the manic and depressive symptoms manifested (with special attention to the rate of mood change, intensity, change of behavior observed by others, lack of insight), under what circumstances the episodes occurred, were the mood episodes associated with substance use (which can represent a confounding variable), was any episode serious enough to warrant psychiatric hospitalization, were there psychotic features (thought disorder, perceptual disturbances, grandiose, or paranoid delusions), and were there any suicide attempts (how many, method for each, context, triggering events, level of planning). If the diagnosis of bipolar disorder is ruled out in this case, we have to explore other diagnostic possibilities. A rigorous diagnostic process will have an impact on Ms. L.'s treatment plan and potential outcomes.

A1.3. *Obtaining vital signs.* This is to identify potential signs of alcohol withdrawal, especially if the patient did not disclose a substance-related disorder in the initial phase of the therapeutic alliance building.

A1.4. *Collaborating with primary care clinicians to obtain more recent physical exam findings.* Clinicians may order further laboratory tests to rule out contributing

systemic medical conditions (e.g., thyroid function tests, liver-associated enzymes, complete blood count), electrocardiogram, and a sleep study, as indicated. It is therefore important to rule out systemic medical causes of psychiatric manifestation (e.g., hypothyroidism) or medical conditions that would affect the treatment (e.g., chronic renal failure in a patient on lithium therapy requires extra psychoeducation as part of the therapy if the patient refused to switch her lithium to another mood stabilizer). Adopting a systematic approach helps to demonstrate the patient that the clinician cares about the whole person, which in turn can help to build rapport.

Case 1 (Continued)

Ms. L. reported that she was never hospitalized. She stated that she went "manic" which meant she would typically clean the house excessively and would have 1–2 nights in a row without sleep, but she would nap during the day, and this happened a few times per year. She reluctantly described herself as being "paranoid" ("I don't like to meet strangers or go to the store alone"), saw shadows, and sometimes heard her name spoken or a baby cry. She was put on lithium carbonate when she told her previous physician about these symptoms. She had never experienced grandiose feelings. She often thought about dying, but she had never attempted to hurt herself. On examination, she scanned the room nervously. She was overweight, and her blood pressure was elevated.

Case 1 Answer 2 (Question 2—What is your first step in clarifying her diagnosis? Based on your diagnostic hypotheses, which psychotherapeutic approaches would you recommend at this stage?)

Because of the symptoms at presentation, we must rule a major depressive disorder (morbid thoughts, insomnia, comorbid anxiety). Even if she would meet diagnostic criteria for major depression, given the reported history of abuse, we must screen for posttraumatic stress disorder as well, since their co-occurrence is high and their respective symptoms overlap. The bipolar disorder diagnosis in this case was not substantiated (she didn't meet criteria, both in terms of type and duration of symptoms). Moreover, the "paranoid" feeling could be due to hypervigilance from posttraumatic stress disorder, so could her visual and auditory perceptual disturbances. Even if Ms. L. had a diagnosis of bipolar disorder, posttraumatic stress disorder would need to be considered, as well. Besides posttraumatic stress disorder, other diagnoses on the differential include panic disorder and alcohol dependence (both as coping skill and causal factor). Ms. L. admitted to increasing her drinking to aid her sleep. She could also develop a depressive and/or sleep disorder from excessive alcohol use.

Based on such hypotheses, the potential treatment approaches for this patient would include a combination of supportive approach to establish therapeutic alliance and help her develop a sense of safety, Alcoholics Anonymous meetings, motivational interviewing, cognitive behavioral therapy (to examine cognitive distortions such as catastrophic thinking, vulnerability to illness), problem-solving therapy, brief dynamic therapy, or interpersonal therapy for role disputes (e.g., to deal with her daughter, helping her in setting clear and firm boundaries).

Case 1 (Continued)

You consulted with your colleague who had a patient with a similar history of trauma and who recommended EMDR, saying it was effective. Since the approach was not familiar to you and because your patient decided to address her drinking problem, you preferred to use motivational interviewing and CBT techniques (e.g., using symptom log, challenging dysfunctional beliefs, breathing exercises, and gradual exposure to stressful situations, like going to the store by herself). She was adherent to recommendations. Her panic attacks decreased significantly after implementation of the above therapies.

A few months later, she reported that her panic attacks had returned since she saw her primary care physician who ordered an invasive screening procedure for her. She refused to go see her physician again. "He didn't explain what he was doing and his tone of voice was . . . I don't know, it made me feel I had done something wrong." But the worst was the crying, which seemed incontrollable and out of the blue. She did not feel like gardening anymore, which used to be her passion. She also had long-standing disturbing images. However, this started again recently when she caught her daughter breaking into her house to steal money, and the daughter responded by threatening her mother and insulting her when confronted. Again, Ms. L. became scared to live alone. She disclosed to you for the first time that she was raised by an abusive stepmother who mistreated and humiliated her handicapped sister and would use corporal punishment whenever they were "bad."

Teaching Point

A recent article revealed that childhood adversity appears to be associated with bipolar disorder. This review found that people with bipolar disorder were 2.63 times more likely to have suffered emotional, physical, or sexual abuse as children than the general population [41].

Case 1 Answer 3 (Question 3—What will be your new approach with this patient?) Since you are suspecting posttraumatic stress disorder recurrence at this point, using a supportive, trauma-informed approach specifically for the consolidation of a sense of safety is essential before starting a more specific approach like CBT, psychodynamic, or experiential therapy. You could do so by encouraging Ms. L. to tell her story but never push her to talk if she is not comfortable doing so. Once the diagnosis is confirmed, asking the patient how it has affected her life so far can be a helpful, empathic question. Psychoeducation about the impact of trauma on the whole person can provide some reassurance and help address the feelings

of shame, guilt, or helplessness. It is important to foster recovery, empowerment via encouragement of boundary setting (toward her daughter), and self-advocacy (during medical visits with clinicians who fail to demonstrate trauma-informed skills). Group therapy is a good way to establish connections with the outside world while at the same time providing educational tools and inspiration from hearing others' stories and sharing resources, again, in a safe and supportive setting.

Obtaining her consent to discuss her vulnerabilities with her other specialists if they are not in the same health system or practice is not only the standard of care to support this patient but a good way to provide education to colleagues while at the same time facilitating an optimal resolution that would help the patient's self-esteem by not resorting to avoidance. Finally, teaching her some mindful awareness techniques can help decrease anxiety and promote general well-being.

8

Teaching Points

The body and mind are *both* affected by trauma, whether it is emotional or physical; people who have been mistreated tend to mistreat themselves later in life. Self-esteem/self-confidence often needs to be restored. A trauma-informed approach can be summarized using the acronym SAFE:

- *S*creen with *s*upport
- *A*ttentive/*a*dvocacy
- *F*ollow/*f*oster recovery
- *E*xplain/empower

Help the patient "avoid the avoidance," e.g., self-medication with drugs, alcohol, or inappropriate use of medications which are ineffective coping responses that prevent the patient from processing the trauma and making decisions that would promote healing. From the outset of treatment, patients should be advised that therapeutic progress will likely involve discomfort as they learn to cope differently (e.g., being assertive if normally avoidant) [6].

Case 1 Analysis During individual and group therapies, Ms. L. learned to be more able to articulate her needs and to accept her vulnerabilities; she was now more aware of potential triggers and how to use defusion strategies to handle them. She became abstinent from alcohol, changed her diet, and was learning to tolerate difficult emotions (sadness, anger, and fear) by using various outlets: exercise, meditation, and a creative writing group. She was happy to have found a safe space to process her difficult experiences. As a result, she socialized more and was open to expand her support network.

8.2.2 Case 2

Case 2 History

Mr. A. was a 71-year-old man referred to you, the psychiatrist, by the internal medicine physician who admitted him after he was found at his home unconscious in a state of diabetic ketoacidosis. Now medically stable, his treatment team wanted a suicide risk assessment before potentially discharging him to his home. He had not been diagnosed with diabetes mellitus until then. He had always refused laboratory studies, claiming he had had a phobia of the sight of blood his whole life. He was not happy about the psychiatric referral and said sarcastically that he agreed to talk to you only to reassure this "chick doctor." "Poor girl. She's obviously terrorized by law suits. Wants to make sure I won't try to kill myself." He added that he did not try to kill himself. He stated that he was feeling "a little down," but it was due to his daughter not letting him see his grandchildren. "She says I party too much and she doesn't trust me with them." He became upset upon saying this, "I raised her alone, how dare she tell me how to take care of my grandsons!"

He was never hospitalized in a psychiatric facility and had never seen a psychiatrist before, "except when there was a lawsuit." He told you how entertaining it was to "shred experts in court" when he worked as a judge.

Upon reviewing the daily chart at the nurses' station, you note that he was at times very charming with some nurses, contemptuous with most physicians, and inconsistently cooperative with the medication regimen. Sometimes he refused the medications, concerned about side effects. Most of the time, he refused the finger-stick glucose monitoring. He even removed his intravenous line on a few occasions, concerned that the needle would make him bleed to death. His hospital room neighbor repeatedly complained that his TV was too loud; Mr. A. responded in a rude manner and refused to turn the volume down, but otherwise he was not threatening. His sleep was deep with loud snoring, and his appetite was good. He was medically stable and ready to be discharged home. The hospitalist was concerned about his treatment adherence once at home since he lived alone and had poor eating habits. Mr. A. did not seem to grasp the severity of his condition.

Upon starting his psychiatric examination, he asked you a few times to return later because he was busy on the telephone or writing a letter. He had a mixed expression consisting of contempt and charisma. Although he smelled heavily of cologne, his grooming was not impeccable. He wrote a long letter to the hospital and the insurer explaining his frustration of not having had a private room as he requested. His vernacular was sophisticated, and his thought process was mostly coherent yet circumstantial, but he had difficulty paying attention (e.g., he forgot your questions).

He reluctantly agreed for you to contact his daughter. She told you that he had been a distant, intimidating, yet controlling father her whole life. They never discussed the fact that his wife left him. For many months after the separation, he retreated in his study to read, smoke cigars, listen to jazz, or simply stare at the wall. He had a few other relationships with women after that, but they always left him because they could not cope with his inability to listen to them and provide for their emotional needs. His daughter explained that "they felt utilized by him, shown off and then criticized in private (correcting the way they spoke or making negative remarks about their outfits, for instance), instead of feeling accepted for who they were." His daughter got into an argument with him because he would feed her children only fast food and not respect their bedtime routine.

During morning rounds, the hospitalist questioned what to do about his continued minimal cooperation in obtaining blood glucose levels.

Case 2 Questions and Answers

Case 2 Questions

Question 1. Which other test results or investigations and which additional information would you need to obtain?

Question 2. At this point, what are your diagnostic impressions, including your differential?

Question 3. List the indicated psychotherapeutic approaches, and give examples of techniques for each.

Case 2 Answers

Case 2 Answer 1 (Question 1—Which other test results or investigations and which additional information would you need to obtain?)

The first step is a thorough psychiatric assessment consisting of a clinical interview. Complementary evaluation such as Minnesota Multiphasic Personality Inventory (MMPI), psychological testing, screening for alcohol abuse/dependence (CAGE—*cut* down, *a*nnoyed, *g*uilty, *eye* opener—questionnaire), and a cognitive screening tool like the Montreal Cognitive Assessment (MoCA) would be indicated to rule out major diagnostic hypotheses and refine the diagnostic formulation.

Case 2 (Continued)

Mr. A. declined the MMPI test, emphasizing that his time was too valuable. He refused to meet with a psychologist. He scored 27 out of 30 on MoCA, with evidenced limited short-term recall, and he got distracted and digressive after the naming task on MoCA. His affect was irritable.

Case 2 Answer 2 (Question 2—At this point, what is your diagnostic impression, including your differential?)

It is imperative to explore the context of his medical complication of diabetic ketoacidosis. First, because of the serious complication for which he was admitted, we must rule out a major depressive disorder; clarification is required whether he had a suicidal gesture by withholding his treatment with insulin or self-neglect from an undiagnosed severe major depressive disorder. Unresolved grief of relationship with his ex-wife, or complicated grief, should also be considered on the differential diagnosis.

Manifestations of grandiosity such as intimidating comments, emphasis on perceived success, requesting special treatment, and difficulty demonstrating empathy toward the psychiatrist's time (while being mostly aware of his own) can alert us to narcissistic personality disorder. Specific phobia (blood-injection-injury type) seems highly likely based on his extreme avoidance of needles. A mild neurocognitive disorder should be kept in mind given his poor grooming (possibly due to a functional decline in activities of daily living) and limited short-term recall; however, his relatively normal MoCA score could be explained by high premorbid intelligence and education, which may mask a new onset of memory decline.

Substance misuse should also be explored. Since he had mentioned his daughter's complaint about his "partying," you asked how many drinks per day did he typically have. He said he didn't count but would drink maybe "a couple" of glasses whenever he had guests, and sometimes he had friends or neighbors visiting 5 days per week. Often he would fall asleep on the couch because the "strong wine" would make him tired.

Case 2 Answer 3 (Question 3—List the indicated psychotherapeutic approaches, and give examples of techniques for each.)

The common factors of therapy are essential to create a framework supporting of growth and alliance; empathy, positive regard (validation), genuineness (to help model an authentic self), and the development of common goals can set the foundation for more specific therapeutic work. CBT would be an additional effective modality for this patient's blood phobia. It could include cognitive restructuring, relaxation techniques (before any blood draw), and desensitization via gradual exposure (i.e., images of blood or needles and then a needle puncture to a blood vessel and glycemia measurement as a last step). A 12-step program such as Alcoholics Anonymous could not only address his substance misuse (based on his report, he might be abusing alcohol) but also co-dependency issues (both the patient and his daughter might be taking turns in overprotecting the other in a disempowering dynamic—see ▶ Chap. 25). Because of the poor treatment adherence and chronic illness (see ◘ Table 8.10), systemic therapy would be useful in this case. More specifically, family therapy (with daughter) or IPT seems indicated also to help with the significant relationships and coping strategies when interpersonal conflicts arise. A course of short-term psychodynamic therapy would be worthwhile to help working on suffering, unfulfilled emotional needs, grief, or guilt. A genogram (i.e., the patient's family tree with important facts such as births, separations, migration, losses, and medical illness diagnoses) can be used during

that process to identify transgenerational patterns, epigenetic influence (see ► Chap. 14), and commonalities. It can also elicit unaddressed conflicts with lost objects. Art or music therapy is valuable for therapeutic alliance and engaging a potentially difficult patient.

Teaching Point

Co-dependent relationships are a type of dysfunctional helping relationship where one person supports or enables another person's addiction, marginal psychiatric status, immaturity, irresponsibility, or underachievement. Among the core characteristics of co-dependency, the most common theme is an excessive reliance on other people for approval and identity. (See ► Chap. 25.)

8

Case 2 (Continued)

Mr. A. did not show up to his follow-up visit and canceled the two subsequent ones at the last minute. The next time, he showed up accompanied by his daughter. Without being able to pinpoint why, you felt an immediate wave of sympathy toward her. According to her, Mr. A. had been "depressed" due to his son not calling him on his birthday, refusing to get up in the morning and shower. (You learn for the first time about the son, an artist who had traveled a lot.) Mr. A. denied this, saying he did not care, and that he only wanted his son to be happy and not to worry about him. He beamed with pride upon telling you this. When you tried to identify potential triggers, he narrated a dream he recently had of his mother. "I haven't thought about her in so long, she died when I was a little boy." Upon saying the last few words, he choked and tried to hide his tears from you by requesting to end the session immediately. During a subsequent session, he said that he suspected domestic abuse in his daughter's relationship. "I tried to warn her about this guy, she won't hear me."

Case 2 Analysis You identified various dysfunctional assumptions or schemes (see ◘ Table 8.11) including themes of entitlement and abandonment. You suspected that adverse childhood experiences (early death of mother, raised by an emotionally unavailable father) affected his sense of emotional safety and interfered with the development of a healthy narcissism. Being emotionally involved became too threatening; therefore, you reflected to him that he remained involved with others rather superficially to avoid being hurt, creating immature defenses like contempt, entitlement, avoidance, and intellectualization. Disregard of others' distinct sense of self and needs was also one of his characteristics.

You mediated a few conflicts between him and his daughter. After each session, you felt drained and frustrated so you decided to consult with a senior colleague (who is also your mentor) who made you realize that you tended to do the work for them. It could be that their dynamics reactivated some unresolved conflicts which you experienced with your own parents. Then, upon sharing those with your mentor, you had an epiphany regarding your own co-dependency tendencies (which developed as a coping mechanism during your upbringing among parents who had substance-related disorders). You started practicing mindful awareness and became more effective at separating your patients' issues from your own. You reminded yourself that those issues belong to the patient and his daughter and that they could find their own solutions, with your reflective and non-intrusive guidance.

After a few sessions with his daughter and him that catalyzed a resolution of their divergences, he decided to continue to see you privately. He was interested in this "Frankl" approach you told him about, whom he believed sounded much more down to earth than this "phallus-obsessed Freud." Plus, he admitted he hoped his daughter would do the same. You used his desire of modeling to improve interpersonal behavior for his daughter as a momentum and re-boost his ego by praising this empathic and caring attitude. He asked you to be her therapist as well, but you recommended that she finds her own therapist separately. Initially, he had doubts about your competencies since you just graduated from residency, but by not falling into the trap of defensiveness or responding to his harsh comments while maintaining clear boundaries for his self-expression, he most likely felt accepted and developed a sense of trust. You had agreed on therapy goals. You also used some gestalt techniques (e.g., empty chair) to help him to learn to deal with people in his life instead of being demeaning and rejecting.

During the initial phase of psychotherapy, his depressive symptoms seemed to worsen, which tended to happen when there was patient awareness of his or her interpersonal and relational deficits. It had peaked when his son left the home years ago. It would lift when he worked toward meeting those needs [42]. Among those was the need to be heard. He disclosed that his drinking had gotten worse lately (he had occasional binge episodes when frustrated). He agreed to start Alcoholics Anonymous meetings to address the issue.

Working on his fear of rejection or abandonment (reactivating the premature departure of his mother and then later his wife) and accepting such vulnerabilities were an essential part to be able to develop authentic, reciprocal relationships. Working on his grief and forgiving figures who hurt him in the past helped resolve some difficult emotions he had been trying to repress since childhood. Elan Golomb once wrote, "Every narcissist was once a rejected child" [42].

You incorporated some reminiscence therapy sessions into the treatment, and he recorded some life events at home (he had developed a tremor that frustrated his handwriting) to share with you. He voiced his surprise at his ability to "remember more about my past than I thought." Among other events that emerged to his consciousness, he brought up one of the memories he had of his mother. She was in the bathroom once and he heard her cry. His father simply said to him "she lost a lot of blood . . . your little sister won't come." His father told him to not ask his mother any questions regarding this because it would upset her too much. You listened carefully to this loaded memory, and after a few seconds of silence, you asked him how he was feeling at the moment. In the office, he was visibly pale, sweating,

and shaky. You encouraged him to say what was going on inside of him, and you asked if he had any words that came to his mind. He said: "I remember, I was so scared about going to the bathroom and see the blood . . . or maybe a dead baby . . . yes, a dead tiny baby . . . then whenever I would get hurt and bleed I would faint because I was afraid to see . . . I guess, a fetus . . . or even . . . die . . ." He wiped tears, his voice started to tremble, and you asked him if he wanted to stop or continue. "I need to let this out . . . It has affected me for too long. Later of course I realized my fear was crazy, no baby would die because I'm a man but I imagined maybe I would die from exsanguination . . . You know, my mother died because she lost too much blood after giving birth to my sister . . . Back in the days . . . the doctor . . . was not around . . ." Then he remembered seeing the sheets all soaked with blood, his father was crying, and his aunt looked angrily at him as she was pulling a blanket over his mother, "I thought she was sleeping . . . She looked so peaceful . . . I thought she was happy to have a new baby girl . . ."

Despite an initial sadness when he narrated missing his mother (he also realized he had some unresolved angry feelings toward his father), he said that cultivating some relationship with his earlier, more innocent self made him feel at peace and more understanding of his own children. He saw himself as a whole, with strengths and vulnerabilities. He also learned to take responsibility for his attitude and behaviors. He developed a new understanding of his father's own attempt to grieve ("I think he did his best"), some gratitude for those who had helped him in his life, and he tried to forgive himself for the way he had treated others.

You also incorporated some elements of brief psychodynamic therapy, asking him whether he saw a link between his lifelong blood phobia and the circumstances of his mother's death and her own losses. This therapeutic moment was an epiphany, and he was overwhelmed by a mixture of gratitude and astonishment. He was interested in exploring these elements of his childhood with you "in small doses."

At some point, he wanted to offer you a painting by his son to put in your office to replace one which he found to be "ugly." Expressing gratitude for his thoughtful idea, you explained that verbal appreciation was best. He was insistent, and after discussion with your mentor, you settled for a more discrete replica (postcard of the painting). He was happy to leave to you a representation of a meaningful object.

8.3 Key Points: Psychotherapy in Late Life

- Many older adults express a preference for psychotherapeutic over psychopharmacological treatments.
- Many psychotherapies (cognitive behavioral therapy, interpersonal therapy, reminiscence therapy, acceptance and commitment therapy, etc.) can be used effectively with older populations. Because of factors associated with old age (e.g., systemic medical conditions, cognitive decline), some specific adaptations might be necessary for successful implementation of psychotherapy.
- The common factors are essential ingredients for therapy.
- Clinicians need to be aware that even though age can be associated with increased resilience to stressors, patients who have a history of adverse childhood experiences could be at risk of posttraumatic stress disorder reactivation.
- Substance-related disorders are a frequent comorbidity in patients who have suffered trauma, which needs proper assessment and treatment.
- It is never too late to address earlier trauma; some patients disclose their difficult experiences for the first time in late adulthood. Helping them in identifying the triggers is an important task to achieve better symptom control. An integrative approach, including effective communication with other health professionals, is desirable to minimize re-traumatization (e.g., during invasive medical procedures).
- The empty nest syndrome is a common theme of developmental challenges in old age and can precipitate depressive or anxiety manifestations.
- People with personality disorders can be challenging to engage within a psychotherapeutic frame. People with a narcissistic personality are more vulnerable to the losses (physical, social, emotional) associated with old age. What sustains all people is the belief that they are lovable and that they will be loved [42]. One path toward healing for the patient in ▶ Case 2, for example, was encouraging a sense of generativity, by caring and investing love in the patient's offspring and grandchildren. It may set the stage to the eighth Eriksonian developmental stage (see ▶ Chap. 25). Psychotherapy can be used effectively with older adults.
- Whether or not to accept gifts from patients is a complex issue: obtaining supervision and making sure it does not blur, cross, or violate the boundaries of the therapy are important. One has to weigh pros (on patient's sometimes fragile egos) and cons (e.g., the risk of treating those patients differently and enabling certain maladaptive behaviors). Classical training in psychotherapy encourages the therapist to ask what the gift means and uncover unconscious motives.

8.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which approach contains the most crucial elements when addressing posttraumatic stress disorder reactivation in a patient you are meeting for the first time?

A. Psychoanalytic-oriented therapies
B. Behavioral therapy focused on weight loss and exercise
C. Mentalization-based treatments
D. Approach based on common factors theory
E. The therapy with the strongest level of evidence to treat posttraumatic stress disorder and alcohol-related disorder

Answer: D

Always start with supportive, empathic atmosphere, especially during trauma-informed encounter. It will help establish a sense of safety and trust. Therefore, the best choice is D. Other choices are appropriate later on in the process, once the problems have been defined and the goals agreed upon.

MCQ 2. At first sight, which one of the following would *not* be an optimal therapist-patient match?

A. A 69-year-old female with dependent personality traits referred to a 62-year-old female psychoanalyst based on her physician's recommendation
B. A 71-year-old female with history of chronic depression and suicidality and a 30-year-old male therapist who is in the midst of a training in mentalization-based therapy
C. A 74-year-old male with early major neurocognitive disorder and a 74-year-old behaviorist
D. A 59-year-old male with chronic substance use and a 39-year-old male who is a musician
E. An 85-year-old female with complicated grief and a 61-year-old male primary care physician

Answer: C

The therapist's preferred orientation and the patient's cognitive limitations represent a mismatch (cognitive symptoms might be a limitation to CBT). Their matching age might not be sufficient to compensate for such a specific expertise. If the therapist strongly identifies with that specific theory, the motivation to expand knowledge or perspectives to adapt to the patient's needs might be limited. Statements B, D, and E are examples of good scenarios. In scenario B, D, and E, the current interests of the therapist could be beneficial to the patient (mentalization-based therapy for a woman with depressive disorder and suicidality, music and art therapy for a patient with an addiction, and IPT done by a primary care physician). Statement A is not as good; the fact that the patient was referred does not mean she is ready for therapy, and a directive approach from the primary care physician (although most likely well meaning) might be enabling dependent behavior (a PST or brief psychodynamic approach might be more suitable than the psychoanalysis as stated in statement A). But this dynamic could be identified during therapy and worked through once both parties become aware of the referral process. If they reevaluate the indication for therapy and the potential goals and if they can agree on them, what seems like an initial mismatch might give rise to transformative opportunities such as the development of self-efficacy if the patient becomes more able to voice her needs and stay in therapy by choice. Therefore, the correct answer (or least optimal dyad) is C.

MCQ 3. Group therapy is effective because of all *except*:

A. Increased socialization enhances brain health (like in depressive disorders).
B. It is a form of exposure that helps alleviate distorted perceptions of others (like in posttraumatic stress disorder).
C. It optimizes the development of mentalization skills by increasing the opportunities to challenge perspectives in self and others.
D. The patients are expected to become the therapist at some point during the process.
E. Common factors also apply to group therapy.

Answer: D

Table 8.3 lists the advantages of group psychotherapy. As stated in ▶ section Group Therapy, besides being cost-effective, group therapy promotes socialization and improves the ability to mentalize, and supportive therapists continue to use their common factors to facilitate the process. Even though supportive interactions filled with validation and sympathy are encouraged between participants, it is never the patient's duty to be a therapist of others. Those who are the trained and licensed professionals should monitor the process and make sure they are a mediating and supportive presence. Therefore, the correct answer is D.

MCQ 4. The following are developmental/behavioral challenges associated with narcissistic personality disorder *except*:

A. Attainment of high level of mentalization.
B. Abandonment sensitivity.
C. Other people are essentially functions (body, status, bank account, etc.) to serve the person's ego; they can feel manipulated by the patient as a result.
D. High comorbidity with mood disorders and substance-related disorders.
E. Difficult to engage in therapy.

Answer: A

By definition, most people with personality disorders have had difficulty in their primary attachment relationships. (See ▶ Chap. 25.) Therefore, they can be interpersonally sensitive to rejection, despite demonstrating limited empathy (statement B and E), and will have difficulty acknowledging other human beings as having needs of their own and have no scruples in using them (as in statement C, which is the opposite of A), and after many years of distress, dysfunction, and poor coping, they are at risk of developing comorbid disorders such as depressive, anxiety, and substance use disorders. Therefore, the correct answer is A, as patients with such a personality type have difficulty mentalizating, but once they are able to think about other people's thinking, they are easier to engage, and their prognosis may improve.

MCQ 5. What are the best approaches when a patient is offering the therapist a gift? Choose all that apply.

A. Accept and give back a gift of an equivalent value.
B. Refuse; therapists are givers and, therefore, should never take anything away from their patients.

C. Use the "curious and interested" stance, and see this as an opportunity to discuss levels of meanings (to give, to offer that specific gift).
D. Accept and hide it so other patients do not see and get the wrong idea.
E. Get input from a colleague, a supervisor, or mentor.

Answer: C

Giving back a material gift is not only unnatural but might appear dismissive of the patient's gesture that calls for attention and reflection. Refusing can be offensive, and such "black or white" responses are not helpful because one should take the context into account. Hiding the gift could convey a conflicting message to the patient if he or she expects to see it in your office, and there is a risk of shaming the patient for not having given the therapist a "good-enough" gift. Statement C is therefore the answer, and E is a good second best when unsure about how to examine the parameters and has the most therapeutic response.

MCQ 6. You get late to an appointment because you were sick during the night and overslept. What is appropriate in terms of self-disclosure to a patient who has developed a possible erotic transference toward you?

A. Give all the details of your night and condition, reassuring the patient that you are feeling better and not contagious.
B. Just apologize and say your car broke down.
C. Start by apologizing, and inquire about the impact of this delay on him or her.
D. Explain that your spouse snores and it caused you some problems and your spouse expresses apologies.
E. Apologize profusely, and swear this will never happen again.

Answer: C

Lying is not recommended and impacts the authenticity and fairness of the relationship. Apology is necessary and a reassuring proof that we, too, are fallible human beings. It can be a precious form of reparation especially if the patient grew up in a narcissistic family where authority figures thought they never made mistakes. And because of that fallibility, we should not make unrealistic promises. Therefore, the correct answer is C. This situation is a good opportunity to use common factors (reassurance, validation), cognitive restructuring (examine and question schemas that might have been reactivated by the tardiness), and mentalization: by being receptive to the here and now, we allow the patient to "test" or challenge certain theories of the mind. The appendix lists important principles such as apology and boundaries.

Appendix

In his book *The Gift of Therapy*, Irvin Yalom addresses core themes in therapy divided in 85 short chapters. The title for each chapter could be used as helpful guidelines easy to memorize. Here are some examples:

- Remove the Obstacles to Growth
- Avoid Diagnosis (Except for Insurance Companies)
- Therapist and Patient as "Fellow Travelers"
- Let the Patient Matter to You
- Acknowledge Your Errors
- Create a New Therapy for Each Patient
- The Here-and-Now—Use It, Use It, Use It
- Blank Screen? Forget It! Be Real
- Encourage Self-Monitoring
- Give Yourself Time Between Patients
- Express Your Dilemmas Openly
- Never Be Sexual with Your Patient
- Look for Anniversary and Life-Stage Issues
- Dreams—Use Them, Use Them, Use Them

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Ethics, Mental Health Law, and Aging

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9.1 Background

9.1.1 Demographic and Epidemiological Factors

Psychiatric illness does not discriminate by age. According to the United Nations' 2015 *Ageing Report*, "population ageing – the increasing share of older persons in the population – is poised to become one of the most significant social transformations of the twenty-first century" [1]. According to this UN report, the number of people who are aged 80 years or over, the "oldest-old" persons, is growing faster than the number of older persons overall [1]. As the rate of aging in the population accelerates, the prevalence of psychiatric illness among older adults is increasing. As a more racially and ethnically diverse group lives longer, this will, in turn, require clinicians to be aware of emerging issues in mental health law. As social demography evolves across time, the law will need to be sensitive and responsive to the needs of a vulnerable population.

It has been estimated that between 2015 and 2030, the number of people in the world over 60 years old will grow from 901 million to 1.4 billion, which represents a 56% increase [1]. By 2050, the global population of older persons is expected to reach nearly 2.1 billion [1]. To put this in perspective, in 1870 the population of the US population over the age of 65 was approximately 3%, whereas by 2050 the same group over 65 years will be more than 20% [2]. Geospatially, the older population is growing faster in urban centers than in rural areas. In Canada, the proportion of the senior population (aged 65 and older) has been increasing steadily over the past 40 years [3]. According to demographic projections, the proportion of Canadian seniors is expected to increase rapidly until 2031, when all the baby boomers will have reached age 65. Between 2015 and 2021, the number of seniors is projected to exceed the number of children aged 14 and younger for the first time ever in Canada [3]. As individuals live longer, it is likely we will have increased contact with older adults; while such relationships will bring increased opportunities for learning, it may also pose an increased risk of attitudes of ageism [2].

As the baby boomer population ages, healthcare providers caring for older patients will need to increasingly be educated about psychosocial, legal, financial, and cultural matters pertaining to this vulnerable, diverse group. Decreased premature mortality from heart disease, cancer, chronic lower respiratory disease, and other chronic illnesses will lead to older individuals developing competing contributors to morbidity and mortality, chief among them being neurocognitive disorders [4]. There are ethnic and cultural factors clinicians will need to consider, particularly in the face of rapidly changing immigration policies in many nations, as to various treatment alternatives and how the role of ethnicity in pharmacokinetics, pharmacodynamics, and pharmacogenomics of drug-metabolizing enzymes may contribute to differential drug responsiveness [4]. It is no longer sufficient as a clinician to have only a rudimentary knowledge of laws and policies, particularly in the area of mental health. The need to be aware of one's own cognitive biases in terms of ethical values is equally important. In this chapter, we address ethical and legal issues that are relevant to clinical practice with older adults with psychiatric illness.

9.1.2 Ethical Theories and Frameworks

Broadly speaking, ethics can be considered a set of moral standards for behavior on how individuals *ought* to act [5]. Ethics deals with questions of what is right or wrong. Some may suggest that "ethics are ethics," and as such, they apply equally to all people; it is not possible, according to some, to have one set of ethical principles for one group of people and then apply these differently to another group. Not all universally agree, however. Being an older adult, what some consider aged 65 and older could influence how ethical principles are applied, just as it does for children [6]. Either way, some ethical issues are more germane and relevant to clinicians working in geriatric psychiatry by virtue of the population of older adults with whom they work [7]. For example, how might one's ethical reasoning around issues of distributive justice toward the end of life differ if one were working with minors as opposed to older adults? Similarly, how paternalistic a clinician acts in dealing with an older adult suffering from progressive deteriorating mental capacity due to a major neurocognitive disorder may differ if the same person instead had delirium with fluctuating mental capacity with periods of intact decisional capacity.

At times clinicians will be asked by their patients, and/or their family members/surrogate (or substitute) decision-makers (SDMs), to disclose their personal biases, whether cognitive, ethical, moral, or religious, and how those biases may be affecting their recommendation for a specific plan or course of treatment. Even when not challenged about their own biases and values as they pertain to treatment recommendations, clinicians should be forthcoming about this information so as not to appear disingenuous or dishonest. Patients and families/SDMs tend to respect and seek clinicians' expertise lending weight to the expression "In my opinion..." provided the opinion is backed up by evidence. As such, it is important for clinicians to a priori understand their own preferences and biases.

Modern psychiatric ethics has changed dramatically over the past 50 years, in large part due to its relationship with other specialties in medicine and the law [5]. As such, it can be helpful for clinicians to appreciate the value of ethical theories, frameworks, and reasoning. Ethics can be grouped into three broad areas:

1. Meta-ethics: understanding the *nature* of ethical properties, including the right or the good
2. Normative ethics: focusing on the *standard* and principles used to determine if an ethical action is right or good

3. Applied ethics: resolving the *application* of an ethical principle to determine what is the right or good action to take in a particular situation

Another distinction to keep in mind is the type of ethical theory one adopts to deal with a particular problem. As noted in Table 9.1, a *consequentialist* approach to a problem is concerned with the consequences of a particular action, whereas a *non-consequentialist* approach, also known as a *deontological* approach, is focused on the intentions of a person in making a decision. A non-consequentialist approach is focused on particular actions and whether an individual adheres to obligations and duties because it is the correct action. Contrast these ethical approaches with an *agent-centered* approach, where the focus is on the overall ethical status of individuals and less on the morality of certain actions.

Consequentialists typically take the position that the merit of any act can be found in the ultimate consequences. Within this camp are included theories of utilitarianism, ethical egoism, and the common good. A *utilitarian* theory focuses on the amount of degree of pleasure and/or pain that would be produced. The "greatest happiness" principle in utilitarianism holds that one must always act to bring about the greatest aggregate of happiness. In this respect, issues of involuntary psychiatric treatment of an unstable patient may be justifiable by some through an argument from utilitarianism [8]. An *egoistic* theory, on the other hand, focuses on the ethics of self-interest where the agent calculates the greatest benefit for oneself. Moral agents ought to do what is in their own self-interest as a prerequisite to self-respect and respect for others; in other words, the principle of self-interest trumps altruism. Under ethical egoism, clinicians might approach situations only from the position of what benefits themselves. A *common good* theory suggests that the best society ought to be guided by the general will of the people, and this will produce the best for people as a whole. Actions should contribute to communal life, and the focus is on respect and compassion for others. To take involuntary hospitalization as an example, a common good approach might be used to justify a psychiatrist's right to detain someone who is dangerous in the interest of public safety, while at the same time this could generate tension around individual clinician's responsibility to their patients or other third parties.

There are other ethical perspectives. A *duty-based* approach, in Kantian tradition, sees doing what is right as not about the consequences of our action (no control) but instead having the proper intention. A *rights-based* approach, very commonly adopted in psychiatry, focuses on the best ethical action as that which protects the rights of those affected. Ethical theories of *fairness or justice*, on the other hand, focus on just ethical principles that would be chosen by free and rational people in situations of equality. In this regard, all free people should be treated alike, and the focus is on the fair action, not the consequence.

Agent-centered theories include virtue ethics and feminist theories. *Virtue ethics* is concerned with the whole or entirety of an individual's life, not just discrete individual actions. A person of good character is one who has attained certain virtues, and the theory focuses on the importance of having role models, education, and training in order to be virtuous. In psychiatry, for example, virtue ethics has been applied to what desirable qualities would be found in a virtuous psychiatrist, including those of compassion, tolerance, and prudence. A *feminist approach* focuses on experiences of women and other marginalized groups for ethical deliberations. An ethic of care is a legitimate and primary ethical concern and not impersonal justice. One of the most well-known ethical paradigms, particularly in Western medical ethics, is principles-based ethics (principlism) [9, 10]. There are four core ethical principles in medicine that compete with one another, and clinicians are called upon to weigh these when dealing with any particular ethical or moral dilemma. These include

1. Respect for autonomy – respecting individual's abilities to make reasoned informed choices
2. Beneficence – considering the benefits of treatment against the risks and costs to act in a way that benefits the individual
3. Nonmaleficence – avoiding causing harm to patients
4. Justice – distributing the benefits, risks, and costs fairly treating similar patients alike in similar circumstances

In the first half of the twentieth century, beneficence dominated, resulting in physicians taking a paternalistic approach. Concurrently, concepts of social justice played an important role, justifying, for example, the legal sterilization of developmentally disabled persons. In the 1970s and beyond, the patient's autonomy began to move to the top of the hierarchy, and in the twenty-first century, autonomy is generally considered the dominant value, with social justice falling to the

Table 9.1 Taxonomy of ethical theories

Approach	Theory	Description
Consequentialist	*Utilitarism*	Greatest benefit to the most people
	Ethical egoism	Self-interest
	Common good	Best for overall community
Non-consequentialist (deontological)	*Duty-based*	Having the proper intention
	Rights	Right to dignity
	Fairness or Justice	Treated without discrimination
	Divine command	God creates what is ethical
Agent-centered	*Virtue*	Entirety of person's life
	Feminist	Traditionally focus on principle of "care"

bottom. The courts in the USA seem to have followed these trends in the relative importance of the tenets of principlism by supporting the primacy of autonomy. For example, in obstetrics, a pregnant woman has the right to refuse treatment that would save the life of a viable fetus in the third trimester.

Many public policies, social services, and other government-funded interventions for diseases such as major neurocognitive disorders are influenced by ethical values and norms [7, 11, 12]. Perhaps the single most cited ethical value in terms of protecting older persons is autonomy, the ability for individuals to self-govern and make decisions for themselves. Autonomy is fundamental and critical to older adults with psychiatric illness. As shown in Table 9.2, references to how autonomy is referred to and relied upon in practice often depend on issues of what time it is being referred to. For example, precedent autonomy (past), executional autonomy (current), and prospective autonomy (future) carry different weight based on issues of temporality. Although autonomy has become a pillar within the bioethics community, there are variations in cultural norms and societies as to how much value is placed on the role of autonomy.

There are numerous examples of how various cultural groups may place more or less weight on the value of autonomy. For example, among Christian fundamentalist Russians and some Southeast Asian immigrants, it is the cultural norm for the elder to play a passive role in complex medical decision-making pari passu ("on equal footing") with accepting the role of the dependent elder, sometimes to the point of not wanting or expecting to be told a serious, life-threatening diagnosis. Societal norms of ethics can run up against cultural relativism, forcing clinicians to try to reconcile their own beliefs, the patient's theoretical ethical rights, and the patient's cultural values. For cultural minorities, it is important for the clinician to directly inquire how much the older patient wants to be an active participant in medical decision-making and how much they want to defer to their family.

Narrative-based ethics is another relevant theory not only for persons with psychiatric illness who may have lost their sense of agency but also for older adults who by virtue of their age have a life history to share [13]. Narrative ethics refers to both the story being told and the telling of such story. Indeed, clinicians working with older patients suffering from major neurocognitive disorder, for example, understand that an individual's ability to construct their own narrative can be challenged when physicians are called upon to be coauthors of their life story, at times through obtaining collateral evidence from others. From a clinician's standpoint, a patient's narrative can be a critical determinant of medical decision-making when the patient loses, temporarily or permanently, their decisional capacity. The patient's narrative involves values or opinions they have expressed over a lifetime that can inform what they would have chosen if capable of providing informed consent or refusal. For example, if a patient expressed to his family that he never wanted to end up permanently on a ventilator or ever to be forced to live in a nursing home, this could at least inform decisions about aggressiveness of care in the absence of an advance directive. These "life narratives" can conflict with the wishes of surrogate decision-makers, creating an ethical and legal dilemma that sometimes requires careful education of the surrogate and, on occasion, redress by the court.

Table 9.2 Types of autonomy and temporality

Forms of autonomy	Description	Temporality
Decisional autonomy	Ability to make one's own choices	Present
Dispositional autonomy	Focus on person's life as a whole at the time	Present
Emotional autonomy	Grounded in human feelings	Present
Executional autonomy	Implementation of one's decisions	Present
Functional autonomy	Engagement in activities of daily living and mobility	Present
Precedent autonomy	Precedence over competing current interests	Past
Prospective autonomy	Looking forward from perspective of individual	Future
Rational autonomy	Grounded in logic and reason [subjective or objective]	Present
Relational autonomy	Reliance on others in decision-making	Present
Value autonomy	Independent views that align with personal value system	Present

9.1.3 Legal Overview

Mental health law as an area of practice has existed for decades. In recent years, the field of elder law has emerged as a relatively new area to deal with the impact of laws affecting seniors. Historically, in the USA, the *Older Americans Act*, passed in 1965 was intended to help older citizens by providing grants to US states for community-based social and health-related services [14, 15]. Elder law is essentially rooted in the *Older Americans Act* and evolved as a specialty of law directing services to the needs of older people [16]. In 2003, the *Elder Justice Act* was passed in the USA as comprehensive legislation to develop a mechanism to "prevent, detect, treat, intervene in, and prosecute elder abuse, neglect, and exploitation" [17]. Similarly, in Canada there have been amendments to federal legislation to protect seniors. For example, in 2012 the *Protecting Canada's Seniors Act* amended section 718.2(a) of the *Criminal Code* to allow sentencing judges to consider vulnerability due to age as an aggravating circumstance for sentencing purposes [18].

As the field of elder law has grown, lawyers began dealing with older adults as a potentially vulnerable group and offered specific legal services catered to their unique needs. Academic conferences, journals, and courses focusing exclusively on elder law were developed. Some have even referred to the development of "geriatric jurisprudence" in reference to attempts to combine jurisprudence and geriatrics, essentially a medicolegal theory of aging [19]. In mental health law, the framework of *therapeutic jurisprudence* grew out of a need to study how legal rules or practice promoted the psychological well-being of the people affected [20]; in elder law, the framework of *geriatric jurisprudence* appears to have a similar aim but focused on older adults [21]. In California, for example, problem-solving "elder courts" were commenced that allowed judges to focus on the various needs of older individuals all at the same time, including, for example, cases comprising civil or criminal matters, elder abuse, and guardianship/ conservatorships [22]. Lawyers practicing in the area of elder law have been cited as focusing on the four "Cs": (i) know who your *client* is, (ii) understand the importance of *confidentiality*, (iii) be alert to the potential of *conflicts of interest*, and (iv) inquire into the *capacity* of the client [16, 23].

How does one determine who their client is? At face value it may seem obvious, but when one's client lacks decisional capacity or has decisional capacity but cannot meet his or her needs despite a desire to remain independent, serving the needs of the individual can become a delicate fiduciary balancing act that represents an outcome that protects the senior physically and financially while granting the maximum amount of autonomy. For example, a cognitively intact patient, who lives alone and wants to remain at home despite several injurious falls resulting from weakness after a stroke, may not have the ability to live safely at home. The offspring may want to place the patient in a residential care facility against his will. If the family consults an elder care attorney explicitly to help "Dad," which client does the attorney serve?

9.1.4 Informed Consent

Informed consent is grounded in both ethics and law. The doctrine of informed consent was developed in large part in an attempt to redress some of the inequality of information that characterized the doctor-patient relationship. Voluntarism is critical to informed consent as it embodies respect for the person as a human being and as a moral agent with fundamental rights in society [24]. Informed consent allows individuals the basis to determine their own course of action regarding their healthcare. Whether or not others agree with a patient's healthcare decisions is irrelevant, so long as the patient has the capacity to make their own healthcare decisions. For clinicians seeking to obtain consent to treatment, there are generally four factors to consider: (i) consent must relate to the treatment; (ii) consent must be informed; (iii) consent must be given voluntarily; and (iv) consent must not be obtained through misrepresentation or fraud. In order for consent to exist, it must be informed (knowledgeable), given when capable (mental status), voluntary (free of coercion or duress), not given under fraud or misrepresentation (impairs consent), and disclosed (whether implied or expressed).

Some questions to consider when obtaining informed consent include: What is the *nature* of the consent given? What *effect* will the consent have? Is the consent *valid*? How does one *manifest* informed consent (written, verbal, video)? Assuming a patient is capable to make an autonomous decision, clinicians still need to determine which course of action is feasible in a given context. What are the reasonable consequences of each treatment option? Oftentimes, the consequences of specific treatment options are not, or cannot, be known as to how they may impact a patient's ability to make an informed decision. If there is a rare chance of an adverse outcome with a specific treatment, a clinician may or may not choose to disclose such information depending on the probability of that event occurring. Standards of disclosure may differ from physician to physician, impacting a patient's ability to make an informed decision. Clinicians have a duty to disclose material and probable risks, and this duty to disclose continues even as the facts change.

Whether it is in clinical or research settings, there can be problems of proof in working with older adults with psychiatric illness. Was the patient provided enough information at the time consent was obtained and is the clinician reasonably confident that there was no coercion involved? At times, a clinician providing information about a specific medication may be acting as a learned intermediary between the patient (who typically has the least information) and a pharmaceutical company (who generally has the most information). Some older patients may exercise their "right not to know" about specific diseases or trajectories of their psychiatric illness. The amount of information provided to a patient may also depend on cultural differences and perceptions of how physicians are perceived. This concept applies to the ability of patients to be able to provide informed consent in a particular situation despite lacking overall decisional capacity. For example, a patient with short-term memory impairment suffering from an early stage of major neurocognitive disorder might be able to understand the risks and benefits of a procedure and give consent, although he or she might forget the conversation several hours later.

9.1.5 Mental Capacity

As noted above, clinicians are required under law to ensure they determine whether someone has provided their informed consent to treatment. As such, one of the main roles of clinicians is to determine whether their patient is capable to consent to treatment. This is particularly important for older patients who may lose their ability to make truly independent choices due to clinical factors, including major or mild neurocognitive disorder or major depressive disorder [7]. Capacity and competence are often terms used

interchangeably, although some have distinguished the two where mental capacity is determined by clinicians and competence is a binary judgment determined by a judge [25]. Decisional capacity forms the basis for determining legal competence. A psychiatrist or another physician can determine decisional capacity, but only the court can establish incompetence, and cognitive impairment or decline does not always mean there will be a legal determination of incompetence.

Mental capacity includes the ability to utilize information in order to come to a decision that is congruent with the patient's values, beliefs, and wishes. Across jurisdictions, there are different legal standards and statutory tests in deciding whether someone is capable to consent or not. Notwithstanding statutory differences, in general there are four legally relevant criteria to explore in deciding whether someone is incapable; note there is always a presumption of mental capacity. These criteria include the ability to [25]:

1. *Communicate* a choice.
2. *Understand* the relevant information.
3. *Appreciate* the situation and its consequences.
4. *Reason* about treatment options.

The following is a case example. A bedbound but cognitively intact 82-year-old man with a presacral pressure ulcer demands to go home at the end of a prolonged hospitalization, even though he lacks the physical capacity to provide essential self-care, including meal preparation, shopping, timely dressing changes, transfers, toileting, and access to his physician. A social worker's assessment indicates that community resources are insufficient to meet these needs. However, the patient keeps insisting that he can get enough help by asking a neighbor or his ex-wife to help him and refuses to enter a nursing home, which he calls a "snake pit." He knows the neighbor only by her first name, and he cannot provide her telephone number. His ex-wife is his age and does not live nearby. Which of the four legally relevant criteria of mental capacity does this individual possess? Promoting autonomy endorses his preference, even if such a course contradicts medical recommendations. However, the patient's reasoning appears deeply flawed, if not fanciful, and he therefore may lack decisional capacity for discharge destination. The principles of beneficence (ensuring the availability of necessary treatment) and nonmaleficence (preventing harm to the patient that inevitably would result from a discharge directly to home) are likely to override his autonomy because of his unrealistic thinking.

One must also consider what aspect of cognitive capacity is being evaluated; some patients may lack decisional capacity for one task yet retain capacity for another. A patient with early stage of major neurocognitive disorder due to Alzheimer disease may retain capacity for informed consent for a procedure yet lack capacity for finances. Capacity assessments are often conducted for the following: consent to treatment, independent living, financial management, testamentary capacity, research consent, sexual consent, voting, or driving [7, 26]. When a clinician makes a finding of incapacity, it is critical to remember that one is ultimately making a human judgment that occurs in a social context.

All central nervous system illnesses, grouped as "neuropsychiatric" disorders, can impact an older adult's decisional capacity. One may find that capacity can fluctuate over time, a patient can be deemed incapable at one point in time and then be capable shortly thereafter, or alternatively a clinician may find there is progressive cognitive decline that has influenced one's capacity to make decisions [6]. As such, clinicians should not adopt a mindset of arbitrarily assessing patients' capacity every 6 months, for example. There could be a significant change in mental status that requires reevaluation at different points in time.

Many older adults are understandably preoccupied with ensuring that they have sufficient financial savings for retirement. Most people do not anticipate they will lose their capacity to make important or, for that matter, even basic decisions about financial matters, or they may believe that any such cognitive incapacity will occur very late in life. As such, the outcome of a financial capacity assessment can deeply affect an older adult's sense of autonomy, particularly if it is being challenged by a clinician due to the presence of a major neurocognitive disorder [27]. Many neuropsychiatric disorders can influence one's financial skills. It is critical that assessments are objective, well documented, and tracked across time. Such assessments may include clinical interviews, standardized neuropsychological tests, or performance-based evaluations [26, 28]. A clinical assessment of mental capacity of an older adult often includes the following five steps: (i) determination of the specific type of decisional capacity to be assessed, (ii) collection of collateral information about the older adult from significant others and healthcare professionals, (iii) general assessment of mental state, (iv) specific assessment of decisional capacity, and (v) professional judgment of decisional capacity that integrates these components [29].

9.1.6 Advance Directives

Advance directives are legal documents that offer individuals an opportunity to express their prior capable wishes in the event they become mentally incapacitated at some point in the future [6, 30]. Advance directives have many different terms, as noted in Table 9.3, depending on one's jurisdiction. They have also been referred to as living wills, Ulysses contracts, and powers of attorneys. Where an individual is found to be incapable, decisions can be made according to their previously expressed values, wishes, and beliefs. Some advance directives are *instructional* in nature in that individuals can include detailed instructions about what to do in a given situation, whereas others are *proxy* in nature whereby someone else is named as an agent to make decisions for the incapable person.

Legal, ethical, moral, and religious issues often surface in clinical settings where a family member contests the wishes of an older adult who no longer retains mental capacity.

Table 9.3 Types of advance care planning documents

Name	Description
Advance agreement	Term used by the *English Mental Health Act* Legislation Committee to describe plan of care between patient and treatment provider
Advance directive	General term for document with statutory authority for capable person to state wishes of what should happen to them if becomes incapable
Advance healthcare directive	Term used in Newfoundland and Labrador and Prince Edward Island
Advance refusal	A stronger version of advance directive that highlights refusal rather than "directed"
Advance statement	A weaker version of advance directive in that person's wishes are stated rather than "directed"
Authorization	Term used in Nova Scotia
Healthcare directive	Term used in Manitoba and Saskatchewan
Joint crisis plan	Currently a research intervention in the United Kingdom where facilitator negotiates with person and comes to some agreement
Living will	Term used to highlight that the document can only be used while the person is alive. In wider use in the USA than Canada
Mandate in case of incapacity	Term used in Quebec
Mill's will	Term used to refer to John Stuart Mill's which highlights self-determination and the right to refuse and accept treatment
Nexum contract	Advance agreement that follows a contractual model in that it is inherently bilateral
Odysseus contract, pact, or transfer	Greek term for Ulysses emphasizing different aspects of the document
Personal directive	Term used in Alberta and Northwest Territories
Physician's Order for Life-Sustaining Treatment (POLST)	A legally binding advance directive signed by patient [or surrogate] and physician as an order through enactment a California, USA, statute. Original kept by patient and placed in a conspicuous location [e.g., on refrigerator door] to prevent emergency medical services from inappropriately initiating or not initiating resuscitation and transport
Power of attorney [continuing, durable, enduring, springing]	Terms used in New Brunswick and Ontario
Pre-commitment contract	Used to highlight that individuals with recurrent and treatable conditions could make a wish before becoming ill
Psychiatric advance directive	Widely used term in the USA stressing the importance of autonomy
Psychiatric will	Original term proposed by Thomas Szasz in 1982 to protect patients from coercion or psychiatric neglect
Representation agreement	Term used in British Columbia
Ulysses commitment contract	Term used to reflect a commitment to follow through on the self-binding contract
Ulysses contract	Roman term used to highlight different issues around self-binding wishes
Ulysses clause	Proposed in this article to reflect that a legal provision can be included into the advance directive making the document irrevocable
Ulysses directive	Term avoids reference to any contractual relationship as through a Ulysses contract
Ulysses statement	Less strong than a Ulysses directive or contract
Voluntary commitment contract	Term highlights that document is not entered into under undue influence or coercion

Unfortunately, many individuals do not engage in advance care planning until they have been diagnosed with a terminal illness. This creates questions surrounding mental capacity at the time that the advance directive was made. Some argue that patients have become saddened, depressed, or hopeless once the terminal illness diagnosis was made, and this may have influenced their ability to execute the advance directive. If family members dispute the advance directive of a loved one, it can become necessary for legal and medical professionals to analyze the capacity of the person at the time it was

made. Where no witnesses were present when the advance directive was made, it becomes even more difficult to assess the capacity retrospectively. Some lawyers and others assisting in preparing such documents have started videotaping individuals at the time of execution of these instruments as valid proof.

Even if a patient was capable at the time the advance directive was completed, it may still be an extremely difficult task to interpret those wishes in the context of a specific healthcare dilemma. Imagine if a patient were to state as part of their advance directive, "I would like to receive medical interventions which will improve my health care condition and which will not result in significant pain." This type of statement opens a myriad of questions because it is still quite broad. What does "improve" a healthcare condition mean? What should be considered "significant pain?" Older adults need to ensure their goals recorded in an advance directive are outlined in such a way as to provide specific guidance while at the same time providing flexibility for novel healthcare situations. Ensuring that advance directives can be readily found in the event of an emergency is another important consideration.

A patient's preferences for life-sustaining treatment can vary over time, and this can pose a dilemma when an otherwise valid advance directive has not been updated despite a significant change in the patient's health status. Ethically, clinicians should honor their best interpretation of expressed or clearly inferred current values, beliefs, and preferences when it appears an advance directive contradicts these preferences. A patient whose earlier advance directive indicated that she wanted everything done to keep her alive may not reflect the misery she has expressed to family after being forced to move to a care home following a stroke after the advance directive was prepared.

9.1.7 Decision-Making for Older Adults Without Family and Guardianship (The "Unbefriended Patient")

Clinicians may find themselves in situations where their patients lack capacity, and there are no surrogate decision-makers available [31]. Many approaches are used to make decisions for incapable older patients who do not have a family. These have included hospital committees and advance directives, where available, or a public guardian and trustee, or even computer-based systems [30]. The length of stay in hospitals for incapable patients without family members can be significantly longer than the average length of stay for incapable patients with family members. Unless considered medically inappropriate, the default approach is to follow a course of life-sustaining care that meets the medical standards for that illness. It takes a significant amount of time to proceed through court processes when appointing a legal guardian. During that time, patients are cared for by hospital staff where there is nowhere else for them to go. Third, even contacting or attempting to locate family members of such patients can be time consuming and stressful [30].

Two legal standards are generally used for decision-making in this context, one being "substituted judgment," where the patient's wishes are known to the surrogate, or a "best interest" standard, where the patient's wishes are not known [6]. Understandably, not having the ability to choose a surrogate decision-maker can have a serious impact on the mental well-being of an aging patient. Some patients may place more importance on the surrogate rather than the decision the surrogate makes. Individuals who find themselves in such situations would like to know that the appointed individual who cares about their well-being is acting in their best interests. Patients without family are forced to rely on individuals whom they may not know well or to rely on others whom they do not know at all as in the case of a public guardian and trustee.

While it is possible for some patients to ask a friend to become their surrogate decision-maker, other patients without families live in long-term care homes where their friends/co-residents are of a similar age. Whether these friends have the time, energy, or resources to vigorously act, or at times fight, for the wishes of the patient is questionable [30]. Furthermore, accepting the responsibility to act as a surrogate decision-maker is not always readily accepted even by direct or indirect family members. The responsibility of deciding on treatment options, do-not-resuscitate orders, and funeral arrangements, for example, can become overwhelming. This is particularly the case if a patient suffers from a long term, debilitating illness in which the surrogate decision-maker is tasked with caring for the individual for a long period of time, even years, as is the case with many patients with major neurocognitive disorder. Despite good intentions, an exhausted or frustrated proxy at times may make surrogate decisions that deviate from the patient's wishes. The conflict in such decisions easily can be overlooked by clinicians when they are consistent with the treating team's biases, e.g., not to offer intensive-level care to a nonagenarian because of a diagnosis of Alzheimer disease-related neurocognitive disorder, when, if investigated more carefully, it would be learned that the patient had early Alzheimer disease and was socially interactive and independent in all activities of daily living except bathing. Potential red flags for conflicts of interest should be sought, such as the caregiver arguing for withdrawal of life support when that caregiver would be the beneficiary of an inheritance.

The most powerful surrogate decision-making mechanism is a guardian, whereby the court appoints a third party to make decisions for a person with a disability [32]. Guardianship is often done when a patient is deemed incapable and there is no next of kin available. This may also occur when family members of the patient are unable to come to a consensus regarding the patient's care, even after mediation. While some may argue that the legal rights and autonomy of the patient are stripped once a guardian is assigned, this may be the only method of caring for an older adult who is found incapable. Areas of the patient's life over which the guardian has control need to be explicitly stated so that conflicts do not occur. A guardian must be able to establish that he or she

is using all information available to make a decision congruent with the patient's previously expressed capable wishes. In recent years, a new model of *supported decision-making* has surfaced that offers support to individuals with disabilities to make their own decision rather than relying exclusively on someone else to make decisions for them [32].

Shared decision-making often occurs within families, as different family members may try to influence a patient's or surrogate's healthcare decisions. Not uncommonly, the designated proxy may want to consult other family members or influential community leaders (e.g., priest rabbi, imam) before making a decision in order not to create a rift that could distance the proxy from the rest of the family or community, creating a potential conflict of interest with the patient's wishes. Although not formally part of the consulting psychiatrist's role, identifying potential familial, religious, or cultural conflicts that could interfere with the fiduciary responsibilities of the surrogate fall within the unique skill set of the psychiatrist.

9.1.8 Involuntary Commitment and Long-Term Care

Involuntary psychiatric commitment refers to the act of detaining an individual in a designated psychiatric facility against their will. As autonomy is a fundamental tenet of healthcare, involuntary commitment should be used only in circumstances warranted under law. In this sense, involuntary commitment laws are known as laws of exception. Generally, one can be committed involuntarily if they are deemed to be a danger to self and/or other(s) and/or are unable to care for themselves due to psychiatric illness. The law specifies the precise standard to be followed. Many medical and legal issues arise during the evaluation of patients. To what extent does one have to be a danger to self or others in order to pass the threshold of being involuntarily committed? When is the test of whether the individual constitutes a risk no longer a matter of public safety and a clinician is actually applying a best interest standard? How long an individual *can* be held against their will differs from how long one *should* be held. In cases where involuntary detention is being contested, patients should be provided all relevant information to appeal the finding of a clinician if requested.

The application of these rules and principles in mental health law can at times be difficult to apply in practice. Clinicians are not lawyers; lawyers are not clinicians. Most physicians would prefer not to appear before a court of law or tribunal where they must explain why they found someone needed to be involuntarily detained. Physicians often enter into negotiations with patients (and sometimes their lawyers), in a model of shared decision-making, to discover a suitable compromise that can achieve the twin goals of providing appropriate healthcare and ensuring public safety. The aim of clinicians should be to assist patients to reintegrate back into the community.

Who should bear the risk to care for older adults with psychiatric illness on a long-term basis? Long-term care is not only an ethical issue in terms of allocation of resources from a distributive justice perspective but also an ethical consideration in terms of what is the right action to take. There are often health policy and economic consequences in terms of offering or removing community resources but also consequences in terms of how governments legislate policy responses toward implementation [33]. When modern-day hospitals were first developed, it was never intended that individuals would reside indefinitely in them or for ultimate responsibility to fall upon healthcare providers to become de facto caregivers forever more. In some cases, this becomes unavoidable.

9.1.9 Elder Abuse

While elder abuse, neglect, or mistreatment occurs in all segments of the population, it may be more pronounced among individuals who suffer from psychiatric disorders. Such abuse can be in the form of emotional or physical abuse, financial exploitation, maltreatment, and neglect of care-taking, to mention a few [34]. Elder abuse often contains three elements: harm, a trust relationship, and intent [6]. It may not be surprising that the source of abuse frequently is from the older adult's own family members. As a clinician these issues require extreme sensitivity, particularly when one sees palpable signs of abuse, which are not always physical or tangible. Some victims may be particularly reluctant to come forward to address their valid concerns due to embarrassment, shame, lack of support, or an unwillingness to disrupt their current situation [34]. Clinicians may be the first to note such changes in their patients' demeanor, mood, or attitudes due to the confidential nature of their relationship, which may require further information from collateral sources. In most jurisdictions in the developed world, healthcare providers, including physicians, social workers, and nurses, are mandated to report a finding of elder abuse where they have reasonable cause to believe it has occurred.

Lawyers who represent the interests of older adults with psychiatric illness can be among the first to learn about potential elder abuse (particularly in financial matters); as such, they too may have a duty to report abuse, neglect, or exploitation [35]. Older adults may be willing to discuss legal matters, such as wills and estate planning, with healthcare providers. If an issue of elder abuse, neglect, or maltreatment arises in the context of a lawyer-client relationship, there will be an ethical conflict on the part of the lawyer on whether to protect the confidence of their client or to divulge the matter to authorities. In this regard, lawyers should be guided by their professional rules of conduct and other statutory obligations.

Psychiatrists may encounter victims of elder maltreatment when they are asked to consult on older adults for a possible depressive disorder, failure to thrive, or neuropsychiatric symptoms with a major neurocognitive disorder,

particularly agitation or aggressiveness. The patient may not be able or willing to admit being abused because of cognitive impairment, a sense of humiliation, intimidation by the caregiver, fear of retribution, or fear of losing a caregiver who, in effect, is the perceived lifeline against institutionalization. When investigating these disorders in vulnerable, older adults, elder maltreatment should automatically be considered as a potential contributor. During the interview, discretely separating the patient and caregiver permits the psychiatrist to ask nonthreatening, leading questions, such as: "Do you feel safe at home?" and "Do you think you're getting the care you need?" When elder abuse is strongly suspected, the psychiatrist can ask more direct questions, such as "Do you get enough to eat?" "Do you ever feel that you're being punished at home?" "Do you ever get yelled at?" If marks or behaviors of possible physical abuse are present, such as unexplained ecchymoses, pattern bruises (a bruise resembling the object with which the patient was struck or a circumferential bruise around the arm from being grasped forcefully), or flinching when the patient is touched suddenly, the psychiatrist should request a consultation from an elder-abuse or forensic expert, if available. (See ▶ Chap. 34, ▶ section Screening for Elder Mistreatment and Neglect.)

9

9.1.10 Managing Risk of Violence in Older Adults with Psychiatric Disorders

An issue that often arises in psychiatry is the determination of risk for violence associated with individuals who suffer from psychiatric illness. Brain disease such as major neurocognitive disorder can contribute toward criminal behavior. (See ▶ Chap. 29.) Mental health and violence are key considerations for older adults, particularly in the context of domestic violence. Between 20–30% of older adults, the majority being women, experience or have experienced domestic violence [36]. Whereas physical abuse may decrease with age, rates of emotional abuse appear to be stable across the lifespan [36]. Managing risk of violence in older adults can be particularly challenging from an ethical position of balancing individual rights with societal interests. Older adults with psychiatric illness are vulnerable in part due to frailties associated with aging and from psychiatric illness. Some of the issues clinicians may be faced with include managing sexually disinhibited behaviors, delusional misidentification syndrome, homicide-suicide, sleep disorders, and the role of alcohol [37]. Physicians will be called upon to consider whether their patients should have access to firearms in their possession [38].

9.1.11 End-of-Life Discussions

The ethical debate around end of life has existed for years. End-of-life discussions with patients and family members can be extremely difficult, particularly in cases of late-stage major neurocognitive disorder and other degenerative diseases where no prior competent wish was made [7]. In 2016, the Canadian Government passed federal legislation [Bill C-14] supporting medical assistance in dying (MAID), the term adopted by the government rather than "physician-assisted death," based on a 2015 Supreme Court of Canada case of *Carter v. Canada* [39]. In *Carter*, the Supreme Court held that criminal laws prohibiting assistance in dying limited the rights to life, liberty, and security of the person under the *Canadian Charter of Rights and Freedom*. Under this legislation, MAID is available to persons in the following circumstances:

- Being an adult (at least 18 years old) who is mentally competent ("capable") to make healthcare decisions
- Having a grievous and irremediable medical condition
- Making a voluntary request for MAID which does not result from external pressure
- Giving informed consent to receive MAID after having been informed of the means that are available to relieve their suffering, including palliative care
- Being eligible for health services funded by a government

While the law does not define what constitutes a "grievous and irremediable medical condition," this has been left open to interpretation, and the law is likely to be challenged constitutionally. Another open question for Canadians will be how appellate courts will handle requests for MAID, particularly in those cases where there is serious psychiatric illness and an advance directive.

In the USA, as of 2016, five states (Oregon, Washington, Vermont, Colorado, and California) have enacted legislation permitting physician-assisted suicide, while Montana permits aid in dying through a court ruling. The remaining 44 states and the District of Colombia consider assisted suicide to be illegal. (See ▶ Chap. 33.)

Older patients who have diminished capacity often rely on decision-makers including physicians, hospital committees, or public guardians to carry out their wishes [30]. While some patients may argue their values and wishes are well-known by their primary care physician, these patients are more likely to be admitted to an acute care setting as they near the end of life. As a result, situations may arise where someone has never met the physician tasked with caring for their health. Relying on acute care physicians for end-of-life decisions would lead to inconsistent practices as each physician would have their own personal values and beliefs which may unwittingly be imposed on the patient. Without advance directives in place, it is difficult to expect physicians to know the wishes and values of such patients. In other situations, clinicians or institutions may hold conscientious objections based on religious values to assisting patients in MAID. In these cases, clinicians may be asked to suspend their personal views and advocate for such individuals even where it is a referral of care.

9.1.12 Physicians' Roles and Responsibilities

The ethical values of clinicians will not always align squarely with those of their patients in terms of when something is perceived as paternalistic, interventionist, or beneficent [40].

In an effort to reduce ageism, some medical student and resident groups have developed a "Council of Elders" group to help them discern attitudes of older adult patients through a council of other older individuals [41]. Physicians need ongoing training and guidelines to assist in evaluating and making determinations that are not only legal, but also ethical so they are done in a fair and consistent manner. In many cases, involvement from family members/SDMs is welcome and endorsed by patients. In other cases, however, patients may choose to make decisions independently. Tensions between healthcare providers and patients' family members can heighten to the point that focus on what is best for the patient is lost. For patients lacking decisional capacity, clinicians need to remind family members that their role is not to do what the family or surrogate wants but what, in their best clinical judgment, is medically the most appropriate course of action within the context of what the patient would have wanted based on knowledge of the patient's beliefs and preference. Clinicians have an ethical duty first and foremost to their patient as the person receiving care.

While the older adult is the patient, concerned family members will often speak to physicians privately in an effort to develop a particular plan of action that is, according to them, in the best interests of the patient. In this context, physicians must be careful not to participate in decisions that create, or appear to create, an actual or perceived conflict of interest between the patient and others. Whether there is evidence of truth or dishonesty, financial gain or loss, or any other benefit or cost, what matters in the end is the patient's authentic decision that is made while decisionally capable.

In the years ahead, clinicians will need to grapple with ethical, legal, and professional implications of incorporating new technologies into clinical practice. Many older adults who will turn 65 years old in the years ahead will be computer literate, texting savvy, and familiar with electronic technologies for healthcare delivery [42]. Many clinicians have already been introducing technology-enabled services into their practice to interview patients for clinical purposes or have appeared before quasi-judicial tribunals to provide testimony. Advances in the field of "telehealth" have also been informing the development of an emerging area of "telelaw," whereby older adults with less mobility or those living in remote and rural areas are accessing legal services remotely [43]. There are ethical issues associated with the move toward technology-based services including access to healthcare, equity, and fairness. As the demographics of older adults change, there is likely to be an increasing willingness by them to adopt various technologies in an effort to maintain greater autonomy.

9.2 Case Studies

In the following below, two case studies are provided to address some of the issues related to clinical, ethical, and legal considerations for older adults suffering from psychiatric illness.

9.2.1 Case 1

Case 1 History

Ms. M., a widow and former smoker but otherwise in good health, prepared a living will at age 74 specifying that she did not want cardiopulmonary resuscitation, including emergency intubation. At the age of 81, she fell ill with influenza A despite annual vaccination and developed a severe viral pneumonia followed by a superimposed bacterial pneumonia associated with respiratory failure that did not respond to antibiotics and bilevel positive airway pressure. Her daughter stated that her mother was very active, loved to go on cruises, and enjoyed socializing with friends in her senior living community. Her medical record indicated that she was scheduled to undergo an elective lumpectomy for early breast cancer. The patient's oldest son and designated surrogate decision-maker, who lived 400 miles away, wished to honor his mother's advance directive. The on-call psychiatrist was asked to determine if the patient had decisional capacity and diagnosed the patient with delirium.

Case 1 Questions and Answers

Case 1 Questions

Question 1. Ethically, what is the most appropriate course of action and accompanying reasoning?

Question 2. What considerations for life-sustaining measures should be discussed with Ms. M. as soon as feasible?

Case 1 Answers

Case 1 Answer 1 (Question 1 – Ethically, what is the most appropriate course of action and accompanying reasoning?)

Many adults fear the devastating effects of functional dependence, of being in a persistent vegetative state, or indefinitely being hooked up to a ventilator in a nursing facility and therefore check the "do not resuscitate" box on pre-printed advance directive forms, such as the State of California's *Physician Order for Life-Sustaining Treatment*. However, most older adults adapt to changes in their health status and recognize that life can be enjoyed despite loss of some forms of independence. In this case, Ms. M. lifestyle and decision to undergo treatment for cancer clearly indicate that she wants to live. Her advance directive, presumably still legal, is 7 years old. The son may be an inappropriate surrogate decision-maker, despite his selection by the patient. He lives far away and apparently is unaware of or indifferent to her current lifestyle, as described by the daughter. If the clinician finds persuasive evidence that the surrogate decision-maker is not acting in the best interest of the patient or there is a strong likelihood that he or she is not honoring current stated or clearly inferred but undocumented preferences, it may be appropriate not to follow the surrogate's requests. That said, the son in this case is acting in a manner consistent with a document that is legally binding in many jurisdictions. In such cases, it may be necessary for individuals to obtain legal advice or representation in the matter.

Case 1 Answer 2 (Question 2 – What considerations for life-sustaining measures should be discussed with Ms. M. as soon as feasible?)

The psychiatrist may be called on in the future to reassess the patient's decisional capacity regarding life-sustaining measures in light of her fluctuating mental status. In such a determination, it is critical that she be educated about her status and prognosis first so that continuation or withdrawal of life support is done with informed consent. Although treatment for an anticipated reversible condition does reflect beneficence, medical standards do not support aggressive interventions that contradict a patient's prior competent wishes. Her recent behavior offers no evidence of impaired capacity, let alone 7 years ago. However, susceptibility to delirium may signal an undiagnosed major or mild neurocognitive disorder, and delirium is a risk factor for developing a major neurocognitive disorder.

Case 1 Analysis This case illustrates a situation that can arise when an individual's prior competent wish, as recorded in an advance directive, needs to be interpreted alongside a "current wish" that may have changed. A conflict can arise between what the individual originally requested in the advance directive and what the physician may perceive to be in the individual's best interests. This is particularly relevant in situations where it is no longer clear that the person in question would still agree with the decision previously made. Similar situations can pose a legal or ethical dilemma for the physician when an otherwise valid advance directive has not been updated, despite a significant change in the patient's health status. This case highlights the need to ensure that older adults revisit their advance directives regularly, perhaps annually, in the event that the document is triggered due to a finding of mental incapacity. When an advance directive appears to contradict the patient's current values, beliefs, and preferences (clearly expressed or inferred), the physician will need to explore the situation very closely. It does not necessarily mean that the physician must follow the patient's current values, beliefs, and preferences simply because it is the most recent expression. Similarly, if there is no reason to believe that the prior competent wishes documented in the advance directive have changed, and there exists ample corroborative evidence to that effect, then the physician may be expected to follow such wishes. Continuation or withdrawal of life-sustaining treatment is accomplished with the patient's full informed consent when capable.

9.2.2 Case 2

Case 2 History

You are the consultation-liaison psychiatrist on the psychosomatic medicine service being asked to see Mrs. B., a 76-year-old woman with a history of major depressive disorder, who was admitted with right hip fracture due to a fall in her home. She requires a preoperative evaluation for a hip fracture repair with replacement, but her admitting physician was unclear about Mrs. B.'s ability to clearly provide informed consent for that procedure and questioned whether she might be depressed. A ward social work assessment note indicated that Mr. B. was widowed and lived with her 47-year-old unemployed son in a house she owned. Of late, she was failing to attend scheduled appointments with her psychiatrist as she previously did, did not seem to be taking her antidepressant sertraline consistently, and was using excessive quantities of prescribed narcotic pain medication for her chronic lower back pain. You found that the social worker at the local community agency had recently visited Mrs. B. while at home and found it difficult to interview her alone without her son. Her house was in need of cleaning and minor repairs, and Mrs. B. was unkempt and unable to give a consistent history.

Today, you were unable to reach her son to obtain collateral information. You did obtain collateral information from her primary care physician who corroborated that Mrs. B. was failing to attend regular scheduled appointments as she previously did, focused on seeking more pain medication, and it was unclear if she adhered to her treatment with sertraline. Her last medical visit was 1 month previously. At that time, her Mini Mental State Examination (MMSE) score was 21 out of 30 points. Upon current examination, Mrs. B.'s mental status revealed significant depression and anxiety, but no psychotic symptoms. Her repeated MMSE was again 21 out of 30. She endorsed right hip and lower back pain, despite taking her pain medication. You ask her about her understanding of the risks and benefits of the treatment with sertraline and the planned hip surgical procedure. She tells you in a calm manner that sertraline will help with her "spirits" and the surgical procedure will "fix" her hip. When you provide her with information about risks and alternative treatment options, and query about her understanding, she replies, "It will be okay." You wonder whether she has the capacity to make the decision to restart treatment with sertraline and to proceed with the hip replacement surgery.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. Why is the clinical examination important in Mrs. B.'s case?

? Question 2. What is the gold standard for capacity determination? What are the common instruments for assessing medical decision-making capacity?

? Question 3. What is the relationship between Mrs. B.'s cognitive abilities and incapacity?

? Question 4. What factors influence medical decision-making capacity? How would you address these factors in the capacity evaluation in this case?

Case 2 Answers

Case 2 Answer 1 (Question 1 – Why is the clinical examination important in Mrs. B.'s case?)

Because decisional capacity for medical decisions is always presumed unless proven otherwise, clinicians may fail to recognize incapacity and generally question a patient's capacity only when the medical decision to be made is complex with significant risk, as is the case presented herein, or if the patient disagrees with the physician's recommendation [44]. As previously stated in this chapter, the criteria for obtaining valid informed consent to medical treatment have three elements [45]; therefore, Mrs. B. must:

1. Be given adequate information regarding the nature and purpose of proposed treatment with sertraline and the surgical procedure, as well as the risks, benefits, and alternatives to the proposed treatment, including no treatment
2. Be free from any coercion
3. Have the ability for medical decision-making capacity

The element of medical decision-making capacity is generally met based on evaluating the four abilities cited earlier in this chapter [46]. Mrs. B. must have the ability to:

1. Understand the relevant information about proposed diagnostic investigations or treatment.
2. Appreciate her situation (including her current medical situation and underlying values).
3. Reason using her thought processes to make a decision.
4. Communicate her choice.

As in Mrs. B.'s case, probing is often required in assessing a patient's understanding of the proposed medical treatment and her medical decision. The patient's decision must be based on her values. She must show the ability to reason effectively (i.e., the process of being able to manipulate the information provided). In Mrs. B.'s case, her failure to answer specifically your questions about risks and alternative treatments raised concern about her capacity and should result in a formal capacity assessment. As stated previously in this chapter, a patient's capacity is both situational and temporal, and capacity evaluations should occur in the context of a specific medical decision that needs to be made. Some patients may lack capacity for circumscribed periods of time (e.g., patient with delirium); some are permanently incapacitated (e.g., patient with advanced major neurocognitive disorder) or may have limited capacity. As in Mrs. B.'s case, those with limited medical decisional capacity may be able to make some diagnostic and treatment decisions (generally less risky decisions such as restarting treatment with sertraline in this case) but not others (riskier medical decisions such as hip surgical procedure in this case). As evidenced in this case, physicians commonly hold patients to higher standards when judging capacity for higher risk situations [47].

Case 2 Answer 2 (Question 2 – What is the gold standard for capacity determination? What are the common instruments for assessing medical decision-making capacity?)

Any physician can make a determination of incapacity, not just a psychiatrist. In general, the physician proposing the respective treatment should assess the patient's capacity. The gold standard for capacity determination is a clinical examination by a physician. A physician may choose to evaluate a patient's decisional capacity using a combination of clinical judgment and standardized capacity assessment instruments. A number of instruments have been developed for assessing capacity to make medical decisions. Capacity assessment instruments that can be performed in an office visit and that have robust likelihood ratios and moderate to strong levels of evidence include the Aid to Capacity Evaluation, Hopkins Competency Assessment Tool, and Understanding Treatment Disclosure [48]. The MacArthur Competence Assessment Tool for Treatment and the Mini Mental State Examination (MMSE), which has been found to correlate with clinical judgments of decisional incapacity, have also been used to aid in the capacity assessment [25, 48]. ◘ Table 9.4 includes some commonly used instruments to assist in assessing mental capacity that have moderate to strong levels of evidence of support [48]. There are many others, but among these the Aid to Capacity Evaluation was validated in one of the largest research studies, is free, and available online for which training materials are provided.

Case 2 Answer 3 (Question 3 – What is the relationship between Mrs. B.'s cognitive abilities and incapacity?)

Physicians frequently assess a patient's cognition by using cognitive screening tests such as the Mini Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA) and may use these tools as a proxy for capacity. However, their usefulness in assessing patient's capacity has been under debate. Some studies found evidence of a strong relationship between capacity and MMSE scores. MMSE scores less than 20 were found to increase the likelihood of incapacity, and scores less than 16 further increased the likelihood. Scores between 20 and 24 were found to have no effect on the likelihood of incapacity, and scores greater than 24 significantly lowered the likelihood of incapacity [48]. Mrs. B.'s MMSE score of 21 would generally suggest no effect on the likelihood of incapacity. The MMSE does not test executive functioning like reasoning and judgment. For this reason, the MoCA may be a better screening instrument.

Case 2 Answer 4 (Question 4 – What factors influence medical decision-making capacity? How would you address these factors in the capacity evaluation in this case?)

Mrs. B.'s capacity is potentially influenced by a variety of factors, including situational (e.g., reduced social support, isolation), psychosocial (e.g., parent-child relational problem, possible elder maltreatment), medical status (e.g., poor health, poor adherence to medical treatment, history of falls), and neuropsychiatric disorders (e.g., depressive disorder, neurocognitive disorder). The physician performing the capacity assessment should do so in the context of a specific decision, so that the physician must be fully knowledgeable about the proposed decision including the potential risks and benefits. In Mrs. B.'s case, the psychiatrist proposing treatment with sertraline could also assist in the opinion on the hip surgery provided that he or she observed Mrs. B.'s orthopedic

Table 9.4 Common capacity instruments [48]

Test	Abbreviation	Time to complete (minutes)	Comments
Aid to Capacity Evaluation	ACE	10–20	Freely available; uses the patient's own medical situation and diagnosis or treatment decision; an eight-question tool that assesses understanding of the problem, proposed treatment/alternatives, option to refuse treatment, foreseeable consequences of the decision, and the effect of an underlying psychiatric disorder on decision; it provides objective criteria for scoring responses
Hopkins Competency Assessment Tool	HCAT	10	Freely available; a four-paragraph essay tool written at three reading levels of 6th grade, 8th grade, and 13th grade (completed high school); the examiner reads aloud, while the patient reads the same material, starting with the 13th-grade example, followed by six questions; if score < 3 on higher-level essay, the 8th-grade and then 6th-grade level essays are used. Scores < 3 suggest incapacity
MacArthur Competency Assessment Tool for Treatment	MacCAT-T	20–25	Available from Professional Resource Press
Understanding Treatment Disclosure	UTD	< 30	The tool provides three subscale scores; the tool has a scoring manual that provides objective criteria for scoring responses

surgeon explaining the surgical procedure to Mrs. B. Since direct observation of another physician's informed consent process is rare, and documentation often limited, the psychiatrist performing the capacity evaluation may need to contact the surgeon directly to review the surgeon's explanation and his or her impression of the patient's understanding. If doubt remains regarding the patient's capacity to have provided consent for the procedure, the psychiatrist is ethically bound to challenge its validity, even if willingly given by the patient.

Because capacity exists on a continuum, it can be transient. Language barriers and educational level of the patient should be taken into consideration. The nature of the decision should be explained in plain language, using the patient's own words if possible, and reviewing the information as needed. The physician should consider whether the patient's capacity can be optimized or capacity reassessed at a later time (e.g., optimizing hearing and vision function by providing hearing and vision aids; patient with moderately severe Parkinson disease whose ability to communicate could be improved with antiparkinsonian medication adjustment). Problematic relationships, as well as linguistic, cultural, and educational barriers, can preclude reliable capacity assessments and should result in referral of the patient to a clinician with expertise in cognitive capacity assessments. Undiagnosed depressive and/or anxiety disorder or other neuropsychiatric disorders can confound a capacity assessment. Therefore, the psychiatrist must determine whether the psychiatric disorder is affecting Mrs. B.'s decision-making. A patient can feel unworthy of medical treatment and refuse therapy, or nihilistic thinking in the context of major depression could lead to a patient's claim of being an unworthy surgical candidate. It is important to note that a diagnosis of psychiatric disorder alone does not per se render a patient incapable of medical decision-making. Referral of a medical patient (as in Mrs. B.'s situation) to a psychiatrist may be required for confirmation of incapacity or when there is psychiatric diagnostic uncertainty.

As stated previously, Mrs. B.'s physician relied on standardized measures of cognition to aid in her capacity assessment. In her case, MMSE score provided support for further performing a formal capacity assessment because her score was bordering between low and the gray area score of 20–24. However, physicians should not rely solely on the MMSE score for determining incapacity, but rather patients with a low MMSE score should be given relevant information about a healthcare decision and have their capacity for that medical decision explicitly addressed. Because capacity is decision specific and is transient, Mrs. B. was found to have capacity for one medical decision and not for another, and she should be retested when future medical decisions arise.

Case 2 Analysis You decide to evaluate her capacity for medical decision-making using the Aid to Capacity Evaluation, which is based on making decisions about her actual problem; you ask the questions based on the decision about whether to have sertraline restarted and the hip replaced. She is clearly able to communicate her choice, and you find that she appreciates and understands her medical problems of major depressive disorder and hip fracture ("I am depressed and I have hip pain from the broken bone") and the proposed treatment ("I need to take an antidepressant, and they are planning on fixing my hip") and that she can refuse the proposed treatment ("It's up to me to have the antidepressant started, and the surgery, or not"). Although she is found to be able to answer questions about the risk, benefit, and the foreseeable consequences of accepting or declining the treatment for major depressive disorder, she is unable to answer questions about the risk of surgical complications including death and the rehabilitation

required after hip surgery. You decide that Mrs. B. does appreciate the foreseeable consequences of accepting or declining the treatment with sertraline but does not so for the treatment of her hip problem. Weighing the moderate risk of the hip surgery and her responses to the Aid to Capacity Evaluation, you decide that she lacks capacity to make the decision about the proposed hip surgery.

You eventually discuss the situation with her son and agree that he will make the decision as her surrogate decision-maker under her previously implemented healthcare power of attorney. You inform him that capacity decision is treatment specific, and while she has now capacity for treatment with sertraline, she might also have capacity for future, less risky decisions. Her son eventually makes the decision that her pain due to hip fracture is significant and urgent to merit the risks and decides to proceed with the hip replacement procedure. A social worker followed up at her home to explore if there were any concerns of maltreatment after discharge from the hospital. At 6-month follow-up, Mrs. B. is fully remitted from her depressive symptoms, is ambulating well, and is happy that she "decided" to have the surgery.

9.3 Key Points: Ethics, Mental Health Law, and Aging

- As a result of advances in medical treatment, clinicians are likely to see an increase in the number of older individuals with psychiatric illness including major neurocognitive disorders.
- It is important for clinicians to be aware of their own cognitive biases in terms of ethical values and principles adopted in clinical practice. There are various ethical theories clinicians can adopt in reasoning through complex dilemmas arising in practice.
- Advance care planning can play a critical role in assisting patients to achieve their own health outcomes in a manner that complies with prior capable wishes, preferences, and values. Older adults with psychiatric illness should be assisted in advance care planning and provided resources for doing so.
- Among the myriad of issues related to ethics, mental health law, and aging, neither does age nor mental health constitute, in and of itself, incapability. Every effort should be made to ensure that older patients with psychiatric illness are allowed to voice their decisions, goals, and concerns.

9.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following statements is correct?

A. Autonomy refers to the fiduciary duty.
B. Nonmaleficence balances benefits against risks when making decision.
C. Beneficence refers to the obligation of a physician to avoid harm.
D. Justice refers to fair distribution of psychiatric services or resources.

Answer: D

Fiduciary duty refers to the duty that a physician must act in the patient's best interests, whereas autonomy refers to the obligation of a physician to respect a patient's rights to make his or her informed choices without being coerced. Thus, statement A is incorrect. Nonmaleficence is a central guiding principle of the ethical practice of medicine, first expressed by Hippocrates, and translated into Latin as *primum non nocere*, "first do no harm." Beneficence refers to the fundamental commitment of a physician to provide benefits to patients and to balance benefits against risks when making decisions, whereas nonmaleficence refers to the obligation of a physician to avoid harm. As many treatments involve some degree of harm, the principle of nonmaleficence would imply that the harm should not be disproportionate to the benefit of the treatment. Therefore, statements B and C are incorrect. Justice refers to fair distribution of psychiatric services or resources; thus, statement D is correct.

MCQ 2. Mr. C. was a university educated single man in his mid-seventies who resided in the community. He had a lengthy history of schizoaffective disorder, substance abuse, and antisocial personality traits. Many of the shelters in the city barred him from entering because he was aggressive and manifested disruptive behavior. When he was brought to hospital on the most recent occasion, he was declared incapable to consent to treatment by a clinician who based his finding in part on results from the MacArthur Competence Assessment Tool. The psychiatrist proposed several treatments but then decided to start Mr. C. on an antipsychotic medication, olanzapine, which he had taken in the past but refused on this admission. The psychiatrist asked Mr. C. numerous questions, including: How have you reached your decision about the proposed treatment? What things were important to you in making this decision? Which one of the following criteria best align with these questions?

A. Ability to communicate a choice
B. Ability to understand the relevant information
C. Ability to appreciate the situation and its consequences
D. Ability to reason about treatment options

Answer: D

The ability to communicate a choice relates to whether Mr. C. would have been able to make a decision about which treatment he might want based on his expressed beliefs and values or previous decisions. This ability can often be preserved even where there may be impairments in other decision-making abilities. The ability to understand refers to one's ability to

comprehend basic information about a problem and the risks and benefits associated. One might explore Mr. C.'s level of education and intelligence as to whether he could understand the relevant information. The ability to appreciate the situation and consequences refers to whether Mr. C. is able to recognize the reasonably foreseeable consequences of not taking the medication and whether he has the ability to see how the problem applies to his own situation if he decided not to take the medication. The ability to reason refers to Mr. C.'s ability to describe how a solution would affect his everyday life and demonstrate an ability to rationally and logically think through the process of how he determined his choice not to take this medication.

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Common Clinical Psychiatric Diagnoses in Late Life

Contents

Late-Life Depression

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10.1 Background

10.1.1 Definition

The classification of depressive disorders has been changed with the recent introduction of the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* (DSM-5). The broad category of mood disorders has been removed, and the depressive disorders have been separated from the bipolar disorders. Within the depressive disorders, DSM-5 diagnoses include [1]:

- Disruptive mood dysregulation disorder
- Major depressive disorder (MDD)
- Persistent depressive disorder
- Premenstrual dysphoric disorder
- Substance/medication-induced depressive disorder
- Depressive disorder due to another medical condition
- Other specified depressive disorders and unspecified depressive disorders

The DSM-5 defines a patient with a major depressive episode as someone who is experiencing depressed mood, along with at least four other associated symptoms, whereby daily functioning is affected. Table 10.1 provides highlights of the DSM-5 criteria for a major depressive episode [1]. For a complete review of the DSM-5 diagnostic criteria for depressive disorders, the reader is referred to the DSM-5 manual [1].

Contrary to what some may believe, depression is not part of normal aging. Late-life depression is often underdiagnosed and undertreated, consequently leading to a poorer quality of life and difficulty in social and physical functioning [2]. Late-life depression includes both older adults who are presenting with depression for the first time later in life (known as late-onset depression) and aging patients whose depressive disorders initially presented in earlier life. About half or more of the cases of late-life depression is late-onset depression [3]. Late-life depression is usually considered as an index episode of depression that occurs in someone after the age of 60 years; however, the cutoff age may vary. Suicide rates in the older adults may be declining, but they are still higher than in younger adults, and suicide is usually associated with depression [3]. (For further details, see ▶ Chap. 28, *Psychiatric Emergencies in Older Adults.*) Recognizing and treating depression in older adults are not only important but can also be challenging.

Table 10.1 Highlights of the DSM-5 criteria for a major depressive episode [1]

Major depressive episode
Five (or more) of the following symptoms present most of the day during a 2-week period (of which symptom 1 or 2 must be present): (1) depressed mood, (2) markedly diminished interest or pleasure in activities, (3) change in appetite or significant weight change, (4) insomnia or hypersomnia, (5) psychomotor agitation or retardation, (6) fatigue or loss of energy, (7) feelings of worthlessness or inappropriate guilt, (8) poor concentration, and (9) recurrent thoughts of death, recurrent suicidal ideation with or without a plan, or a suicide attempt
Medical/substance-induced conditions are excluded

10.1.2 Epidemiology

According to the data from the Canadian Community Health Study—Mental Health, the annual and lifetime prevalence of MDD in the general population in Canada is 3.9% and 9.9%, respectively [4]. The lifetime prevalence of MDD across the world ranges from 1% (Czech Republic) to 16.9% (USA) [5]. Depression is more common in females versus males [4], and the prevalence of MDD in the older adults has been estimated at anywhere between 7.2% and 38% [6, 7]. Most studies suggest that the prevalence of MDD is lower in older adults compared to younger adults [4, 6]. However, the rate of depression is higher in older adults who are living in hospitals and long-term care settings versus those who live in the community [8].

The disease burden in health-adjusted life years for MDD is greater than the combined burden for breast, colorectal, lung, and prostate cancers [9]. Depression is also associated with major productivity losses and leads to considerable cost for both the individual and society [9, 10]. There are also associations between MDD and many chronic medical conditions, including heart disease, arthritis, asthma, back pain, chronic pulmonary disease, hypertension, and migraine [9], adding to the healthcare burden.

The recurrence rate of a major depressive episode within 3 years is high, anywhere from 26.8% to 34.7% [9]. Over a period of 23 years, the recurrence rate rises to 65% [10]. Individuals who have been depressed for the past year were also more likely to have an alcohol or substance use disorder [4]. Generalized anxiety disorder is also strongly associated with MDD. According to the data from the Canadian Community Health Study, lifetime prevalence of this comorbidity is 39.2% [4]. Literature also suggests that a history of depression is associated with an increased risk of later developing mild and major neurocognitive disorders [7, 11, 12].

Depression is the most common psychiatric disorder associated with suicide. The 12-month prevalence of suicide attempts for someone with MDD for the past year was more than 20-fold higher compared to those without MDD (6.6% versus 0.3%) [4]. In fact, it has been estimated that about 15% of patients with MDD will die by suicide [13]. The highest suicide rate is in the age group of adults over 65 years of age [7]. However, it should be kept in mind that most studies on MDD and suicide were based on inpatient populations. And thus, the numbers may be lower for those who live in the community.

10.1.3 Etiology

Various psychological models for the development of depression have been proposed over time. The classical conditioning theory posits that depression is learned through associating certain stimuli with negative emotional states. The social learning theory states that behavior is learned through observations, imitation, and reinforcement, leading to the behaviorist theory that negative behavior such as depression is learned and, thus, can also be unlearned. Aaron Beck's theory that depression stems from a "cognitive triad" (see Fig. 10.1) has formed the basis of cognitive behavioral therapy. Sigmund Freud argued that depression could be linked to loss or rejection by a parent, laying ground for psychodynamic psychotherapy. (See ▶ Chap. 8 for further details, *Psychotherapy in Late Life*.)

However, few theories have been proposed to specifically explain depression in the geriatric population. Some risk factors identified for depression in the older adults include bereavement, sleep disturbance, disability, prior depression, and female sex [14]. In patients with late-life depression, significant life events precede the depressive episode in more than 50% of the time [10].

Heritability of MDD for the general population has been estimated at 37% from meta-analysis of twin studies [15]. The gene coding for the serotonin transporter has been linked to the onset of depression in adults [16]. There have been many studies looking for neurobiological correlates of depression. Dysregulation of the hypothalamic-pituitary-adrenal axis function is not only thought to be related to the development of depression [17] but is also found to be a predictor for suicide risk in late-life depression [6]. Genotypes associated with increased cortisol secretion are also risk factors for late-life depression [6]. Low levels of plasma brain-derived neurotrophic factor (BDNF) and tissue-type plasminogen activator (tPA) have both been implicated in depression in the geriatric population [16, 18].

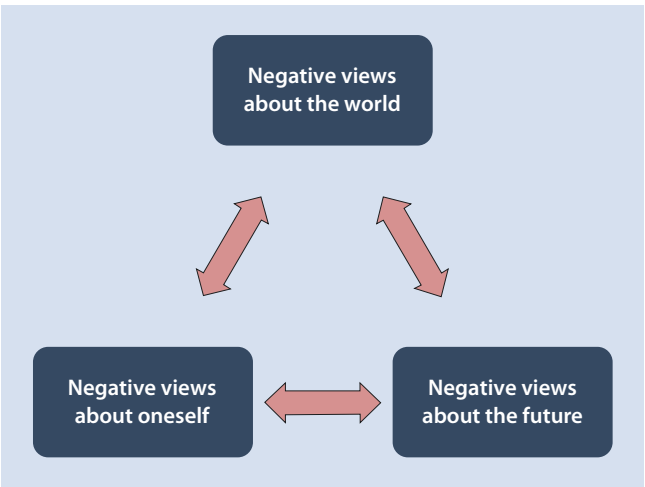

Fig. 10.1 Aaron Beck's cognitive triad

Neuroimaging studies have provided growing evidence that links late-onset depression to cardiovascular disease. The frequency of depression after having a stroke has been estimated at 33% [19]. Not only is there a greater risk for depressive symptoms in those with cardiovascular disease and cardiovascular risk factors, but evidence also suggests that depression itself increases the odds for having a new diagnosis of cardiovascular disease [20]. According to the "vascular depression" hypothesis, cerebrovascular disease causes white matter lesions in axonal pathways in the prefrontal and limbic regions, which are thought to be involved in emotional regulation and decision-making strategies, hence leading to late-onset depression [17, 21].

There have also been studies linking cytokine-based immunotherapy (such as interferon treatment), elevated levels of tumor necrosis factor-α, interleukin 6, and interleukin 1β [beta] with depressive symptoms and suicidality [6, 22]. A recent Danish study found an association between infection and an increased risk of suicide in those who are hospitalized [23], suggesting that infections, as triggers of inflammation, which upregulate the inflammatory response, can lead to depression and suicidal symptoms [22].

All of these studies and growing evidence point to the idea that depression is a complex disorder not caused by a single etiology or gene but is a consequence of various interactions between many sources of vulnerability.

10.1.4 Clinical Description

In someone with a major depressive episode, the depressed mood or loss of interest or pleasure must be present nearly every day, for most of the day. Some patients who are depressed may not endorse feeling sad but would complain of feeling "numb" or "blah." Others may also report feeling more "irritable" rather than feeling "down." Fatigue or insomnia is a usual presenting complaint. However, excessive sleeping may also occur in some. While psychomotor disturbances such as agitation or retardation can be part of the presentation, they are less common but, when present, can be indicative of greater severity of the depression [1]. Other symptoms during a depressive episode can include feelings of worthlessness or guilt, decreased energy levels, changes in appetite or weight, or problems with thinking or concentrating. Thoughts of suicide or death can also occupy the depressed person's mind, believing that others in their life would be better off without them.

Anxiety can also be a prominent feature in someone who is depressed. Complaints of feeling "edgy" or "keyed up" are common. It is important to note that higher levels of comorbid anxiety in depression patients are associated with higher suicide risk, longer duration of illness, and greater likelihood of treatment nonresponse [1]. Psychosis, when

Table 10.2 Comparison of predominant features in early-onset vs. late-onset depression [6, 25]

Early-onset depression	Late-onset depression
More family history of depression	More structural brain changes and cardiovascular risk factors
More depressive thoughts (suicidal thoughts, thoughts of worthlessness)	More anhedonia, apathy
Express depressive symptoms	Less expressed depressed mood but more somatic complaints
At risk for suicide	High risk for suicide
Mild cognitive impairments	More cognitive impairments
More substance misuse comorbidity	More medical comorbidity

accompanying a depressive episode, can be mood congruent (i.e., when content of delusions or hallucinations is consistent with themes of personal inadequacy, guilt, death, nihilism) or mood incongruent.

Depression that occurs later in life has been associated with a more somatic presentation [24]. Older persons are more likely to emphasize body aches and pains rather than endorse feelings of sadness. However, assessment of these concerns can be challenging as these complaints may be the result of actual health issues, as the older patient is also more likely to have medical conditions given their advancing age. Comorbidity between depression and physical illness varies from 6% to 45% [25]. The geriatric depressed patients are also more likely to present with sleep disturbance (shorter sleep duration and sleep is more fragmented), fatigue, psychomotor retardation, and feelings of hopelessness (see Table 10.2) [6, 25].

It has been suggested that if anxiety is present in a geriatric patient, it should be considered as a sign of depression, as about 38–58% of geriatric patients who have MDD also meet DSM criteria for an anxiety disorder [25]. When anxiety is present, it is usually described as tension and unrest or even feelings of fear [25].

The geriatric person with depression is also more likely to complain of poor memory and concentration, decreased processing speeds, and diminished executive function, to the extent where the person may be presenting with symptoms similar to a major neurocognitive disorder, known as "pseudodementia" [6, 7]. These symptoms tend to resolve as the person's mood improves with treatment. However, further complicating the issue is the increased possibility of a co-occurring depression and neurocognitive disorder. Studies suggest that depression itself increases the risk of developing major neurocognitive disorders by twofold [11, 12]. The reverse is also true, whereby patients with a major neurocognitive disorder (particular Alzheimer disease or vascular etiology) are at increased risk of developing depression. Studies estimate that about 11–24% of people with Alzheimer-related major neurocognitive disorder also meet criteria for MDD [26]. This reciprocal risk relationship between depression and cognitive decline not only makes diagnosis challenging but also impacts the treatment plan for the patient.

Other common comorbid disorders with MDD include substance-related disorders, anorexia nervosa, bulimia nervosa, and borderline personality disorder [1], although these seem to be more common in the younger patients compared to the older patients.

10.1.5 Diagnostic Evaluation

Clinical History

Quite often, depression can take an insidious course and is not recognized easily by the patient nor the clinician. In the geriatric patient, there are often co-occurring medical conditions, making assessment and diagnosis more difficult. As with any other psychiatric conditions, the first step in evaluation entails obtaining a detailed clinical history. History should be obtained from collateral sources, if possible, as the geriatric person may not be the most reliable historian. The geriatric patient may be more focused on somatic symptoms and not endorse "sadness." The presence of cognitive deficits (either from an underlying cognitive disorder or from the depression itself) may also make the patient a less reliable historian. However, one should also keep in mind that, on occasion, the family member or caregiver providing collateral information may also not be reliable or accurate for a variety of reasons; thus, it is the clinician's job to filter through the information and form their own impression.

It is common for a significant adverse life event to trigger an episode of depression in the geriatric patients. Thus, patients in these situations should be inquired about the presence of depressive symptoms if the opportunity arises (e.g., the patient is asking the family physician for "sleeping pills" after death of a spouse). Late-life depression has been linked with a number of risk factors such as female sex, being widowed or divorced, previous history of depression, adverse life events, persistent sleep difficulties, and recent bereavement [26].

As suicide is most commonly associated with depression, it would be important to evaluate the person for suicide risk factors (see Table 10.3) and the presence of suicidal ideation. Data from the Centers for Disease Control and Prevention show that there is an average of 14.9 suicides out of every 100,000 people over age 65 in the United States [27]. An average of 1.3 seniors die by suicide in Canada every day—hanging and firearm use being the most common methods of suicide in older men and self-poisoning and hanging in older women [28]. If suicidal ideation is present, then the patient should also be asked about intent or plans. For someone who is thought to be at risk, safety strategies or hospitalization should be considered.

Table 10.3 Suicide risk factors during a major depressive episode [9]

Suicide risk factors	Presence of suicidal or homicidal ideation, intent, or plans
	Male sex
	Age > 65 years
	Access to means for suicide (e.g., guns, knives)
	Previous suicide attempt or self-harm
	Family history of suicide attempt
	History of legal problems
	Stressful life events (e.g., loss of loved one, loss of independence)
	Presence of psychotic symptoms (especially command hallucinations)
	Presence of severe anxiety symptoms
	Presence of alcohol or other substance use
	Comorbid personality disorders
	Chronic systemic medical illness (including chronic pain and cancer)

Teaching Point

Older adults not only tend to underreport depressive symptoms but may also under-endorse and minimize suicidal symptoms [28]. In this instance, actions do speak louder than words. When assessing for suicidality, the recent history of giving away one's possessions, reviewing one's will, or being preoccupied with death should alert the clinician for a more thorough assessment.

The presence of psychotic symptoms should also be thoroughly assessed as this may impact treatment decisions. The type of psychotic symptoms endorsed may affect the person's safety risk. For example, a patient with command auditory hallucinations to kill oneself would be considered at higher risk versus a patient with paranoid delusions that they are being spied upon. If psychotic symptoms are present, it would also be important to know whether they started prior to the onset of the mood symptoms. In that scenario, the provisional diagnosis would be a psychotic disorder rather than a depressive disorder.

When obtaining the past psychiatric history, it is especially important to inquire about past manic or hypomanic symptoms. A history of a previous manic or hypomanic episode would indicate a diagnosis of bipolar disorder, even if the person is currently experiencing depressive symptoms meeting criteria for a major depressive episode.

Teaching Point

It is very important to rule out the possibility of bipolar disorder in someone presenting with depressive symptoms as the treatment plan would be very different for someone with bipolar disorder (i.e., would be considering treatment with a mood stabilizer versus antidepressant monotherapy).

The presence of past depressive episodes and any successful or failed treatment in the past can also help guide the management plan. A thorough substance use history is important as some patients with depression will actually increase substance use (alcohol or drugs) to "self-medicate." Chronic substance use may, in itself, be the cause for the depressive or other psychiatric symptoms. Substance abuse also increases the risk for suicide [28].

As stated previously, cognitive complaints are often seen in a geriatric person with depression. However, an underlying neurocognitive disorder may also precede the onset of depression. As well, depression itself is a risk factor for major neurocognitive disorder [12]. Although studies have clearly shown a strong association between depression and risk for neurocognitive disorder, what remains unclear is whether depression is a prodrome for neurocognitive disorder (as proposed by some). Nevertheless, a thorough history to delineate the time line of the depressive and cognitive symptoms will help form the diagnosis.

Physical Examination

Given that the geriatric patient is more likely to have comorbid physical illness, a thorough physical examination is pertinent to identify any medical conditions as diagnosis and management plans may be impacted. A patient with hypothyroidism, which can be associated with the presence of depressive symptoms, may show signs of dry rough skin or thinning hair and may have a slowed heart rate. A person with side effects from their antidepressant may show signs of akathisia and not be able to sit or stand still. A neurological exam may also be useful, especially if cerebrovascular events are suspected. Assessment of pain is also important as it can contribute to and co-occur with depression [29].

Laboratory Investigations

In anyone presenting with depressive symptoms, especially a geriatric person with first-onset depression, it would be important to rule out any comorbid systemic medical conditions as the cause of the depressive symptoms. Routine laboratory work-up for depression should include a complete blood count (CBC) and tests of renal and hepatic function, thyroid function, and electrolytes. In the geriatric person, calcium, albumin, magnesium, phosphate, and serum B_{12} should be considered, especially if nutritional status is a concern. In someone with a diabetes mellitus history, hemoglobin A1c and fasting glucose may be considered to monitor their glucose control. This would also be important if the person is

on certain antipsychotic medication (either as antidepressant augmentation or because of the presence of psychotic symptoms) given the increased metabolic risk. Lipid profiles may also be helpful in that case.

If infection is suspected, a chest X-ray or urinalysis may help to identify the source of infection. A person with a significant cardiac history may warrant an electrocardiogram, especially with the increased risk of depression in those with a recent myocardial infarction [20]. Medications used in the treatment of depression may also increase the risk of QT prolongation (as with some selective serotonin reuptake inhibitors, tricyclic antidepressants, and antipsychotic medications). Neuroimaging may be considered especially if psychotic symptoms or cognitive deficits are present.

10.1.6 Differential Diagnosis

As major depressive episodes may occur in someone with a bipolar disorder, the diagnosis of bipolar disorder should always be considered when evaluating someone with depressive symptoms. A depressed person with a prominent irritable mood (rather than expressed sadness) may also be difficult to distinguish from manic episodes with irritable mood or mixed features. A mood disorder due to a general medical condition is also a possibility until medical conditions are ruled out. Hypothyroidism, multiple sclerosis, and Parkinson disease are some common conditions that may cause depressive symptoms. Substance/medication-induced depressive disorder should also be considered in someone actively using or withdrawing from a substance use. Perhaps less of a concern in the older adults, but not rare, some symptoms in attention-deficit/hyperactivity disorder also overlap with depression—namely, distractibility and low frustration tolerance, manifested as irritability. As well, some personality disorders (particularly borderline personality disorder) may also have overlapping symptoms with depressive disorders. In a person presenting with psychotic symptoms in addition to their mood symptoms, a schizophrenia spectrum disorder may be considered. In a geriatric depressed patient with cognitive deficits, neurocognitive disorders would be a consideration.

10.1.7 Treatment

Psychological Treatments

Structured psychotherapies have been shown to be effective in the treatment of mild to moderate MDD [29, 30]. In moderately severe and low-risk depression, the choice between psychological and pharmacological treatments may be a combination of patient preference and the availability of the treatment modality [30]. Other factors to take into account in the geriatric population would be if the patient has comorbid systemic medical disorders that may impact the efficacy of the psychological treatment (some psychotherapies have more evidence over another depending on the systemic medical disorder). Cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and behavioral activation are recommended by both the Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 guidelines and American Psychiatric Association (APA) 2010 guidelines as first-line psychotherapies in the acute treatment of MDD (see ◘ Table 10.4) [29, 30]. Several meta-analyses have found CBT to be as effective as antidepressant medication and that the combination of CBT and antidepressant is more effective than either alone in the general adult population [30]. CBT remains the most established evidence-based first-line psychological treatment for depression in both the acute and maintenance phases of treatment. Maintenance therapy should be considered for those with recurrent MDD, chronic MDD, or any risk factors for recurrence (e.g., presence of residual symptoms, ongoing psychosocial stressors) [29]. In the maintenance phase, both CBT and mindfulness-based cognitive therapy are considered first line [30].

Some studies have suggested that older adults exhibit an equal, if not greater, preference for psychological treatments than pharmacological treatments for depression [26]. As well, there are many older adults who cannot take or tolerate antidepressants because of their medical conditions. CBT, behavioral activation, problem-solving therapy, brief dynamic therapy, and reminiscence therapy have all been shown to be effective interventions in older adults with depression [26]. (See ▶ Chap. 8.) Problem-solving therapy is one of the few therapies studied in older adults with cognitive impairment and executive dysfunction [30]. The efficacy of

◘ **Table 10.4** Recommendations for psychological treatments in acute treatment of major depressive disorder in the general population [29, 30]

	CANMAT guidelines	APA guidelines
First-line options	Cognitive behavioral therapy, interpersonal therapy, behavioral activation	Cognitive behavioral therapy, interpersonal therapy, behavioral activation
Alternative options	Mindfulness-based cognitive therapy, problem-solving therapy, short-term psychodynamic psychotherapy, cognitive behavioral analysis system of psychotherapy, telephone-delivered cognitive behavioral therapy and interpersonal therapy, Internet- and computer-assisted therapy, long-term psychodynamic psychotherapy, acceptance and commitment therapy, videoconferenced psychotherapy	Psychodynamic psychotherapy, problem-solving therapy, family therapy, marital therapy

IPT as a stand-alone intervention for late-life depression is still uncertain, as most studies looking at the efficacy of IPT have been done in conjunction with medication [26].

Pharmacological Treatments

Despite some literature questioning the efficacy of antidepressant medications, they remain a recommended treatment in the Canadian and US treatment guidelines for major depression. The initial selection of an antidepressant will largely be based on anticipated side effects, the safety and tolerability of these side effects for the individual patient, previous response in prior episodes, cost, potential interactions with other medications, and patient preference. Table 10.5 lists the recommended antidepressants from the CANMAT and APA guidelines [29, 30].

The response rate of antidepressants in older adults is generally thought to be similar to the younger patients—about 30% response rate with placebo and 60% with treatment [28]. However, in the older adult, there are also many other factors to consider when looking at antidepressants. Although effective, the potential side effects and anticholinergic properties of tricyclic antidepressants limit their use. The use of tricyclic antidepressants, as well as selective serotonin reuptake inhibitors (SSRIs), has been associated with an increased risk of falls in the older adults [28, 29]. SSRIs have also been associated with an increased risk of syndrome of inappropriate antidiuretic hormone secretion (SIADH)/hyponatremia, especially in the older patient with other risk factors for this condition [28]. Comorbid systemic medical conditions may prevent the use of certain medications (i.e., avoid use of SSRI in someone at risk of gastrointestinal bleeding). In the older adults, who are more likely to be on multiple medications, there are also significant cytochrome P450 interactions to consider as many of the psychiatric medications are involved with the isozymes (see Table 10.6). When taking all these factors together, the selection of an antidepressant for a geriatric depressed person is no longer simple. While there have been trials looking at whether certain diagnostic specifiers (melancholic, atypical, anxious) will respond to certain antidepressants, the results have been nonspecific [31].

Treatment-resistant depression is a term used to describe cases of depression that have failed two or more trials of antidepressants. In patients who do not respond or only partially respond to an antidepressant, the decision to switch or use adjunctive strategies remains quite controversial. As a first step, it is preferable to always question the diagnosis in what

Table 10.5 Treatment recommendations for antidepressants in acute treatment of major depressive disorder in the general population [29, 30]

	CANMAT guidelines	APA guidelines
First-line options	Bupropion SR or XL, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine, vortioxetine, agomelatine*, mianserin*, milnacipran*	Bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, paroxetine, sertraline, venlafaxine
Alternative options	Amitriptyline, clomipramine, moclobemide, phenelzine, quetiapine/quetiapine XR, reboxetine*, tranylcypromine, trazodone, vilazodone, levomilnacipran*, selegiline transdermal*	Amitriptyline, desipramine, doxepin, imipramine, isocarboxazid, nortriptyline, phenelzine, tranylcypromine, trimipramine, selegiline transdermal*

*Not available in Canada

Table 10.6 Cytochrome P450 drug metabolism (psychotropic medications)

Enzymes	Inhibitors	Inducers	Substrates
CYP1A2	Citalopram, fluvoxamine, fluoxetine, paroxetine, sertraline	Carbamazepine	Agomelatine, asenapine, clozapine, duloxetine, fluvoxamine, imipramine, mirtazapine, olanzapine, risperidone
CYP2C9	Fluoxetine, paroxetine, valproic acid	Carbamazepine	Amitriptyline
CYP2C19	Fluoxetine, fluvoxamine, paroxetine	Carbamazepine, valproic acid	Amitriptyline, citalopram, clomipramine, diazepam, imipramine
CYP2D6	Bupropion, citalopram, escitalopram, duloxetine, fluoxetine, haloperidol, paroxetine, sertraline		Amitriptyline, aripiprazole, clomipramine, desipramine, donepezil, duloxetine, haloperidol, imipramine, nortriptyline, paroxetine, risperidone, sertraline, venlafaxine, vortioxetine
CYP3A4 and CYP3A5	Fluvoxamine	Carbamazepine, topiramate	Alprazolam, buspirone, haloperidol, levomilnacipran, mirtazapine, quetiapine, sertraline, trazodone, venlafaxine, vilazodone, zolpidem

appears to be a "treatment-resistant" disorder or expand its differential and uncover comorbidities that may be complicating the course. While switching to another antidepressant is better for minimizing polypharmacy, the time it takes to wean off of an antidepressant and to start a new one may be the time that the patient cannot afford due to significant dysfunction, especially in a geriatric patient. There is some literature to suggest that adjunctive second-generation antipsychotics (particularly aripiprazole and quetiapine) may be beneficial in the treatment of MDD [32]; however, the safety profile of these medications, especially in the older adults, has made this strategy a concern. Adjunctive lithium and triiodothyronine are also treatments recommended by the Canadian and US guidelines, but the lack of more recent studies using them in combination with newer antidepressants relegates them as second-line rather than first-line combinations [31]. A recent Danish study also found that the concomitant use of a statin (through its direct anti-inflammatory effects) and an SSRI is associated with a decrease in both psychiatric hospital contacts in general and psychiatric hospital contacts due to depression specifically, compared to the use of an SSRI alone [33]. One should keep in mind that most studies done on the efficacy of antidepressants and adjunctive strategies are done in the general adult population and that evidence for the geriatric population is still lacking.

Neurostimulation Treatments

Neurostimulation is an expanding area of research and clinical interest. Electroconvulsive therapy (ECT) is considered as one of the most effective treatments for MDD, with response rates of up to 70–80% [34, 35]. (See ▶ Chap. 6.) ECT is a procedure that requires the passage of small electric currents through the brain to elicit a brief seizure. Despite requiring general anesthesia and having some potential side effects (see ◘ Table 10.7), there are no absolute contraindications to the use of ECT. Given its well-established efficacy in treatment-resistant depression and favorable evidence for its use in geriatric depressed patients [35], ECT may play an important role in patients with severe late-life depression.

Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive brain stimulation method that uses powerful focused magnetic field pulses to stimulate neural tissue in the brain, without causing a seizure. (See ▶ Chap. 7.) Literature supports that rTMS is an effective treatment for depression and possibly treatment-resistant depression [34]. While ECT may be more effective in treating depression compared to rTMS [34], the lack of required anesthesia and its benign cognitive safety profile may lead one to choose rTMS over ECT. However, there is still a lack of studies looking at its use in older adults, and further evidence is needed to confirm efficacy and tolerability in this population.

◘ **Table 10.7** Risks of electroconvulsive therapy

ECT risks	Acute confusion
	Memory loss (retrograde and anterograde)
	Nausea
	Headache
	Jaw pain
	Muscle ache
	Medical complications due to anesthesia

There is also some evidence for the use of transcranial direct current stimulation (tDCS) in treating depression. tDCS is a noninvasive treatment that delivers a continuous low-amplitude electrical current to a specified cortical region using scalp electrodes. While there is increasing evidence that supports its use for treating depression in the general population, further research is required looking at its utility in older populations.

Vagus nerve stimulation (VNS), which involves implanting an electrode around the vagus nerve that delivers intermittent electrical signals to the brain, is an approved treatment modality for major depression. There is very little data on VNS and its use in the depressed geriatric patients, and thus, given its invasive nature, should be considered with caution.

Other neurostimulation modalities that are still considered investigational for the treatment of major depression include magnetic seizure therapy (MST) and deep brain stimulation (DBS). MST induces a seizure by using high-intensity repetitive magnetic pulses. It is currently being investigated as an alternative to ECT, with the possible advantage of having fewer cognitive side effects. DBS is the most invasive of the brain stimulation modalities, requiring the implantation of electrodes under neuroimaging guidance to target specific neuroanatomical areas. Studies of DBS in depression have been limited to small nonrandomized open-label trials [34, 35]. Further research in this area is needed to identify appropriate brain targets before moving forward with clinical trial in older adults.

Alternative Treatments

Light therapy or phototherapy involves daily exposure to artificial bright light, which is thought to alter circadian rhythms and modulate the serotonin and catecholamine systems, leading to its antidepressant effect [36]. While it is generally known as an established treatment for seasonal MDD, there are also favorable studies supporting its use in nonseasonal MDD [29, 37]. Research suggests that sleep deprivation can have rapid antidepressant effects; however, relapse after discontinuation is often rapid as well, limiting its use in treatment of depression. Physical exercise is thought to be effective as monotherapy in mild to moderate MDD and in moderate to severe MDD can be considered as adjunctive therapy [36, 38]. Other physical treatments such as yoga and acupuncture are both recommended as adjunctive therapies in treating mild to moderate depression [29, 36].

The use of natural health products in treating various medical illnesses, including depressive disorders, is gaining in popularity. The strongest evidence is for the use of St. John's

wort, a wildflower thought to have a direct effect on serotonin receptors, monoamine oxidase inhibition, and neuroendocrine and ion channel modulation [36]. It seems to have comparative efficacy to antidepressants in treatment of mild to moderate MDD [39]. There have been some favorable studies looking at its benefits in late-life depression; however, the potential cytochrome P450 interactions with this herbal medication suggest that it should be used cautiously in the geriatric population. Limited evidence also exists for the use of omega-3 fatty acids, S-adenosyl-L-methionine (SAM-e), and dehydroepiandrosterone (DHEA) in the treatment of MDD. Again, as with most treatment modalities, very little data exists on their use in the geriatric population, and further research is warranted.

10.2 Case Studies

The following two case studies are used to illustrate common diagnostic challenges and treatment concerns that are associated with treating a geriatric patient with depression.

10.2.1 Case 1

Case 1 History

Mrs. G. is a widowed 77-year-old retired bank teller, who has been brought to the emergency department by her son and daughter as they have been worried about her mood for the past couple of months. This afternoon, when they were both over for a visit, hoping to convince their mom to go out to dinner with the family, Mrs. G. admitted to them that she felt so terrible that she wanted to die. Her family became very concerned and decided to bring her to the hospital for assessment.

Mrs. G. was assessed by the emergency physician who did not feel that there were any acute systemic medical illnesses and referred her to the emergency psychiatric team for an assessment of her suicidal risk. During her assessment with the on-call psychiatrist, Mrs. G. admits that she has been feeling lonely and down for about the past 3 months. Her husband of 53 years had passed away 6 months ago suddenly from a massive heart attack. Mrs. G. thought she managed quite well initially. Even though she was sad that he was gone, she was still able to do what was needed at the time—making funeral arrangements and dealing with the lawyer and all the necessary paperwork. Then, about 3 months ago, it all just "hit" her. She was feeling very lonely, particularly at nighttime when she would just lie in bed, staring at the ceiling and not be able to fall asleep. She continued to feel worse as time went on, walking around the house aimlessly during the daytime, looking for something to do, eventually end up sleeping on the couch, so she would no longer have to think. She became more and more withdrawn and stopped calling her family and friends as she just did not feel like talking to anyone. Mrs. G. was still keeping up with her personal hygiene but stopped doing housework about a month ago. In the past 2 weeks, she has not felt much like cooking and is just eating crackers and peanut butter. In the past 2 days, she has been thinking that it would just be easier if she could just join her husband in death and be at peace.

Before the arrival of her family at her house today, she was actually looking at her medications and thinking it would be nice to take all of her "sleeping pills" at once. She became very scared by her own thoughts. When her children arrived, she told them what she had been thinking. Currently, while she does not have any plans to kill herself, she is afraid those thoughts would come back when she goes back home alone as she does not see any reason to live.

Mrs. G. states that she has never felt like this before in her life. She has always been a very upbeat and energetic person. While she may have gone through some difficult periods in the past, she states that she has always managed to get through these times without help. She has never needed to see a psychiatrist for any reason. She denies ever drinking alcohol excessively and denies the use of any illicit drugs.

Medical history revealed that she had a left side stroke about 10 years ago with full recovery. She has hypertension and hyperlipidemia; both these conditions are treated and under control. She was recently told by her primary care physician that she is "borderline diabetic." She also had a fairly significant gastrointestinal bleed about 5 years ago due to a peptic ulcer. She had a remote tonsillectomy and an appendectomy about 15 years ago.

Mrs. G. has a younger sister who went through a "nervous breakdown" after a miscarriage. Mrs. G. thinks her sister may have been on a medication for her "nerves" for a period of time but does not know of her specific diagnosis or the name of the medication.

Mrs. G's medications included rosuvastatin 10 mg daily, metoprolol 12.5 mg bid, aspirin 81 mg daily, pantoprazole 40 mg daily, clopidogrel 75 mg daily, and lorazepam 1 mg qhs prn (started by her primary care physician after her husband passed away; she takes it about three times a week).

Laboratory investigations ordered by the emergency physician included CBC, electrolytes, creatinine (Cr), estimated glomerular filtration rate (eGFR), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), alanine aminotransferase (ALT), random glucose, and a urinalysis. Other than a slightly high random glucose of 13.4 mmol/L (241.2 mg/dl), all other blood test results were within normal limits.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What other information do you need to help with assessment? Any other investigations that should be considered?

? Question 2. What is your differential diagnosis and provisional diagnosis?

? Question 3. What is your acute management plan?

Question 4. Is there a way to predict response to treatment?

Question 5. How long would you continue Mrs. G.'s sertraline for?

Case 1 Answers

Case 1 Answer 1 (Question 1—What other information do you need to help with assessment? Any other investigations that should be considered?)

A1.1. Obtaining further collateral information would help in making an accurate diagnosis. If the histories provided by the patient and her family greatly differ, then the reliability of Mrs. G. as a historian would need some consideration. As well, given that depressive symptoms are the presenting complaint, it would be important to rule out past history of manic and hypomanic symptoms (even if she has never been diagnosed or seen by a psychiatrist) as that would not only alter diagnosis but also treatment plan.

- Both her children agreed that the mood symptoms began around 2–3 months ago and that it has been getting progressively worse. It was not until today that they heard about their mother's wish to die. They have never seen their mother like this in all their lives. They both describe her as a very even-keeled person, never one to go into the extremes of emotions. They are both very worried as they see their mother becoming more and more despondent in the past weeks. When their father first passed away, Mrs. G. was understandably upset, but both children thought she was doing fairly well as she was able to organize all the necessary arrangements and did not "fall apart." It seems that now, when there is nothing for her to focus on and occupy her mind about, her mood just started to drop.
- Neither of the children can recall a time when their mother's mood was extremely low in the past. They also deny any periods where she would be unreasonably "happy" with increased energy or decreased sleep.
- Both her daughter and son deny the presence of psychotic symptoms. Memory was not noted to be a concern.

A1.2. Further investigations to rule out other causes of depressive symptoms would be helpful as this appears to be Mrs. G.'s first presentation of psychiatric symptoms. For example, thyroid dysfunction should be ruled out as hypothyroidism can be associated with depressive symptoms. Low vitamin B_{12} may also contribute to depressive symptoms. In addition, as Mrs. G. has not been eating well lately, one may want to check her nutritional status and other minerals such as magnesium, phosphate, zinc, albumin, and calcium levels. Given that Mrs. G. is "borderline diabetic," ordering a hemoglobin A1c would also be helpful in gaining a better sense of her recent glucose control.

A1.3. Brain imaging is likely not necessary at this point as Mrs. G. is not demonstrating any neurological deficits or any symptoms suggestive of psychosis or cognitive decline. If these symptoms were present, it would be reasonable to do imaging given her past history of stroke (to rule out new stroke) or other intracranial pathologies.

Case 1 Answer 2 (Question 2—What is your differential diagnosis and provisional diagnosis?)

A2.1. The most likely diagnosis is major depressive disorder, single episode, late-onset.

- Not only is Mrs. G. feeling sad and lonely, she is also experiencing changes in sleep and appetite, endorsing feelings of hopelessness, decrease in interest and pleasure in activities, as well as suicidal ideation. She meets the criteria for a major depressive episode.
- From patient history and collateral information, depression has never been an issue in the past, making this her first episode.

A2.2. Other diagnoses to consider include:

- Bereavement—it is normal for people to experience sadness after the loss of a loved one. However, during the bereavement process, while one may experience "survivor guilt," one usually does not have active suicidal thoughts, which Mrs. G. did experience.

Teaching Point

It is normal for people to grieve after the loss of a loved one, and it would be important to not pathologize the normal grieving process after a significant loss. However, the presence of active suicidal thoughts or psychotic symptoms should alert the clinician to a possible depressive disorder. Also, bereavement may be a "precipitant" to clinical depression; thus, persons going through grief should be assessed regularly for emergence of a significant depression.

- Depressive disorder due to a medical condition—as blood work for thyroid function and vitamin B_{12} is still pending, it is possible that her depressive symptoms are due to an underlying medical condition. Given her remote history of left side stroke, some studies proposed an association with specific left brain lesions (lesions close to frontal pole and anterior and basal ganglia lesions) and occurrence of poststroke depression; however, Mrs. G.'s current depression did not appear to be temporally associated with a stroke event.
- Bipolar disorder—although Mrs. G. has no history of previous manic or hypomanic symptoms, it is possible for her to develop manic/hypomanic symptoms in the future if she has a late-onset bipolar disorder (but only time will tell). Thus, it would be important to monitor for any mood change after antidepressants are initiated.

Case 1 Answer 3 (Question 3—What is your acute management plan?)

Mrs. G. has significant depressive symptoms along with passive suicidal thoughts. Even though she no longer has an active suicidal plan to overdose on her medication, she is worried that her suicidal thoughts would return. Despite having supportive children, Mrs. G. does live alone and had a recent significant loss. It would be reasonable to consider a short inpatient hospitalization to monitor her safety risk.

Pharmacological intervention would include consideration of starting an antidepressant. As Mrs. G. has never been on an antidepressant in the past, trial with an SSRI would be a reasonable first step. Sertraline or escitalopram would both be acceptable choices. In a geriatric patient, paroxetine is generally avoided because of its anticholinergic side effects and fluoxetine because of its long half-life. Given the risk of SIADH/hyponatremia with SSRI use in the older patients, her sodium level should be monitored once pharmacotherapy is initiated, generally within the first month. Serum sodium levels should be checked in such cases especially if there is concurrent medication use that can cause hyponatremia (e.g., diuretics). As well, the use of SSRI is linked with increased risk of gastrointestinal bleeds, especially in light of concomitant use of aspirin or blood thinners (although use of pantoprazole, a proton pump inhibitor, may be protective). Thus, Mrs. G. should be advised of these risks and monitored, especially in view of her past history of bleed. Her dose of SSRI should be monitored and optimized as needed, with the goal of full resolution of depressive symptoms.

Grief is also likely contributing to Mrs. G.'s depressive symptoms. Grief counseling and/or IPT (with a focus on loss) can be considered to help her through the process of mourning for her husband's death. (See ► Chap. 8.)

Case 1 Answer 4 (Question 4—Is there a way to predict response to treatment?)

There has been much research into the area of predicting response to treatment with antidepressants. The process of finding an effective regimen may take many months at times, which may worsen outcome. It is particularly important to shorten this recovery time in the geriatric patients because of the possible impact on medical comorbidities. Imaging studies seem to suggest that loss of brain volume and higher ischemic white matter lesion burden in the brain are associated with poorer treatment response in late-life depression [40, 41]. There are also studies providing evidence that high signal lesions in brain computer tomography (CT) or the T2 sequence of brain magnetic resonance imaging (MRI) may characterize patients at risk of delirium or other neurocognitive disorders after treatment with a TCA or ECT [25]. The presence of cognitive deficits or psychotic symptoms is also associated with poorer prognosis [25]. However, more vigorous research will be needed before treatment response can be reliably predicted.

Case 1 Answer 5 (Question 5—How long would you continue Mrs. G.'s sertraline for?)

Assuming that Mrs. G. responds well to treatment with sertraline and achieves complete remission of her depressive symptoms, current guidelines for seniors recommend that she continues on treatment for at least 12–24 months to minimize risk of relapse [26].

The highest risk for relapse is generally within the first year of antidepressant discontinuation. Psychoeducation should be provided to Mrs. G. so that she can monitor for any of the early warning signs of relapse (e.g., social withdrawal, changes in sleep pattern). A slow taper of her antidepressant over months, while monitoring closely for relapse of symptoms, would be recommended.

Case 1 Analysis Mrs. G. reflects a fairly typical case of late-life depression. In half the cases, there is a precipitating traumatic life event—in Mrs. G's case, it is the death of her spouse. Although she seemed to have managed well immediately after her husband's death, once the hustle and bustle settled, she was left with nothing to do and a lot of time to ruminate. What likely began as normal bereavement in the first few months eventually turned into a full-blown major depressive episode.

Because of the possible suicidal risk with Mrs. G., pharmacological intervention was initiated early on. However, given the circumstances of her depression, some type of psychotherapy support to help her through her grief would also be helpful. (See ► Chap. 8.) Behavioral activation and increasing socialization would be beneficial for her loneliness. As this is her first depressive episode, psychoeducation regarding diagnosis and treatment is very important to improve adherence to therapy. For example, some patients may take the antidepressant only on the "bad days" but not on days where they are feeling slightly better. It would be important to convey to Mrs. G. that antidepressants do not work that way and that she needs to take the medication daily. It would also be important for Mrs. G. to know that it may take 2–4 weeks before she would notice any benefits with the medication, although full resolution of symptoms may take 6–8 weeks. If she was to experience side effects, the best course of action would be to persevere if they are tolerable, waiting to see if the side effects would resolve with time.

Mrs. G. should be monitored closely within the first few weeks of starting an antidepressant to not only assess for side effects but to monitor for the emergence of any hypomanic or manic symptoms. The dose of the medication should be optimized at regular intervals and as needed, keeping in mind that the average therapeutic dose for the geriatric population tends to be lower than the average for younger patients [26].

It is important to note that despite treatment interventions, about 10–20% of patients will continue with chronic depressive symptoms [26]. If switching antidepressants or adjunctive strategies (i.e., augmentation with lithium or bupropion) fails, then other modalities such as ECT or rTMS should be considered in order to achieve maximum improvement.

10.2.2 Case 2

Case 2 History

Mr. T., an 82-year-old married retired contractor, has been referred to your outpatient clinic for assessment of memory impairment and depressive symptoms. He was accompanied by his son George to the appointment. Mr. T. tells you that he is here today only because of his family and that he did not really think he needed help from a psychiatrist. Mr. T. admits that he has not been feeling himself lately as he and his wife are currently going through "a spell." This is his second marriage, and they have been together for 10 years. For the past 6 months, he has been wondering if his wife Nancy is seeing another man. He has noticed her to be constantly whispering on the phone, hanging up whenever he walks into the room. He tells you that his wife has also been going out more often on her own under the guise of having joined a Tai Chi group. Whenever he would talk to her about his suspicions, she would just respond by saying that he is "a silly old man" and that she would never do something like that to him. Still, Mr. T. does not feel reassured, and he admits that this issue has been weighing on his mind. Mr. T. has had a couple of arguments with his wife because of this, and he feels like he has been operating on a "short fuse." When you ask him if he feels sad or down, his response was "wouldn't you be if your wife was cheating on you?" He then said he is not really feeling sad or depressed, just worried whether his marriage is going to last through this hurdle. He admits to having sleepless nights recently and has not been eating as much as he no longer has much of an appetite. He is still going out for his weekly coffee time with his friends and swimming at the community pool, but he states that he does not really enjoy his time out anymore. He has not really been engaged in his woodworking hobby either as he finds it hard to focus, with his mind always wandering off to his wife and this "other man."

Mr. T. did not think that he has any memory problems. While he agrees that his memory is not as good as it used to be, he attributes his forgetfulness to being distracted by his marital issues. He tells you he can still drive and do what he needs to do to get through the day.

You were able to speak separately with George for collateral information. George started noticing a change in his dad about 6–9 months ago. It started with his father not looking his cheerful self and seeming more distracted and preoccupied. However, when George had asked him about the change initially, Mr. T. had denied anything to be wrong and told George it was his imagination. Throughout the recent months, Mr. T. seems increasingly more disorganized and more forgetful. He used to really enjoy wood carving but has not been doing it as much—George is not sure if it is lack of interest or if it is because Mr. T. becomes too confused in terms of planning the carving and knowing what tools he should use. The few times that Mr. T. did try to carve something, he would give up in frustration as the carving would not turn out the way he wanted. He has noticed his father to have more problems with keeping track of appointments and seems to have to write everything down these days. He thinks his father is still able to manage his bank accounts and does not think there are any issues with using the microwave or coffeemaker (most of the cooking is done by his stepmother). George admits that as he does not live with his father, he is not sure what Mr. T. is able to do at home and what he is not. George tells you that Nancy did not attend the appointment today because his father did not want her to come.

George thinks that Mr. T. is quite unhappy these days. His father finally told him his suspicions about his stepmother 1 month ago. George did not think that his stepmother is the type of person to be unfaithful. Nancy herself has denied Mr. T.'s accusations to George. Mr. T. has never voiced any wish to harm Nancy or this "other man," nor has he ever told George that he wished he were dead.

Mr. T. admits that he has actually gone through a period of low mood two times in the past. The first was in his 30's when he was having some issues at work and was unemployed for about 4 months. He had felt worthless at the time as he was not able to support his family (he had two young children at home at the time) and had to rely on his wife's income. He recalled having a hard time dragging himself out of bed as there was nothing to wake up for. After a few months, his wife confronted him and told him to "be a man," and he eventually "got himself together" and found a job and felt much better about himself. The only other time in his life where he felt really down was when his first wife died from a car accident 20 years ago. Although they had had their ups and downs, he really missed her when she died unexpectedly. That first year after her death was very difficult for him as he had a hard time enjoying anything without her and did not feel that life was worth living without her. He felt very much alone as his kids were all grown up and living their own lives. He had taken an early retirement the year prior to her death, so he had nothing to do but spend time on his own at home at the time. Eventually, he came out of this "dark time" on his own. He never sought help for either of these time periods in his life.

Mr. T.'s medical history includes type 2 diabetes mellitus with neuropathy, hypertension, history of myocardial infarction 10 years ago, benign prostatic hypertrophy, osteoarthritis, and chronic obstructive pulmonary disease. He had bilateral cataract extractions and left knee arthroplasty done a few years back (he cannot recall exact date).

He did bring his medications with him today, and they included metformin 1000 mg tid, ramipril 2.5 mg daily, atenolol 50 mg daily, sitagliptin 100 mg daily, tamsulosin 0.4 mg daily, aspirin 81 mg daily, simvastatin 20 mg daily, fluticasone/salmeterol Diskus 250/50 mcg 1 puff bid, and acetaminophen 650 mg bid.

Mr. T. used to "smoke a joint or two" when he was younger but stopped using cannabis after he had his children. He typically will have a glass of wine with dinner on most nights and denies any history of alcohol overuse. In the past 2 months, he admits to having an extra whiskey at night as he has not been sleeping too well.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What is your differential diagnosis?

Question 2. What investigations would you do at this time?

Question 3. How do you know if this is a depression versus a neurocognitive disorder?

Question 4. The provisional diagnosis at this time for Mr. T. is recurrent major depressive disorder with psychotic features. What is the role for atypical antipsychotic medication in his treatment plan?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is your differential diagnosis?)

A1.1. Major depressive disorder, recurrent, with psychotic features.
- Even though Mr. T. did not actually endorse sadness, he does exhibit other symptoms that may suggest depression. It is important to remember that denials of sadness are not uncommon in the geriatric depressed patient. However, Mr. T. has been more irritable and also has been experiencing insomnia, loss of appetite, lack of interest, and poor concentration. These symptoms support a possible depressive episode.
- It is likely that Mr. T. has a past history of depressive episodes. Even though he never sought psychiatric help for any of those "dark times" in the past, his descriptions of how he struggled through those periods suggest he likely met the criteria for a major depressive episode at the time. Given this history, it is highly possible that he is having a recurrence of his depressive disorder.
- Collateral history from Mr. T.'s son George also supports a diagnosis of depression. George has noticed Mr. T. to be "unhappy" and less cheerful. He is also noted to be more disorganized and forgetful, which may be in keeping with the "pseudodementia" presentation that is sometimes seen in older adults who become depressed.

A1.2. Major neurocognitive disorder, with behavioral disturbance.
- It is also possible that Mr. T.'s forgetfulness may, in fact, be due to an early stage of major neurocognitive disorder. He is noted to have some executive dysfunction in terms of his ability to organize and plan. George had noted that he was doing less of his wood carving, although admittedly George was not sure if this was due to lack of ability or lack of interest.
- Unfortunately, George's knowledge of Mr. T.'s daily function is limited as he does not live with his father. It would be helpful at this point to speak with Mr. T.'s wife Nancy to gather additional information about his function at home or recent changes in cognition. For example, is Mr. T. having any difficulties with the television remote, cell phone, computer, or any other electronic devices/gadgets/appliances at home? Is he keeping up with his personal hygiene without reminders? Has he had any issues with becoming disoriented or confused in a familiar place? Has he been making any mistakes in his banking or personal finances?
- If indeed Mr. T. does have an underlying neurocognitive disorder, then it is possible that his delusions may be part of the psychotic features that are common in the mild-to-moderate stage of a major neurocognitive disorder. Mood disturbances (including depression and anxiety) are also common early in the course of cognitive decline.

A1.3. Delusional disorder, jealous type.
- As we do not have a clear history of which came first, change in mood, memory, or the development of delusions, it is possible that Mr. T. may have a primary psychotic disorder, such as delusional disorder. Many patients with delusional disorder also develop irritable or dysphoric mood as a reaction to their delusional beliefs. As Mr. T. does not have features of disorganized speech or behavior, negative symptoms, or significant dysfunction due to the psychotic symptoms, it is less likely that he would have schizophrenia or schizoaffective disorder.

A1.4. Bipolar disorder, manic episode with irritable mood.
- Mr. T. is noted to be more irritable, has been sleeping less as he has trouble falling asleep, and is more distractible. However, he lacks some of the other features of a manic episode such as inflated self-esteem, racing thoughts, and increase in goal-directed activity. Thus, this is lower on the differential.

A1.5. Delirium.
- It is possible that Mr. T. may have an underlying urinary tract infection that may be leading to his forgetfulness and psychosis. There is no history suggesting that these symptoms developed acutely, nor is there a history of fluctuation in his alertness or awareness, which suggests that delirium would be less likely.

A1.6. Mood disorder or psychotic disorder due to another medical condition.
- As there is currently no information regarding a physical work-up, a medical condition cannot be ruled out (e.g., hypothyroidism leading to depressive symptoms).

Case 2 Answer 2 (Question 2—What investigations would you do at this time?)

Baseline laboratory studies for Mr. T. should include CBC, Cr, eGFR, GGT, AST, ALT, thyroid-stimulating hormone, electrolytes, calcium, albumin, magnesium, phosphate, and serum B_{12}. Given his history of diabetes mellitus, fasting glucose and hemoglobin A1c should also be considered to rule out poor blood glucose control as a reason for his irritability (or if extremely unstable, be the cause for delirium). With many sexually transmitted infections on the rise [42], a venereal disease research laboratory (VDRL) test can be considered to rule out a syphilis infection as the cause of Mr. T.'s psychosis.

Urinalysis and culture would be helpful to rule out a urinary tract infection. If he has any respiratory symptoms, a chest X-ray should be done as well.

Given the presence of his psychotic symptoms of delusions, it is highly possible that Mr. T.'s management plan may include the use of an antipsychotic medication. Therefore, it is desirable to perform a baseline electrocardiogram to rule out any underlying cardiac arrhythmias (e.g., prolonged QTc interval).

Brain imaging should also be considered as this is a first presentation of psychosis for Mr. T. He has significant cardiovascular risk factors including a history of diabetes mellitus, hypertension, and previous myocardial infarction, which increases the possibility of a cerebrovascular event as the etiology of his mood and psychotic symptoms. It would also be helpful to rule out brain tumor as the cause of his current symptoms.

Case 2 Answer 3 (Question 3—How do you know if this is a depression versus a major neurocognitive disorder?)

Differentiating between a major depressive disorder with "pseudodementia" symptoms and a major neurocognitive disorder with behavioral symptoms relies largely on history. A history clearly delineating the onset of cognitive decline before the emergence of mood and psychotic symptoms would suggest a primary major neurocognitive disorder. However, for many patients, especially if insight is poor and collateral information is lacking, trying to determine whether the symptoms are due to a mood disorder or a neurocognitive disorder can be challenging.

In many cases, the clinician would have to treat the depression first (e.g., with an antidepressant) and monitor whether there is any improvement in cognition after resolution of the depressive symptoms, in order to determine if the patient has an underlying neurocognitive disorder.

Case 2 Answer 4 (Question 4—The provisional diagnosis at this time for Mr. T. is major depressive disorder with psychotic features. What is the role for atypical antipsychotic medication in his treatment plan?)

There is evidence for the use of antipsychotic medications as adjunctive strategies in the treatment of resistant depression [31, 32]. Treatment guidelines also support the concomitant use of antidepressants and antipsychotics when treating a depressive episode with psychotic features [31].

There has been much attention in the use of antipsychotic medications in the population with major neurocognitive disorders because of the increased risk of stroke and all-cause mortality [43]. This risk is less clear in the cognitively intact geriatric population [44]. The risk of other side effects such as extrapyramidal side effects, QTc prolongation, and hypotension suggests that, when used, caution should be exercised and the patient be closely monitored.

Teaching Point

As there is often a paucity of studies in the geriatric age group, there are many times where a clinician may have to use evidence-informed rather than evidence-based treatment and extrapolate from studies done in the general population. When using medications (not just antipsychotics), it needs to be recognized that the older adults often require lower doses and may be more sensitive to side effects. Close monitoring for response and issues that may arise is essential.

Case 2 Analysis In Mr. T.'s case, it was not easy to determine whether he had a primary depressive disorder, a neurocognitive disorder, or even a psychotic disorder as his symptoms seemed to have onset around the same time. There exists such a great overlap of symptoms and presentations in these disorders that making an accurate diagnosis is challenging. Lack of insight and poor quality of collateral information only contribute to the conundrum. It is not unusual for a clinician to be faced with having to develop a management plan without knowing with absolute certainty what the diagnosis is.

With Mr. T., his past history of previous depressive episodes increases the likelihood that this is a recurrence of his depression. It is also possible that, while he is currently in an acute depressive episode, his cognitive changes are, in fact, due to an underlying early major neurocognitive disorder, and not to "pseudodementia." In the second scenario, the use of antipsychotic medications to treat his delusions would then potentially increase his risk of mortality. Close monitoring and constant reassessment are imperative, in trying to minimize risks. The need for continued treatment is something that should be evaluated regularly. In Mr. T.'s case, he was eventually started on a combination of sertraline and aripiprazole and responded well. The CANMAT guidelines suggest that an antidepressant should be continued for at least 6–9 months in the general population [31]. Similarly, the APA guidelines suggest a period of 4–9 months [29]. In the older population, the antidepressant should be continued for longer, possibly 12–24 months [26]. For Mr. T., as this is a recurrent depression, he could potentially remain on the antidepressant indefinitely. However, it is less clear whether Mr. T. should also be maintained on the adjunctive antipsychotic for the same length of time. The decision to taper and discontinue his aripiprazole is one that should be made with Mr. T.'s input. Ongoing side effects and other potential risks (e.g., risk of stroke and mortality if Mr. T. does have an underlying major neurocognitive disorder) would also affect the decision. Mr. T. needs to understand the possible risk of recurrence if he were to only

continue with sertraline treatment. Once the decision is made to taper medications, he would need to be monitored closely.

10.3 Key Points: Late-Life Depression

- About 15% of patients with MDD will die by suicide, with the highest suicide rate in the 65 years and over age group. In someone presenting with depressive symptoms, it would be important to thoroughly assess for suicidal risk factors and the presence of suicidal ideation, plans, and intent.
- There has been a growing amount of studies linking the *hypothalamic-pituitary-adrenal* axis, BDNF levels, tumor necrosis factor-α, the interleukins, and various genotypes to the development of depression. It is important to keep in mind that depression is not caused by a single etiology or gene but is a consequence of various interactions between many sources of vulnerability.
- Not every depressed person will endorse feelings of sadness. In patients with late-onset depression, they are more likely to emphasize body aches and pains rather than endorse feeling sad.
- In a geriatric person presenting with anxiety, depression should always remain at the top of the differential list as a large percentage of geriatric patients with MDD also have comorbid anxiety disorders.
- Depression increases the risk of developing a major neurocognitive disorder. The flip side is also true; patients with a major neurocognitive disorder are at increased risk of developing depression.
- In someone presenting with depressive symptoms, it is important to rule out a possible bipolar disorder as treatment for both disorders will likely be different.

10.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following is *not* true, when treating a geriatric depressed individual?

A. The pharmacokinetic changes in the geriatric patients may decrease the rate of absorption and modify bioavailability, decreasing the dosage of medication needed for treatment.
B. As risks and side effects are minimal with the SSRIs, one does not need to monitor when initiating these drugs versus using an atypical antipsychotic.
C. Evidence suggests that late-onset depression may be a prodrome for major neurocognitive disorder; hence, monitoring of cognition over time is warranted.
D. As depressive episodes in the geriatric patients are often triggered by a traumatic life event, psychotherapy should be considered as part of the treatment plan as pharmacotherapy may not address the psychosocial issues.

Answer: B

Pharmacokinetics, which involves absorption, metabolism, distribution across body compartments, and excretion of drugs, changes as we age. Gastric emptying is slowed, small-bowel surface area is decreased, body fat decreases, and total body water increases. These age-related physiologic changes affect the rate with which drugs are absorbed and, ultimately, do affect the doses that are required; therefore, statement A is true. There is a body of literature suggesting that late-onset depressive symptoms are related to increased risk of developing a major neurocognitive disorder. Thus, it would be reasonable to monitor cognition over time to detect early changes in cognition; hence, statement C is true. More than 50% of late-life depression is triggered by a significant life event. While pharmacological interventions are helpful, the underlying stress that led to the depressive episode should be addressed to help with resolving any residual depressive symptoms and, perhaps, to prevent future episodes; therefore, statement D is true. When SSRIs are generally considered safe drugs, they are not without their risks (e.g., risk of falls) or side effects. Thus, a patient being initiated on these medications should still be monitored closely for adverse events. Therefore, statement B is untrue.

MCQ 2. Which treatment strategy is indicated, when a geriatric depressed patient has not responded to an SSRI within 3 weeks of treatment?

A. As the lack of early improvement in that time frame is a predictor of later antidepressant nonresponse, the patient should be switched to another antidepressant immediately.
B. Older patients, when compared to younger patients, do not tend to respond to antidepressant therapy. Thus, the SSRI should be discontinued at week 3 if there is no response, and psychotherapy or neurostimulation treatments should be initiated.
C. As long as the SSRI is well tolerated, the strategy should be to increase the medication slowly until there is some response or if maximum recommended dose has been reached, before considering switching or adjunctive strategies.
D. The patient should be referred for a second opinion as most geriatric depressed patients have high response rates to antidepressants.

Answer: C

While lack of early improvement can be a predictor of response to an antidepressant, switching right away to another antidepressant is not necessarily the first response as medications should be optimized if possible before declaring a failed trial. Thus, statement A is incorrect. Older adults also respond just as well to pharmacological interventions compared to the younger cohort; thus, medications should always be considered in management of depressive symptoms in an older adult; therefore, statement B is incorrect. Unfortunately, choosing the right antidepressant is not always easy; one may have to try a few antidepressants before finding one that is

well tolerated and effective. While a second opinion may be helpful to confirm diagnosis and offer alternative treatment recommendations if the patient had a number of failed trials, a second opinion after nonresponse to one single medication at low doses would be premature. Hence, statement D is incorrect. The correct response in this case would be to try and optimize the medication until the expected response or to the maximum recommended dose, as long as it is tolerated by the patient. The correct answer is C.

MCQ 3. In a geriatric person with depressive symptoms, the presence of which feature would help point toward a diagnosis of bipolar disorder, depressed mood rather than major depressive disorder?

A. Insomnia
B. Poor concentration
C. Irritability
D. Flight of ideas

Answer: D

There exists a great overlap in many psychiatric diagnoses. Insomnia, poor concentration or distractibility, and irritability are overlapping symptoms between depression and bipolar mania. Thus, in a patient experiencing any of those three symptoms, the diagnosis could potentially be either major depressive disorder, bipolar disorder—depressed episode—or bipolar disorder, manic episode. Hence, options A, B, and C are incorrect. While confusion or mental slowing is sometimes seen in a depressed patient, flight of ideas is not a usual symptom in depression but is a possible symptom in someone who is manic. Thus, option D is correct.

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Late-Life Bipolar Disorders

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11.1 Background

11.1.1 Definition

Bipolar disorder, previously known by some as manic depression or manic-depressive disorder, is defined as a mental disorder that is marked by alternating periods of elation and depression. In the *Diagnostic and Statistical Manual of Mental Disorders—5th edition* (DSM-5), this is further subdivided into bipolar I disorder, bipolar II disorder, cyclothymic disorder, substance/medication-induced bipolar and related disorder, bipolar and related disorder due to another medical condition, other specified bipolar and related disorder, and unspecified bipolar and related disorder [1]. The construct of the "mixed" mood episode, a specifier "with mixed features," is garnering attention in the research community and has important treatment implications. For bipolar disorder, one must meet criteria for either a manic episode or a hypomanic episode (see Table 11.1) and a major depressive episode (see Table 11.2). In other words, for it to be considered as bipolar disorder, it is not the normal mood "ups and downs" that one may encounter in life, but the extremes of emotions causing dysfunction. Bipolar disorder is generally an episodic, lifelong illness whose course can be variable. The first episode in bipolar disorder is more likely to be a depressive episode but may also be a manic, hypomanic, or mixed episode. For a complete review of the DSM-5 diagnostic criteria for bipolar and related disorders, the reader is referred to the DSM-5 manual [1].

Table 11.1 Highlights of the DSM-5 diagnostic criteria for a manic and hypomanic episode [1]

Manic episode	Hypomanic episode
Mood disturbance (elevated, expansive, or irritable), nearly every day for at least 1 week	Mood disturbance for at least 4 days
Increased energy and activity and three or more (four if mood is irritable): (1) inflated self-esteem/grandiosity, (2) decreased need for sleep, (3) talkative/pressured speech, (4) flight of ideas/racing thoughts, (5) easily distractible, (6) increased goal-directed activities, (7) high risk activities	Increased energy and activity and three or more (four if mood is irritable): (1) inflated self-esteem/grandiosity, (2) decreased need for sleep, (3) talkative/pressured speech, (4) flight of ideas/racing thoughts, (5) easily distractible, (6) increased goal-directed activities, (7) high risk activities
Medical/substance-induced condition exclusion	Medical/substance-induced condition exclusion

Table 11.2 Highlights of the DSM-5 diagnostic criteria for major depressive episode [1]

Major depressive episode
Five (or more) of the following symptoms present most of the day during a 2-week period: (1) depressed mood, (2) diminished interest/pleasure in activities, (3) change in appetite/weight, (4) insomnia/hypersomnia, (5) psychomotor agitation/retardation, (6) loss of energy, (7) worthlessness/inappropriate guilt, (8) poor concentration, and (9) suicidal ideation/plan or suicide attempt
Medical/substance-induced condition exclusion

Late-life bipolar disorder generally refers to onset of disorder in patients older than 60 years. However, the literature is variable, and some studies will use cutoffs of 50, 55, or 65 years. Thus, the definition of late life can remain somewhat ambiguous. As expected, medical comorbidities are generally higher in this age group, including conditions such as diabetes mellitus, cancer, thyroid disorders, and hypertension [2]. As a result, older adults with bipolar disorders tend to be on multiple medications with various medical complexities. This makes diagnosis and management of the bipolar disorder in this population more challenging.

11.1.2 Epidemiology

Bipolar disorders occur more often than previously thought. The US National Comorbidity Survey Replication finds the 12-month prevalence for bipolar disorders to be 0.9% [3]. The 12-month prevalence is 1.4% for those between 55 and 64 years, 0.5% for 65–74 years, and 0.7% for the 75–84 age range [3]. The Canadian statistics are not dissimilar. The Canadian Community Health Survey reported the estimated prevalence in Canada for 2012 to be 0.87% for bipolar I disorder and 0.57% for bipolar II disorder [4]. The prevalence for bipolar disorders as a whole is likely higher now that the other specified bipolar and related disorder category in DSM-5 includes patients with hypomania lasting less than 4 days. Onset of the disorder can occur throughout the life cycle, with first onset sometimes occurring in the 60s or 70s. However, most cases will have onset prior to age 50 [5], with the prevalence of bipolar disorder declining with age [6]. The ratio of women to men with bipolar disorder is higher in the older population compared to the younger population, 69% vs. 55% [6]. Most studies demonstrate little difference in clinical presentation between late-life bipolar disorder and earlier-onset bipolar disorder [6].

Although bipolar II disorder was considered to be a milder form of bipolar disorder at one time, this is no longer the case. Many individuals with bipolar II disorder spend a significant amount of time in depression, and their

depressive symptoms can cause just as much functional and interpersonal impairment. Even though many with bipolar disorder can return to a fully functional level between their hypomanic/manic and depressive episodes, a significant portion will also have inter-episodic dysfunction. Suicide is not uncommon in those with psychiatric disorders. Literature suggests that 25–50% of patients with bipolar disorder will attempt suicide at least once in their lifetime [7]. The standardized mortality ratio for suicide in patients with bipolar disorder is between 2.5 and 3 compared with the general population [8]. The suicide risk is increased not only with depressive episodes but also with manic episodes. One study suggests that elderly manic patients have an increased cumulative all-cause mortality over 10 years compared with geriatric depressed patients, 70% vs. 30% [9].

Teaching Point
Given the high risk of suicide in bipolar disorders, assessment of any patient presenting in mania or depression must include a full risk assessment.

11.1.3 Etiology

A positive family history is one of the strongest risk factors for bipolar disorders. The risk of bipolar I and bipolar II disorders is increased tenfold among adult relatives of bipolar disorder patients, with the risk increasing with the degree of kinship [1]. Some studies estimate heritability of bipolar disorder to be over 80% [10]. Genetic analyses suggest the possibility of the linkage region on chromosome 6q to be involved for bipolar I disorder and chromosome 8q to be related to bipolar I and bipolar II disorder [10].

However, genetic factors and positive family history seem to be less important with age. There is some evidence to suggest that late-onset bipolar disorder may more commonly be secondary to systemic medical and other CNS illness etiologies [11]. The strongest relationship seems to be that between late-onset bipolar disorder and neurologic illness, including neurodegenerative disorders and cerebrovascular disease [6]. The inflammatory cytokines, particularly TNF-α, and brain-derived neurotrophic factor (BDNF) have both been suggested as staging biomarkers for bipolar disorder [8, 12]. Life stress and trauma, which tend to negatively influence the course of bipolar disorder, seem to be associated with decreased BDNF levels in bipolar patients of all ages [12].

Neuroimaging studies appear to indicate that older patients with bipolar disorder may show increased signs of atrophy and cerebral vascular lesions compared with normal age-matched control subjects [6]. Results of studies indicate a range of changes from enlargement of third and lateral ventricles, reduction in gray matter volumes, and increase in white matter hyperdensities to the presence of right hemispheric lesions in manic patients [12–14].

Teaching Point
Bipolar disorder in late life reflects not only genetic vulnerabilities but also the interplay between comorbid conditions, illness episodes, the effects of treatments, and life experiences throughout the life span [15].

11.1.4 Clinical Description

Bipolar I Disorder

The key feature in diagnosing bipolar I disorder is the presence of a manic episode. While individuals with this disorder may also experience hypomanic episodes or depressive episodes, mania is what differentiates it from the other bipolar categories. During an episode of mania, the mood is typically euphoric and elated, often interspersed with periods of extreme irritability or agitation. Impulsive and disinhibited behaviors, such as increased money spending, sexual promiscuity, and reckless driving, can often occur in mania, often leading to detrimental consequences. And even though an individual may engage in more activities, their lack of concentration and distractibility often leads to unfinished projects. Their thoughts are often hard to follow as there is frequently a flight of ideas. The person will also feel that their thoughts are racing or going much faster subjectively. Their speech may be noticed by others to be very rapid and even to the point of being pressured—hard for others to interrupt. Decreased need for sleep is a very common symptom seen during a manic episode. Despite sleeping less than the person's usual, he or she will feel quite rested and in fact often feel very energetic.

Although depressive episodes usually occur more often than manic episodes in most patients with bipolar disorders, its occurrence is actually not necessary in the diagnosis of bipolar I disorder. In other words, a person can be diagnosed with bipolar I disorder even if they have only ever had manic episodes, whereas a person with only depressive episodes in the past would be diagnosed with a depressive disorder. Depressive symptoms can also occur during a manic episode (as in a manic episode with mixed features), but the symptoms may only last moments, hours, or, very occasionally, days.

Clinical features of geriatric bipolar disorder do differ from those in the general adult population. Cognitive deficits and comorbid systemic medical illness are much more common. Hypersexuality is less common. Comorbid psychiatric disorders are common in bipolar disorder, the most common being anxiety disorders and substance use disorders, although less common in older adult patients.

Teaching Point
When considering a management plan, it is imperative to treat any comorbid conditions to improve chances of full recovery.

Bipolar II Disorder

In bipolar II disorder, the person must have had at least one hypomanic episode and at least one major depressive episode. While the hypomanic episodes themselves may not cause excessive functional impairment in the person's life, impairment from the depressive episodes can be devastating. Thus, while a hypomanic episode may be considered a "less severe" form of a manic episode, bipolar II disorder is often no less impairing than bipolar I disorder.

In bipolar II disorder, the illness often begins with a depressive episode; thus the diagnosis of bipolar II disorder is not actually made until a hypomanic episode occurs. In fact, one may have several major depressive episodes before the first recognized hypomanic episode. It is also possible for someone to have been diagnosed with bipolar II disorder to ultimately experience a full manic episode, in which case, the diagnosis will change to bipolar I disorder.

As with bipolar I disorder, anxiety disorders and substance use disorders are common comorbid conditions with bipolar II disorder, co-occurring in about 75% and 37% of patients, respectively [1]. Eating disorders can also occur in about 14% of those with bipolar II disorder, usually more common in younger patients, with binge-eating disorder being more common [1].

11

Cyclothymic Disorder

Persons with cyclothymic disorder typically experience at least a 2-year period of having numerous periods of hypomanic symptoms and periods of depressive symptoms that are distinct from each other. However, the symptoms are such that they do not meet the full criteria for either a hypomanic episode or a major depressive episode, as the symptoms are usually less severe, less pervasive, and/or of shorter duration. During that 2-year period, the person has not been without symptoms for longer than 2 months at a time. If, after receiving the diagnosis of cyclothymic disorder, that person goes on to experience a major depressive episode, a manic episode, or a hypomanic episode at a later time, then the diagnosis changes and the diagnosis of cyclothymic disorder no longer applies. Substance-related disorders and sleep disorders may co-occur in those with cyclothymic disorder.

Substance/Medication-Induced Bipolar and Related Disorder

The presentation of someone with substance/medication-induced bipolar and related disorder is essentially the same as that of someone with bipolar I, bipolar II, or cyclothymic disorder. However, the disturbance in mood occurs either during, or soon after substance intoxication or withdrawal, or after exposure to a medication. The key exception is the occurrence of hypomania or mania after antidepressant medication use (or other somatic treatments such as electroconvulsive therapy) that persists beyond the expected duration of psychological effects of the medication or other somatic treatment. In that circumstance, the diagnosis is bipolar disorder, not substance/medication-induced bipolar and related disorder.

Depending on the triggering agent, the onset of symptoms may occur anywhere from within minutes (as in stimulant-induced manic or hypomanic states) or days (as in corticosteroids or immunosuppressant medications-induced hypomanic/manic or depressive state).

Bipolar and Related Disorder Due to Another Medical Condition

As with substance/medication-induced bipolar disorders, the clinical presentation of a bipolar illness due to a systemic or other CNS medical condition is often indistinguishable from that of a bipolar I or bipolar II disorder. While in most cases the symptoms of bipolar disorder appear during the initial presentation of the other medical condition, there are also instances where a chronic systemic/CNS medical condition may be the underlying cause. The most common systemic/CNS medical conditions that may lead to a bipolar disorder include Cushing's disease, multiple sclerosis, strokes, and traumatic brain injuries.

Other Specified Bipolar and Related Disorder

This category applies to patients who may have had major depressive episodes but also have experienced symptoms that do not quite meet criteria for a hypomanic episode. Or, if the patient has had a hypomanic episode, he/she has never met criteria for a major depressive episode. The other specified bipolar and related disorder diagnosis may apply if patients have met all criteria for cyclothymic disorder other than the time criteria (i.e., duration of less than 2 years).

With Mixed Features Specifier

DSM IV criteria for mixed episodes required both full diagnostic criteria for both major depressive disorder and mania simultaneously for a mixed episode, whereas the change to DSM-5 only requires full criteria for major depressive disorder and three symptoms of mania/hypomania in a depressive episode with mixed features or full criteria for mania/hypomania and three symptoms of depression in a manic or hypomanic episode with mixed features (see Table 11.3).

Bipolar Spectrum Disorder

The definition for this disorder, not a DSM-5 disorder, was proposed by Ghaemi et al. in 2002 [16] and includes patients with at least one major depressive episode, no spontaneous mania or hypomania, and a series of risk factors including a positive family history of bipolar disorder, antidepressant-induced mania/hypomania, and a list of other clinical features such as the presence of psychosis, postpartum onset, atypical depressive symptoms, hyperthymic personality, and lack of response to several antidepressant trials [16]. This entity requires skilled practitioners to assess and monitor for risk factors for bipolar disorder and to manage it with complex pharmacological combinations.

It is important to note that functional decline, often due to cognitive impairment, is more common in geriatric bipolar disorder and is a source of significant caregiver burden. Geriatric bipolar disorder does not "burn out," and chronic

Table 11.3 Highlights of the DSM-5 diagnostic criteria for mixed features specifier for a manic or hypomanic episode vs. mixed features specifier for a depressive episode [1]

Mixed features specifier for a manic or hypomanic episode	Mixed features specifier for a depressive episode
Three (or more) depressive symptoms are present during the current or most recent episode of mania/hypomania: (1) dysphoria or depressed mood, (2) diminished interest/ pleasure in activities, (3) psychomotor retardation, (4) loss of energy, (5) worthlessness/inappropriate guilt, (6) suicidal ideation/plan or suicide attempt	Three (or more) manic/hypomanic symptoms are present during the current or most recent episode of depression: (1) elevated/expansive mood, (2) inflated self-esteem/grandiosity, (3) decreased need for sleep, (4) talkative/pressured speech, (5) flight of ideas/racing thoughts, (6) increased activities with painful consequences, (7) increased energy or goal-directed activity
Medical/substance-induced condition exclusion	Medical/substance-induced condition exclusion
If both manic and depression criteria is met simultaneously, diagnosis is manic episode, with mixed features	If both depression and manic criteria is met simultaneously, diagnosis is depressive episode, with mixed features

mood episodes, particularly depression, commonly occur. Mortality from suicide and general medical conditions is elevated.

11.1.5 Diagnostic Evaluation

Clinical History

Response to treatment depends on the accuracy of diagnosis. In order to make an accurate diagnosis, a thorough clinical history must be obtained. Patients most often tend to seek help in a depressive state, not in a manic state (especially if the symptoms are more hypomanic than manic). Thus, even when the person is presenting in the midst of a depressive episode, it is imperative to have a clear understanding of not only the symptoms of the current episode, but also of past mood episodes to avoid misdiagnosis.

Evaluation of the patient's risk of suicide is critical, as suicide completion rates in patients with bipolar I disorder can be anywhere from 10% to 15% [17], among the highest rates of all psychiatric disorders. Common suicide risk factors for suicide are listed in Table 11.4 [17]. (Also see ▶ Chap. 28, *Psychiatric Emergencies in Older Adults*.) Once a risk assessment is done, a comprehensive treatment plan should include plans to address and, if possible, minimize any modifiable risk factors.

Cognitive functions can be impaired and slowed during a depressive or manic episode, especially in geriatric patients, to mimic that of a neurocognitive disorder. The person may experience not only memory difficulties but disorientation and confusion. The term "pseudodementia" has been used to describe cognitive difficulties during mood episodes, particularly depression. This pseudodementia is usually distinguished from a progressive neurocognitive disorder by its relatively acute/subacute onset, likely coincidental with the onset of the mood episode, and the lack of prior cognitive disturbance. Once thought to be entirely reversible, there is now evidence that pseudodementia, when prominent, may in fact be a harbinger of an underlying neurocognitive disorder. In addition, it is also important to recognize that chronic psychiatric illness itself will likely have an impact on cognition—in other words, a patient with chronic bipolar disorder is at a higher risk of developing major or mild neurocognitive disorder or other cognitive impairments with age [2].

Table 11.4 Suicide risk factors [17]

Risk factors for suicide	Presence of suicidal or homicidal ideation, intent, or plan
	Male sex
	Age > 65 years
	Access to means for suicide (e.g., guns, knives)
	Presence of psychotic symptoms (especially command hallucinations)
	Presence of severe anxiety symptoms
	Presence of alcohol or other substance use
	Chronic medical illness (including chronic pain)
	Previous suicide attempt
	Family history of suicide attempt

It is very important to assess for the presence of psychotic symptoms. Although not necessary for the diagnosis, delusions (e.g., paranoia, hyperreligiosity, grandiosity) frequently occur in the midst of a manic episode. Auditory or visual hallucinations can also be present. Psychosis can also be part of the symptomatology of a severe depressive episode. Although previous studies suggested that the rate of psychosis may be greater in the older population with bipolar disorder, more recent studies show that the mean rate of psychosis in the older adults is estimated to be 64%, which is similar to that of the general adult population [6].

In the older patient with bipolar disorder, as expected, there is a higher incidence of systemic medical comorbidities, given that comorbid medical complexity increases with age. Older bipolar patients are more likely to have diabetes mellitus, cancer, thyroid disorders, and hypertension compared to age-matched controls [2]. Bipolar disorder is also found to be

associated with an increased risk of having a chronic pain condition [18]. These medical comorbidities impact on the bipolar disorder itself but also have implications in terms of treatment plans, as there may be potential interactions between drugs. Thus, it would be important to identify any of these potential complicating factors when considering management.

A thorough history needs to be taken of the patient's history of illicit substance use, as well as history of alcohol use and use of over-the-counter or herbal medications. The use and abuse of these substances, in and of itself, can lead to depressive, manic, or hypomanic symptoms. In substance-induced mood episodes, if possible, the intoxication should be allowed to run its course (unless the patient is acutely agitated), to allow for the resolution of the psychiatric symptoms.

As mentioned in previous sections, comorbid psychiatric conditions commonly co-occur with bipolar disorders. Goldstein et al. reported the lifetime prevalence of alcohol use disorder in geriatric bipolar patients is 38% [19]. These geriatric patients also had a 20.5% lifetime prevalence of generalized anxiety disorder and a 19% lifetime prevalence of panic disorder. As these conditions can significantly influence the course of the bipolar illness, treatment of any comorbid psychiatric conditions may impact on the recovery from bipolar disorder.

11

Physical Examination

Along with a comprehensive clinical history, a complete physical examination, including a neurological exam, can also be helpful in evaluation of bipolar disorder. With the concern of increasing medical comorbidities in the aging population, any physical illnesses need to be identified at the early stage of diagnosis so that a comprehensive treatment plan can be developed. For example, patients taking antipsychotic medications may show signs of extrapyramidal symptoms, or patients with hyponatremia may present with delirium. These findings will have significant impact on diagnosis and management planning.

Laboratory Examination

As it would be important to consider any comorbid systemic medical conditions as well as the possibility of ruling out delirium, routine laboratory workup for bipolar disorder should include a complete blood count and checking for renal and hepatic function, thyroid, and parathyroid function. As some of the psychotropic medications used to treat bipolar disorder may impact physical health, other tests to consider may include hemoglobin A1c, fasting glucose levels, and lipid profile. In the geriatric patient, calcium, albumin, magnesium, phosphate, and serum B12 may be considered, especially if nutritional status has been a concern. If infection is suspected, consider a chest x-ray or urinalysis to identify the source of infection. A patient with a significant cardiac history will warrant an electrocardiogram, especially if he/she was on any medications that may increase the risk of QTc prolongation (as with most antipsychotic medications).

The role of clinical neuroimaging in bipolar disorder has been controversial. However, in a patient aged 50 years or older with new onset of psychiatric symptoms, or in the case of new onset of psychosis, a case may be made for neuroimaging, especially if there are neurological findings on the physical exam or presence of comorbid cognitive deficits. Neuroimaging can be informative in establishing a baseline to monitor for change and can also potentially be diagnostic, particularly in cases of cerebrovascular disease.

11.1.6 Differential Diagnosis

As a patient with bipolar disorder may experience several depressive episodes before the index manic or hypomanic episode, bipolar disorder should always be considered in the differential diagnosis of patients with major depressive disorder. Conversely, major depression is often in the differential diagnosis for bipolar disorder, especially when the patient presents in a depressive state, and little corroborating history is available for past mood episodes. Irritability is a symptom that can be observed in either a depressive episode or a hypomanic/manic episode. Agitation from severe anxiety may mimic the agitation seen in hypomanic or manic patients, or anxious ruminations can be mistaken for racing thoughts, and a primary anxiety disorder needs to be considered both in the differential diagnosis and also as a comorbid disorder. For those presenting with psychotic symptoms (either in the context of manic symptoms or depressive symptoms), a primary psychotic disorder should be ruled out. Substance/medication-induced disorders should be considered especially in someone who has had a history of substance use. A primary diagnosis of bipolar disorder can only be made if the symptoms remain once substances/medications are no longer being used. Attention-deficit/hyperactivity disorder should also be considered in the differential, as many symptoms of this disorder (e.g., rapid speech, distractibility, and racing thoughts) overlap with symptoms of mania; however, this association is much less likely to apply to older adults. Personality disorders, especially borderline and narcissistic personality disorders, can also have substantial overlap with symptoms of hypomania or mania as mood lability, and impulsivity is common in both conditions. It can be challenging to distinguish bipolar II from borderline personality disorder, given the prevalence of mood symptoms in the latter. In the older population, delirium is common, particularly in the hospitalized patient. Delirium, which can mimic symptoms of mania or depression in an agitated, psychotic, and acutely confused older patient, must be ruled out.

11.1.7 Treatment

Non-pharmacological Treatment

Bipolar disorder is a chronic illness characterized by remissions and relapses. While there is no cure, treatment of the disorder and its symptoms can significantly decrease the associated morbidity and mortality [17]. In addition to pharmacotherapy, patients who suffer from this illness do best

with long-term management by a multidisciplinary team. Literature supports the idea that having a collaborative care model can increase the likelihood of guideline-concordant therapy [20].

Interventions such as group psychoeducation (for both patients and family members), cognitive behavior therapy, and interpersonal and social rhythm therapy have been shown to demonstrate benefits in decreasing relapse rates and increasing functioning and medication adherence [21]. Psychoeducation is often aimed at promoting awareness of stressors and addressing early signs of relapse. In the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, patients who received intensive psychosocial treatment in addition to pharmacotherapy had a significantly higher rate of recovery at year-end, as well as shorter times to recovery [22]. The American Psychiatric Association (APA) practice guidelines also recommend helping the patients establish regular patterns of daily activity and sleep [17]. There is some literature supporting that close social interactions (such as family support) in older adults with bipolar disorder may help limit the length of episode and be associated with less severe symptoms at presentation [23]. It should be noted that many patients with bipolar disorder suffer from chronic refractory symptoms and functional and interpersonal impairment. Recovery model rehabilitation programs can provide support, help to reduce suffering, and optimize functional improvement.

Electroconvulsive therapy (ECT) is highly effective for bipolar depression. Studies support that ECT is as effective for bipolar depression as it is for unipolar depression [24]. ECT has been used to treat mania since the 1940s. Case reports and case series are suggestive of the benefits of ECT on a maintenance basis to prevent mood episodes in patients with bipolar disorder [17]. In the geriatric population, ECT is a reasonable treatment option, especially as geriatric patients may have poorer tolerance for pharmacotherapy due to side effects or drug-drug interactions and often demonstrate superior benefit from ECT. The Canadian Network for Mood and Anxiety Treatments (CANMAT) guidelines suggest that ECT should be considered earlier in patients who have psychotic bipolar depression, in those at high risk for suicide, and in those who are not drinking or eating, leading to compromised physical health [21].

Pharmacological Treatment

Pharmacological interventions remain an integral part in managing individuals with bipolar disorder. In the acutely manic patient, the person's level of agitation is often a barrier to therapy and may present as a safety risk. Thus, treatment of the acute agitation can be a priority. Most guidelines would suggest using oral agents first as they can be as effective as intramuscular agents [21]. It is only in circumstances where oral therapy cannot be administered that intramuscular (IM) injections should be considered. It should be noted that there are no medication treatment guidelines specifically aimed at older adults, and the results from current guidelines are extrapolated to apply to older patients.

The CANMAT guidelines suggest that oral atypical antipsychotics (e.g., risperidone, olanzapine, quetiapine) should be considered first in treatment for acute agitation. If IM medications are needed, then olanzapine, ziprasidone, and aripiprazole or the combination of haloperidol and a benzodiazepine can be considered. If using parenteral olanzapine, avoid concomitant use of IM benzodiazepines due to risk of respiratory depression. Benzodiazepines are useful adjuncts, but should not be used as monotherapy [21].

In treatment of manic episodes, the use of lithium and divalproex has been well established. Antipsychotic medications have also demonstrated efficacy in various studies. The first- and second-line recommendations from the CANMAT guidelines are listed in Table 11.5 [17, 21]. In the 2013 guidelines update, monotherapy with asenapine, paliperidone extended release, and divalproex extended release, as well as adjunctive asenapine, have been added as first-line options. The APA guidelines suggest monotherapy with lithium, divalproex, or olanzapine in a less ill manic patient and either lithium plus an antipsychotic or divalproex plus an antipsychotic for the more severely ill patients.

For the treatment of bipolar depression, monotherapy with lithium, lamotrigine, and quetiapine, as well as combination therapy with lithium or divalproex plus selective

Table 11.5 Recommendations for pharmacological treatment of acute mania in the general population [17, 21]

	CANMAT guidelines	APA guidelines
First-line options	Lithium, divalproex, olanzapine, risperidone, quetiapine, aripiprazole, ziprasidone, asenapine, paliperidone ER, lithium or divalproex + risperidone, lithium or divalproex + quetiapine, lithium or divalproex + olanzapine, lithium or divalproex + aripiprazole, lithium or divalproex + asenapine	Lithium, divalproex, olanzapine, risperidone, lithium + antipsychotic, divalproex + antipsychotic
Alternative options	Carbamazepine, haloperidol, lithium + divalproex, chlorpromazine, clozapine, oxcarbazepine, tamoxifen, lithium or divalproex + haloperidol, lithium + carbamazepine, adjunctive tamoxifen	Carbamazepine or oxcarbazepine in lieu of lithium or divalproex, ziprasidone or quetiapine in lieu of another antipsychotic, clozapine

Note: APA American Psychiatric Association, *CANMAT* Canadian Network for Mood and Anxiety Treatments, *ER* extended release

Table 11.6 Recommendations for pharmacological treatment of acute bipolar I depression in the general population [17, 21]

	CANMAT guidelines	APA guidelines
First-line options	Lithium, lamotrigine, quetiapine, lithium or divalproex + SSRI[a], olanzapine + SSRI[a], lithium + divalproex, lithium or divalproex + bupropion	Lithium, lamotrigine, lithium + antidepressant
Alternative options	Divalproex, lurasidone, quetiapine + SSRI[a], adjunctive modafinil, lithium or divalproex + lamotrigine, lithium or divalproex + lurasidone, carbamazepine, olanzapine, lithium + carbamazepine, lithium + pramipexole, lithium or divalproex + venlafaxine, lithium + MAOI, lithium or divalproex or atypical antipsychotic + TCA, lithium or divalproex or carbamazepine + SSRI[a] + lamotrigine, quetiapine + lamotrigine	Adjunctive: Lamotrigine, bupropion, paroxetine, another SSRI, venlafaxine or MAOI

Note: APA American Psychiatric Association, *CANMAT* Canadian Network for Mood and Anxiety Treatments, *MAOI* monoamine oxidase inhibitor, *SSRI* selective serotonin reuptake inhibitor, *TCA* tricyclic antidepressant
[a]Except paroxetine

Table 11.7 Recommendations for maintenance pharmacotherapy of bipolar disorder in the general population [17, 21]

	CANMAT guidelines	APA guidelines
First-line options	Lithium, lamotrigine, divalproex, olanzapine, quetiapine, risperidone long-acting injection, aripiprazole, lithium or divalproex + quetiapine, lithium or divalproex + risperidone long-acting injection, lithium or divalproex + aripiprazole, or lithium or divalproex + ziprasidone	Lithium, divalproex
Alternative options	Carbamazepine, paliperidone ER, lithium + divalproex, lithium + carbamazepine, lithium or divalproex + olanzapine, lithium + risperidone, lithium + lamotrigine, olanzapine + fluoxetine, asenapine, adjunctive: phenytoin, clozapine, ECT, topiramate, omega-3-fatty acids, oxcarbazepine, gabapentin, asenapine	Lamotrigine, carbamazepine, oxcarbazepine

Note: APA American Psychiatric Association, *CANMAT* Canadian Network for Mood and Anxiety Treatments, *ER* extended release

serotonin reuptake inhibitors (SSRIs) or bupropion and olanzapine plus SSRI, are first-line treatment options (see Table 11.6) [17, 21]. It should be noted that when lamotrigine is used as monotherapy, it does not protect against development of mania. Lurasidone as monotherapy and lurasidone or lamotrigine plus lithium or divalproex has been added as second-line options in the updated CANMAT guidelines. The US guidelines recommend using either lithium or lamotrigine as first-line treatment and, if not effective, then can consider the addition of SSRIs, bupropion, venlafaxine, or a monoamine oxidase inhibitor [17]. The role of antidepressants in patients with bipolar disorder remains very controversial, despite its presence in both the Canadian and US guidelines for treatment of bipolar disorder.

In maintenance therapy for bipolar disorder, it makes intuitive sense that the treatment that worked in the acute phase should be effective in preventing recurrence. Adherence to pharmacotherapy remains a challenge for many patients given the stigma of psychiatric illness, side effects from medications, and patient attitudes. Table 11.7 is a summary of the CANMAT and APA guidelines for maintenance pharmacotherapy for bipolar disorder [17, 21].

Bipolar disorder, particularly bipolar depression, is a complex and challenging disorder to treat and is best managed by specialists. This is especially true of bipolar disorder in the geriatric population where the confounding effects of age, cognition, frailty, and medical complexity magnify the challenges of treatment.

11.2 Case Studies

Common diagnostic challenges and management concerns that clinicians may encounter in older adults with bipolar disorder are illustrated in the following two case studies. The interplay of systemic medical complexities in the geriatric population with various mood symptoms is also emphasized.

11.2.1 Case 1

Case 1 History

Mrs. R., a 67-year-old retired teacher, has struggled with recurrent major depressive episodes throughout her life beginning in her late 20s. It was not until 2 months ago that she started experiencing some manic symptoms. She presents tonight to the emergency room with her husband, who was becoming increasingly concerned that Mrs. R. was "not acting like herself."

At first, her husband noticed some restlessness; Mrs. R. seemed to have a hard time relaxing. It then progressed to an inability to fall asleep and stay asleep. For the past 6 weeks, she has been averaging 3–4 hours of sleep per night, compared to her usual of 8–9 hours. In the past month, she has also taken on some new projects within the home. She decided to renovate their kitchen, their master bathroom, and redo their backyard deck all within the same week. She has contacted numerous contractors and purchased various home improvement magazines and books, but has not been able to progress further into the planning stages as she becomes easily distracted by other things. When her husband asks her to slow down and perhaps just focus one project, she becomes irritated and yells that he never lets her do anything that she wants. He feels that she is much more short tempered in the past month.

In the past week or so, she has spent most of the day in church, praying. Although Mrs. R. is a Christian, she typically goes to church only once or twice a month. She indicated to Mr. R. that she has been going more often in the past week because she needs to repent her past sins. She has a "feeling" that if she does not repent her sins, then something horrible would befall her family.

On mental status examination, Mrs. R. appeared well groomed but dressed a youthful, "trendy" style. She was annoyed at having to come to the hospital as she felt there was nothing wrong with her. Her thought process was tangential but she was able to be redirected with some effort. Initially, Mrs. R. scoffed at the question of suicide but, later on, made the comment that if she had to stay in the hospital any longer, hospital staff might as well "kill me now" as she cannot stand to be in a "prison." Throughout the assessment, she was pacing back and forth in the interview room.

Medically, Mrs. R. is relatively stable. While she does have a history of hypertension and dyslipidemia, both these conditions are well controlled with medications. Her hypothyroidism has also been stable over the past years with her laboratory results being monitored regularly by her primary care physician. She had a previous fracture of her right tibia and fibula about 10 years ago from a skiing accident that did require surgical intervention. She has struggled with chronic pain in her lower right leg as a result.

Her medications, which her husband brought in a dosette, include ramipril 5 mg qam, atorvastatin 40 mg qsupper, escitalopram 15 mg qhs, lorazepam 2 mg qhs, pantoprazole 40 mg ac meals, and levothyroxine 75 mcg qam.

Her vital signs on initial presentation showed a blood pressure of 132/76 mm Hg, heart rate of 103 BPM, and O_2 saturation at 98%. The emergency physician ordered basic laboratory investigations including complete blood count (CBC), electrolytes, creatinine, estimated glomerular filtration rate (eGFR), total bilirubin, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, and thyroid-stimulating hormone, which were all within normal limits.

The emergency physician determines that Mrs. R. may be at imminent risk and asks the question whether she should be on a psychiatric commitment order based on Mrs. R.'s comments about killing herself if she needed to remain in the hospital. She has been referred to you, the emergency psychiatric consultant, for further assessment and management of her suicide risk, mood, and behavior.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What other information do you need in order to make an accurate diagnosis?

? Question 2. What is your differential diagnosis?

? Question 3. Are there any other investigations you may consider to help make your diagnosis?

? Question 4. Given the acuity of presentation, and the risk factors, you decide to admit this patient to the acute psychiatry unit on a psychiatric commitment order. Outline your management plan in the emergency department prior to admission to a ward bed.

Case 1 Answers

Case 1 Answer 1 (Question 1—What other information do you need in order to make an accurate diagnosis?)

A1.1. A thorough clinical history needs to be obtained to determine if there were any triggers or precipitants to the current manic episode. Things that may warrant further clarification may include:

- Was there any history of substance use that may have precipitated the episode?
- Have there been any recent medication changes prior to the onset of symptoms?
- Are there any recent changes/stressors in Mrs. R.'s life?
- Is there any evidence on history to support the suggestion that prior episodes may have included sub-threshold hypomanic symptoms not formally diagnosed?

After some discussion, it was revealed that Mrs. R. has recently purchased some cannabis oil from her neighbor as she has heard from friends that using marijuana may help with her lower leg pain. She did not think that using cannabis oils would be a concern, as she is not smoking it. She cannot recall how much she has been using but thought that the oils were certainly helping to alleviate her pain.

Mrs. R.'s son has been struggling with marital issues and has moved out of his home into Mrs. R.'s home about 3 months ago. Mrs. R. admits she has been quite concerned about her son and is not sure how to help him. She grudgingly admits that her worries may have been keeping her up the last few nights, and perhaps she is not sleeping as much as she does normally.

A1.2. An in-depth past psychiatric history should be obtained from Mrs. R., specifically her past depressive

episodes. How many has she had in the past and what was the severity? Has she ever had psychotic symptoms in context of a depressive episode? It would also be important to assess for any comorbid psychiatric conditions such as anxiety disorder. Knowing her past medication history, especially the use of any other psychotropics may also yield helpful information (e.g., past use of lithium or antipsychotics as adjunct to her antidepressant).

Mrs. R. tells you that she has had about eight or nine times in her life where she struggled with depression. She has never needed a hospital admission but has seen a therapist on and off to help "talk things out." Her current antidepressant escitalopram was prescribed by her primary care physician about 6 months ago; when she thought her mood was dipping low again. Prior to the escitalopram, she was on citalopram 20 mg daily about 5 years ago but only stayed on it for about 8 months as she had significant sexual side effects from it. She was also on a small dose of amitriptyline (5–10 mg) at bedtime in the past to help with insomnia.

A1.3. Collateral history from her husband should be obtained if at all possible. Mrs. R. seems to have very little insight into her current presentation, which may make her an unreliable historian. The patient's husband may be able to offer better insight to the presence of possible psychotic symptoms.

Mr. R. was able to tell you that the patient has been praying at least 3–4 hours a day as she believes that she has done something wrong in the past that she needs to repent for. If he were to interrupt her praying, she would get very angry and start yelling and crying. She would tell him that she is "going to hell" because he will not let her pray.

A1.4. An assessment of her suicide risk must be undertaken, as she did voice some suicidal thoughts. It is likely in Mrs. R.'s case that her expressed thoughts of harming herself are in context of her being held at the hospital (as she has never voiced any prior to her visit to the emergency room). However, given the high suicide rate of patients with bipolar disorder, suicide risk must be thoroughly assessed in all patients with bipolar disorder. If Mrs. R. is indeed thought to present a significant suicide risk, this would have an impact on her management plan (i.e., she would need hospitalization for safety risk reasons).

Mrs. R. denies wanting to harm herself. She admits that she only said she might as well kill herself if she had to be hospitalized, as she does not believe she needs to be at the hospital and wants to go home. She indicated that she needed to go home so she can make phone calls to the contractor and get her home projects started.

Case 1 Answer 2 (Question 2—What is your differential diagnosis?)

Mrs. R.'s differential diagnosis includes the following:

A2.1. *Bipolar disorder, current manic episode, with mood-congruent psychotic symptoms.* Mrs. R. presents with a history of increased agitation and irritability. She has not been sleeping as much as usual, but seems to have increased levels of energy. She has started multiple home projects (goal-directed activity) but does not seem to be able to follow through with any of the projects as she gets easily distracted. Her husband reports her to be hyperreligious (praying most of the day for her sins). These are all symptoms consistent with a manic episode.

A2.2. *Major depressive disorder, with psychotic symptoms.* Mrs. R. has reportedly struggled with recurrent major depressive episodes on and off since her 20s. She has admitted that her worries about her son's marital issues have led to insomnia. Her husband noted her to be more irritable in the past month or so. She does have trouble concentrating (e.g., not able to complete her home projects) and believes she has "sinned" and needs to pray in order to gain forgiveness. However, the increase in goal-directed activity and the lack of fatigue despite sleeping less make this diagnosis less likely.

A2.3. *Schizoaffective disorder, bipolar type.* Her excessive praying and unusual beliefs regarding having sinned began around the same time that her husband noticed the other symptoms. The provided history seems to suggest that mood (i.e., irritability) is the predominant symptom rather than the psychosis, which puts this diagnosis lower on the differential.

A2.4. *Substance/medication-induced bipolar disorder.* Mrs. R. started using cannabis oil around the time of the onset of her symptoms. It is possible that her psychosis is a result of her ingestion of cannabis oil, although grandiosity and paranoia are usually more common in cannabis use. Mrs. R.'s current presentation also occurs in the context of recent current treatment with an antidepressant (escitalopram 15 mg daily). Thus, an antidepressant-induced manic episode cannot be ruled out at this time.

Case 1 Answer 3 (Question 3—Are there any other investigations you may consider to help make your diagnosis?)

- Ordering a urine toxicology screen may be helpful to see if the cannabis oils that Mrs. R. has been using are not contaminated with any other substances. You find out that her results are positive for cannabis only.
- As this is Mrs. R.'s first presentation with psychotic symptoms, it is reasonable to consider brain imaging to rule out any other possible medical cause of her presentation. Given her history of hypertension and hyperlipidemia, a "silent stroke" is a possibility. You find out that the CT scan of her brain showed some generalized cerebral atrophy and diffuse microangiopathic changes that were felt to be age appropriate with no evidence of prior cerebrovascular accident.

Teaching Point
Establishing baseline neuroimaging in a geriatric patient with vascular risk factors who may have cognitive impairment due to vascular pathology is helpful, particularly in the context of a change in pattern of mood disorder.

Case 1 Answer 4 (Question 4—Given the acuity of presentation, and the risk factors, you decide to admit this patient to the acute psychiatry unit on a psychiatric commitment order. Outline your management plan in the emergency department prior to admission to a ward bed.)

- As Mrs. R. did not actually want to stay in the hospital, she becomes very agitated at the news that she needs to stay. She starts to yell and bang at the exit doors, demanding to be let out. Unfortunately, her behaviors are starting to escalate other patients that are in the emergency room. Mrs. R. is not receptive to any attempts at verbal de-escalation and refuses to engage in further conversation. At this point, it would be reasonable to deliver pharmacological intervention to help manage her agitation level. Intramuscular medications should only be considered if Mrs. R. is not cooperative with any oral medications. Mrs. R. was agreeable to taking a small dose of quetiapine (50 mg) per os as her husband told her it would help her sleep. She agreed that her poor sleep recently may have made her a bit irritable.
- As this is her first presentation of manic symptoms, you decide to put her escitalopram on hold. As she has only been on escitalopram for 6 months, it is possible that her current mood episode may be antidepressant induced. The only way to tell if this is a medication-induced manic episode is to discontinue the medication and see if her symptoms persist.

Case 1 Analysis In Mrs. R's case, she has been diagnosed for many years with a presumed unipolar recurrent major depressive disorder. Despite this, antidepressants were only recently prescribed. Within a few months of being on an antidepressant, Mrs. R. developed classic manic symptoms. However, she has had a trial of citalopram in the past without manic symptoms being induced. While she was on another antidepressant amitriptyline in the past for insomnia, she remained on a very low dose. It is certainly within reason to consider antidepressant-induced bipolar disorder as possible diagnosis, regardless. By definition, the only way to say that it is a true bipolar I disorder versus antidepressant-induced bipolar disorder is if her symptoms persist beyond the usual duration of the effects of the escitalopram after it has been discontinued. Ideally, a period of observation off antidepressants without additional interventions would be helpful in confirming if the escitalopram was indeed the trigger for the manic episode. However, complicating factors, such as the need to minimize length of stay in hospital, would likely result in the escitalopram being discontinued and a mood stabilizer/antipsychotic being initiated immediately for her manic symptoms. An additional factor to consider is the role of cannabis use, which potentially may also be the reason for her manic symptoms.

If instead of being admitted to hospital, you had decided to treat Mrs. R. as an outpatient (i.e., if safety was determined to not be an issue, and you felt that she has a very reliable spouse at home who is a great support), you may choose to simply discontinue the escitalopram and adopt the "wait and see" method. In this scenario, going on the premise that Mrs. R.'s manic symptoms were antidepressant induced, her management plan may change as she may not necessarily require treatment with a mood stabilizer or antipsychotic medication (other than for acute agitation). Very close monitoring for a switch to hypomania/mania would be warranted, particularly if she were to try another antidepressant in the future.

Teaching Point
There is a growing body of evidence to suggest that patients who experience an antidepressant-induced manic episode do in fact have underlying bipolar disorder [26].

11.2.2 Case 2

Case 2 History

Mr. K., a 74-year-old widowed retired lawyer, has been referred to your outpatient clinic for a geriatric psychiatry consultation regarding further diagnostic assessment and management for a late-onset psychiatric disorder characterized by mood, psychotic, and cognitive symptoms. Mr. K. was recently discharged from acute mental health unit at the local hospital after a 6-week admission. Mr. K. was brought to the hospital by police at the time of admission as he was found to be quite belligerent and was behaving bizarrely in the downtown area. Mr. K. was dressed inappropriately in T-shirt and shorts when he was found (it was -5° C outside that day). The police officers were not able to follow his conversation as his speech was pressured and tangential, sometimes talking about being a spy trying to bring down a conspiracy. Thus, they brought him to the hospital for assessment. He was subsequently admitted to the acute mental health unit from the emergency department, having been medically cleared by the emergency physician (routine laboratory studies and CT brain imaging were within normal limits, except for urinalysis showing a urinary tract infection; a 3-day course of oral antibiotics was started).

The referring inpatient psychiatrist has included the discharge summary from his hospital stay. You find out from the note that Mr. K. has never had any previous contact with psychiatric care. In fact, according to collateral information from his only daughter, Mr. K. has always been a happy-go-lucky person and has always worked hard in his life to look after his family. Mr. K. retired from his job at a prestigious law firm after suffering a heart attack at 59 years old. Other than the heart attack, Mr. K. has been relatively healthy and has not had any other health issues. His wife passed away from lung cancer 3 years ago and he has been living alone in

condominium at a retirement village ever since. His daughter is his only family as his older brother passed away more than 10 years ago from a stroke.

During his previous stay in the hospital, Mr. K. was started on risperidone 0.5 mg qhs for his bizarre thoughts. He did not sleep very much for the first 3 nights, maybe sleeping 2–3 hours per night, and would often wander up and down the hallways muttering to himself or laughing and giggling nonstop. The attending psychiatrist added clonazepam 0.5 mg qhs, after which Mr. K. started sleeping better. Although he no longer talked about being a spy involved in a conspiracy within a few days of initiating the risperidone, he was still noted to be quite grandiose, constantly talking to everyone, telling others that he is in the midst of a very high-profile trial as he is a very good lawyer. He was often promising other patients who were on the ward that he could help them out and sue the hospital for improper treatment after he gets discharged. His dose of risperidone was then slowly increased over the next week up to 1.5 mg qhs. Unfortunately, at this dose, he was found to have an unsteady gait and so the risperidone was lowered to 1 mg qhs. By the third week, Mr. K.'s demeanor started to change. Instead of spending his days talking with others and being intrusive, he started to isolate himself in his room, only coming out when staff would tell him that it is mealtime. Mr. K. appeared now depressed and admitted to feeling that "there was no point to life." The inpatient psychiatrist subsequently added a small dose of lithium, as the diagnosis of bipolar disorder was being entertained. With a dose of 450 mg of lithium per day, Mr. K.'s mood improved significantly over the next couple of weeks. By the end of his hospital stay, Mr. K. felt that he was almost his normal self and he was discharged back home, with a referral to the outpatient psychiatric clinic for follow-up. His lithium level drawn 3 days prior to discharge as 0.64 mmol/L (or 0.64 mEq/L) (normal therapeutic range for adults is between 0.7 and 1.2 mmol/L, [or mEq/L]).

His discharge medications were risperidone 1 mg qhs, lithium carbonate 450 mg qhs, clonazepam 0.5 mg qhs, enteric coated aspirin 81 mg qam, metoprolol 12.5 mg bid, lisinopril 5 mg qam, rosuvastatin 10 mg qsupper, vitamin D 1000 IU qam, and vitamin B_{12} 1000 mcg qam.

Mr. K. presents to your office for the consultation 4 weeks after being back in his apartment. He is unable to remember many details prior to the hospitalization, or details of his inpatient stay, saying that "everything was a bit of a blur." His daughter, who accompanies him to the medical appointment today, is also not able to offer much information as she was away on vacation the 3 weeks prior to his hospitalization. Mr. K. was able to recall feeling so down when he was on the ward that he did not want to get out of bed or do anything on some days and was pleased that he was no longer feeling this way. He does think that he currently is back to his normal self in terms of his mood, sleep, and activity. However, he has noticed a slight tremor in his hands and some daytime drowsiness that was not present prior to his hospitalization and wonders if it could be due to his medications.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. Do you agree with the inpatient physician's diagnosis of bipolar disorder? What other diagnoses would you consider in the differential?

? Question 2. What is your short-term management plan?

? Question 3. Are there any other factors you need to consider for long term?

? Question 4. After continuing to follow Mr. K. in the outpatient clinic for 18 months without further mood episodes, maintained just on lithium 450 mg daily, Mr. K. wants to know if he can discontinue his psychotropics. What do you tell him?

Case 2 Answers

Case 2 Answer 1 (Question 1—Do you agree with the inpatient physician's diagnosis of bipolar disorder? What other diagnoses would you consider in the differential?)

Despite the late age of onset, and no prior mood or psychotic episodes, it would be reasonable to consider the diagnosis of bipolar I disorder, given the typical presentation. Unfortunately, information is somewhat scant due to Mr. K.'s inability to recall the period prior to his admission. Thus, it is unknown whether he had any mood symptoms in the weeks leading up to his hospitalization. However, he did have some typical symptoms noted early on in his admission suggesting a possible manic episode, e.g., mood lability, pressured speech, decreased sleep, and grandiosity. In addition, he was likely delusional prior to the initiation of risperidone as he was noted to be talking about being a spy involved in a conspiracy. A few weeks into his hospital stay, his mood did switch, and he became more withdrawn, less talkative, and despondent questioning if life is worth living. It seems likely that he switched into a depressive episode at that point (he was likely *not* in a mixed state as his depressive symptoms occurred after the manic symptoms, not during).

Other diagnoses to entertain would be schizoaffective disorder, bipolar type (especially as we do not know whether the psychotic symptoms were more prominent than his mood symptoms at the beginning of his presentation), delirium due to urinary tract infection (this is not the preferred diagnosis as his symptoms persisted well beyond the course of his infection, and there was no mention of fluctuating consciousness, memory deficits, or disorientation), and a major neurocognitive disorder presenting with behavioral disturbance including psychotic and disinhibited symptoms.

Case 2 Answer 2 (Question 2—What is your short-term management plan?)

As it has been more than 4 weeks since his last lithium level and this is a new medication for Mr. K., his serum lithium level should be monitored. In a typical adult with

bipolar disorder, the typical target for serum levels is anywhere from 0.7–1.2 mmol/L (or mEq/L). There is some evidence to suggest that this target should be lowered in the geriatric population, aiming for levels 0.4–0.7 mmol/L (or mEq/L), as symptoms of neurotoxicity can occur in the older population even at "normal" serum levels [25, 26]. In addition to serum lithium levels, renal function (especially as Mr. K. is on lisinopril, which can also compromise renal function), thyroid function, CBC, calcium, and an electrocardiogram (ECG) should be monitored regularly (no less than every 6 months).

Teaching Point

Older patients tend to have more side effects from medications and may often require lower doses when compared to the general adult population because of age-related changes in pharmacokinetics and pharmacodynamics. In addition, as older patients tend to be on multiple drugs, drug-drug interactions also need to be considered, making prescribing for older patients a unique challenge.

Mr. K. should undergo a detailed neuropsychological evaluation to determine cognitive function after his mood symptoms have remitted, as very late-onset mood disorder (after age 60) can be a harbinger of underlying major neurocognitive disorder. Cognitive function should be monitored over time for deterioration.

If not done in the hospital, an ECG should also be obtained, as cardiac conduction abnormalities (including QTc prolongation) can be associated with lithium as well as risperidone use and may be susceptible to cumulative drug effects.

Even though Mr. K. is currently euthymic, he is complaining of tremor and drowsiness, which is likely related to psychotropic medication. As he is currently sleeping well at night, tapering his clonazepam to discontinuation would be a reasonable medication adjustment as it is likely contributing to daytime drowsiness. Both risperidone and lithium may cause hand tremors, thus, decreasing the dose of either of these medications would likely help with this side effect (lithium dosing to be guided by serum levels).

Mr. K. should be educated about lithium toxicity and the common signs and symptoms (see Table 11.8) of this potentially life-threatening condition. His reliability to safely take lithium should be assessed over time.

Case 2 Answer 3 (Question 3—Are there any other factors you need to consider for long-term management?)

It is possible that Mr. K. may be maintained on lithium as monotherapy. A discussion with Mr. K. about the possibility of tapering his risperidone would be reasonable. As polypharmacy is a common issue in the geriatric population, attempts at reducing the number of medications should be made if possible.

Table 11.8 Common signs and symptoms of lithium toxicity

Lithium toxicity	Dizziness
	Nausea and diarrhea
	Vomiting
	Stomach pains
	Hand tremors
	Blurred vision
	Ataxia
	Confusion
	Slurred speech
	Muscle twitches
	Seizures
	Increased deep tendon reflexes

Both the CANMAT and APA treatment guidelines also support concomitant psychosocial intervention during the maintenance phase. Psychoeducation regarding adherence, lifestyle changes (i.e., promotion of exercise), and early detection of prodromal symptoms of recurrence would be beneficial.

Teaching Point

Regular physical activity has been shown to have profound effects for both physical and mental health. Studies support that exercise can have an antidepressant effect and improve self-esteem and cognitive function [27].

Cognitive behavioral therapy (CBT) for the depressed phase of illness may be helpful. Literature also supports a link between bipolar disorders and cognitive dysfunction [2, 8, 28]. Thus, ongoing monitoring of Mr. K.'s cognition and function would be important for early detection of any deficits. Depending on the impairment and whether personal safety becomes an issue, alternative living environments may need to be considered at that time.

Case 2 Answer 4 (Question 4—After continuing to follow Mr. K. in the outpatient clinic for 18 months without further mood episodes, maintained just on lithium 450 mg daily, Mr. K. wants to know if he can discontinue his psychotropics. What do you tell him?)

Bipolar disorder is a chronic episodic illness. Three to 4 years may elapse between the first and second episodes [14]. It is generally recommended for patients with bipolar disorder to remain on treatment indefinitely, as the mood episodes themselves can be quite impairing. Patients are more

likely to stay well if they remain on treatment. As Mr. K.'s first episode involved psychotic symptoms as well as a hospital admission, it would be recommended that he continues on his lithium. However, if after thorough discussion it is still his preference to discontinue the lithium, it would be important to taper him down slowly and monitor closely. Alternative mood stabilizers to lithium, such as divalproex, should be considered if his desire to discontinue lithium is as a result of lithium-specific side effects.

Case 2 Analysis Mr. K. is a gentleman with no previous psychiatric history; in fact, it was not until his 70s that he had first onset of a mood episode. As such, he would have warranted a thorough workup either in the emergency department or early on in his hospitalization to rule out any secondary structural CNS etiologies including major neurocognitive disorders due to multiple etiologies and traumatic brain injury. Neuroimaging would be important as there is evidence for a link between mania and cerebrovascular accidents, especially for lesions in the right hemisphere [29]. Syphilis, though not a disease commonly considered, has been on the rise over the last few years. The rate of reported cases of syphilis has seen a rise of over 100% between 2003 and 2012 [30]. Mania and depression can both present in neurosyphilis [31]. ◘ Table 11.9 lists potential causes of secondary mania [32].

Although Mr. K. was initially started on risperidone by the inpatient psychiatrist, lithium remains a preferred first-line option. In older patients, the general adage of "start low, go slow, but go" is important to remember when initiating medications (see ▶ Chap. 5). As older adults tend to experience more side effects, it would be important to start at lower doses and increase slowly. The typical dose range of lithium required in the older adults is generally between 300 and 600 mg/day, rarely exceeding 900 mg/day, and perhaps even lower in those older than age 80, with a usual dose between 150 and 300 mg/day [33].

◘ **Table 11.9** Potential causes of secondary mania [32]

Category	Systemic medical conditions
Medical conditions	Anemia, hyperthyroidism, vitamin B_{12} deficiency, niacin deficiency
Medications/substances	Antidepressants, corticosteroids, captopril, stimulants, amphetamines, cocaine, opiates
Infectious diseases	Neurosyphilis, encephalitis, human immunodeficiency virus, acquired immunodeficiency syndrome
Neurologic disorders	Major neurocognitive disorders, multiple sclerosis, epilepsy, Parkinson disease, traumatic brain injury, brain tumors, normal pressure hydrocephalus, Wilson disease

Once treatment is established, the challenge would be to help Mr. K. maintain adherence to the treatment plan. As in Mr. K.'s case, most patients with any systemic medical or psychiatric illness will want to know if they would be able to discontinue medications at some point. As bipolar disorder is a chronic episodic disease, the recommendation is to remain on medications indefinitely. However, every patient needs to be considered individually, their wishes taken into account, and the risks versus benefits of continuing therapy be carefully weighed. Thus, for someone who has only had mild symptoms, the decision to stop pharmacological treatment may be considered after a period of time. In these circumstances, monitoring for recurrence, psychotherapies, and psychosocial interventions would play an ever more important role.

11.3 Key Points: Late-Life Bipolar Disorders

- Bipolar disorder is generally an episodic, lifelong illness whose course can be variable. The first episode is more likely to be a depressive episode but may also be a manic, hypomanic, or mixed episode.
- An accurate diagnosis of bipolar disorder depends largely on the clinician as there is no single blood test or neuroimaging test that can diagnose the disorder. It is important to keep in mind when assessing a depressed patient, a diagnosis of bipolar disorder is always part of the differential as he or she may have had past hypomanic or manic episodes, and thus, eliciting a full past psychiatric history is essential.
- Given that medical comorbidities are common in the geriatric population with bipolar disorders, a thorough physical exam and basic workup is important to rule out any other contributors to the presentation (e.g., unstable glucose control can lead to or worsen mood lability). Treatment of comorbid conditions (systemic medical and/or psychiatric) is key to improving the chance of full recovery.
- In a patient who develops mania while being treated with an antidepressant, an antidepressant-induced manic episode cannot be ruled out unless one is able to evaluate the patient without the antidepressant and monitor for the persistence of manic symptoms. However, there is evidence to suggest that many patients who experience an antidepressant-induced manic episode do in fact have underlying bipolar disorder.
- Older adults usually require lower doses of medications compared to the general adult population. It is also important to note that the desired therapeutic range for a medication, such as lithium, may also need to be adjusted with age. Target therapeutic range for lithium in older adults is between 0.4 and 0.7 mmol/L (or mEq/L) vs. 0.7–1.2 mmol/L (or mEq/L) in the younger population.

11.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. In an older patient with a long history of recurrent major depressive episodes, presenting with new onset of manic symptoms for the past 4 days, which of the following is *not* part of the differential diagnosis?

A. Delirium
B. Late-onset bipolar I disorder
C. Late-onset bipolar II disorder
D. Cyclothymic disorder
E. Substance/medication-induced bipolar and related disorder

Answer: D

Given that this is an older patient with new onset manic symptoms, delirium should always be considered as part of the differential until it is ruled out with necessary investigations. The manic symptoms have been present for 4 days, but given more time, it is possible that these symptoms would continue on longer. Thus, at this point, both bipolar I disorder (if the manic symptoms continue for at least 1 week) and bipolar II disorder are possible. Without additional information such as urine toxicology screen, substance use and other medication use cannot be ruled out as cause of the patient's current presentation. As this patient has had previous major depressive episodes, he/she would not meet criteria for a cyclothymic disorder—thus, option D is not part of the differential.

MCQ 2. Which of the following investigations should be done prior to initiation of lithium in an older adult with bipolar disorder?

A. Baseline renal function, thyroid function, and ECG
B. Brain imaging (CT or MRI)
C. Neuropsychological testing
D. Fasting lipid profile and hemoglobin A1c
E. 12-hour serum lithium levels

Answer: A

While brain imaging, neuropsychological testing, fasting lipid profile, and hemoglobin A1c will all likely provide useful information, these investigations are not necessary as baseline workup for lithium initiation. And as the person has not been started on lithium yet, the 12-hour serum levels would not be necessary at this point. Lithium use can increase the risk of renal dysfunction, hypothyroidism, and cardiac conduction abnormalities. Thus, ensuring that there are no underlying issues with the kidneys, thyroid, or heart prior to lithium initiation is essential. Therefore, option A is the correct answer.

MCQ 3. You are the outpatient psychiatrist for a 75-year-old male whom you have been seeing for the past year, diagnosed with late-onset bipolar I disorder. He has been stable on lithium 600 mg daily (last serum levels about a month ago were 0.62 mmol/L [mEq/L]) since his initial mood episode. However, his wife calls you to say that for the past 2 weeks, he has been more confused and forgetful. Today, he became very angry when he could not change the channel on the TV with the remote as he was actually pressing buttons on their cordless telephone instead. What should be your next step?

A. Tell the wife that this is a normal side effect of his lithium and there is nothing to worry about
B. Start him on donepezil as you feel he likely has major neurocognitive disorder
C. Recheck his serum lithium level and renal panel
D. Increase his lithium to 750 mg as he is likely experiencing some depressive symptoms

Answer: C

While some patients may complain of feeling drowsy or lethargic as side effects of lithium, confusion and significant cognitive changes are not typical side effects of lithium, and thus, statement A is incorrect. The patient's change has been fairly acute (within 2 weeks); thus, a major neurocognitive disorder cannot be diagnosed until a delirium has been ruled out. Starting him on a cholinesterase inhibitor would not be the appropriate next step, and statement B is incorrect. It is possible that "pseudodementia" associated with a depressive episode is leading to what appears to be confusion. But without further information on his mood and ruling out other possible causes of acute confusion, increasing his lithium dose would not be the appropriate course of action; therefore, statement D is also incorrect. As the onset of his confusion is fairly acute, a delirium *must* be ruled out. Even though his lithium level from a month ago was within the target range, things can change rapidly, especially if he had an infection or was dehydrated. Thus, lithium levels should be drawn and his renal function checked to ensure acute renal failure or lithium toxicity is not the cause of his current symptoms. Therefore, statement C is correct.

Teaching Point
When monitoring for lithium levels, renal function should always be assessed as renal failure can occur even when lithium is within therapeutic range.

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Late-Life Anxiety Disorders

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12.1 Background

12.1.1 Definition of Anxiety Disorders

Anxiety and fear are both normal human responses to a real or perceived danger, and while they are intimately related and co-occurring phenomena, they are also distinct. Anxiety acts as a warning signal to prompt an individual to anticipate and subsequently cope with or avoid a wide array of real or perceived threats. Whereas anxiety occurs in *anticipation* of threat, fear occurs as a direct *response* to a real or perceived danger. Fear is more related to characteristic autonomic symptoms, including but not limited to tachycardia, increased blood pressure, hyperhidrosis, and nausea, while anxiety is characterized by worry, muscle tenseness, vigilance, and cautionary or avoidance behaviors. Table 12.1 lists key manifestations of fear and anxiety. A malfunctioning "fight or flight" response is thought to be related to the predisposition to panic attacks. From an evolutionary perspective, fear has survived as an important survival mechanism in many animal species. The neurobiology and behavioral manifestations of anxiety and fear have been preserved across a wide array of animal species, reflective of their adaptive significance [1]. Interacting with both fear and anxiety, avoidance is an important coping mechanism across anxiety disorders. Anxiety disorders consist of a heterogeneous group of syndromes that are related to and may interact with depressive disorders, bipolar and related disorders, obsessive-compulsive and related disorders, and trauma and stressor-related disorders (these illness categories are discussed in detail in ▶ Chaps. 10, 11, 13, and 14). Among the geriatric population, anxiety disorders are associated with greater health-care utilization [2, 3], increased medical disability [2, 4], and a reduced quality of life [5, 6]. Further, generalized anxiety disorder in late life is associated with an increased risk of cardiovascular events [7], including strokes [8], as well as an increased risk for progression from mild to major neurocognitive disorder (NCD, formerly dementia) [9].

Persistent anxiety in the absence of imminent danger can result in undue misery and a diminished quality of life [5, 6]. Pathological anxiety is an out-of-proportion response in relation to a stressor. Pathological anxiety is persistent, occurs at inappropriate times, and leads to a significant impairment in functioning. This resulting psychopathology is an anxiety disorder. The *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), defines the following anxiety disorders [10]:

- Separation anxiety disorder
- Selective mutism
- Specific phobia
- Social anxiety disorder (social phobia)
- Panic disorder
- Agoraphobia
- Generalized anxiety disorder
- Substance/medication-induced anxiety disorder
- Anxiety disorder due to another medical condition

Anxiety disorders are a heterogeneous group of related disorders that are characterized by varying degrees of their core symptoms, excessive anxiety (or worry), and fear. Each disorder varies in terms of the eliciting causes as well as the frequency and intensity of these symptoms. In addition to excessive fear and worry, other important symptomology in anxiety disorders includes sleep disturbance, impaired concentration, irritability, and restlessness. Core symptoms of worry and fear have common underlying neurocircuitry, and the different phenotypes that are represented by each anxiety disorder represent differential malfunctioning of the same neural circuits as opposed to unique circuitry specific to each anxiety disorder [11]. Panic attacks have characteristically briefer but more intense episodes of fear, whereas generalized anxiety disorder is characterized by longer but less intense periods of worried anguish. Panic attacks are not pathognomonic of panic disorder; rather, they can occur in a number of psychiatric disorders but play an especially important defining role in panic disorder. In addition to discrete, spontaneous panic attacks, panic disorder is characterized by anticipatory anxiety and behavior changes to cope with panic.

Table 12.1 Manifestations of fear and anxiety

Fear	Anxiety
Racing heart beat	Worry
Sweating	Keyed-up feeling
Nausea	Muscle tension
Shortness of breath	Cautious behaviors
Feeling of imminent death	Avoidance behaviors
"Fight or flight" response	

12.1.2 Epidemiology and Diagnostic Criteria

Anxiety disorders will continue to pose an important and challenging issue for the older population and clinicians alike. Late-life anxiety disorders are difficult to diagnose for a number of reasons, including a difficulty to distinguish adaptive and pathological anxiety in older adults in the context of normal aging, patient minimization of symptoms, and comorbid neuropsychiatric symptoms, including cognitive impairment [12, 13]. In addition, the symptoms in late-life anxiety disorders may differ from those in younger anxiety disorder patients, as older patients may present with more somatic complaints with anxiety related to the experience of systemic medical comorbidities [14].

Teaching Point

Detecting pathological late-life anxiety is often complicated by normal aging, challenging life circumstances including bereavement and disability, minimization of symptoms, the presence of other comorbid general medical conditions, more frequent somatic complaints, and, potentially, cognitive impairment.

Thus, it is not surprising that late-life anxiety disorders may be underreported [15]. While it was once thought that late-life anxiety disorders were uncommon, a number of reviews have suggested that late-life anxiety disorders have a lifetime prevalence of up to 15.3% [12, 15–17]. While anxiety disorders are thought to be the most common psychiatric disorders in geriatric psychiatry, compared to depressive and other psychiatric disorders, they have received comparatively less attention and are less recognized. One proposed reason for this under-recognition is that most anxiety disorders in late-life are thought to be chronic and have their beginnings earlier in life [18].

The DSM-5 does not delineate specific anxiety disorders that affect primarily older adults, even though geriatric-specific syndromes do exist, most notably the fear of falling [19]. Fear of falling can be conceptualized as a specific phobia that is known to impact older adults and can lead to a significant functional impairment. Separation anxiety disorder and selective mutism are thought to occur primarily in childhood, and social anxiety disorder also typically presents early in life [20]. Conversely, specific phobias and generalized anxiety disorder are among the most commonly occurring anxiety disorders late in life [13]. Almost half the cases of generalized anxiety disorder and agoraphobia have a late-life onset, although cases with an earlier onset are thought to be more persistent and severe [21]. Disorders which involve the fear response, like panic disorder, are thought to have a particularly low incidence rate in the geriatric population, although they have been documented to occur, most often, in the context of systemic medical comorbidities [22]. This decrease in incidence may be explained by age-related dampening of physiological autonomic responses [23]. Thus, the new onset of panic symptoms in late life should prompt a thorough search for alternative and comorbid diagnoses with close attention to systemic medical conditions and medication side effects [24].

Table 12.2 highlights the DSM-5 diagnostic criteria of the most common anxiety disorders encountered among older adults. For a complete review of the DSM-5 diagnostic criteria for anxiety disorders, the reader is referred to the DSM-5 manual [10].

Teaching Point

In late life, generalized anxiety disorder and specific phobia (e.g., fear of falling) are the most common anxiety disorders, whereas panic disorder is less common, and new-onset panic requires the consideration of alternative explanations.

12.1.3 Evolutionary Considerations

Anxiety prompts an organism to anticipate and plan for future threats. Our propensity for anxiety and the high prevalence of anxiety disorders are explained by the "smoke detector principle" which suggests that due to the relatively small cost of activating anxiety, compared to the high cost of missing a dangerous threat, we are prone to false alarms, much like a smoke detector [25]. The human environment of evolutionary adaptedness, first coined by John Bowlby of attachment theory framework [26], is a concept that is meant to describe the selection pressures in the environment that led to the development of a given adaptation [27]. The environment of evolutionary adaptedness does not represent a specific place or time, rather a statistical composite of the adaptation relevant to selective pressures that were encountered by ancestral humans [28].

The majority of human psychological adaptations are thought to have evolved in hunter-gather societies in sub-Saharan Africa, as this is where our species is believed to have spent the vast majority of its ancestral history [29]. Because cultural and technological evolution has proceeded at such a rapid rate, the challenges faced by humans in modern society are vastly different compared to the challenges our ancestors faced. The result is a stress-response system that is prone to maladaptive responses [25]. With an evolutionary framework in mind, it is no wonder that we observe the relatively high prevalence of anxiety disorders that we see today. The ubiquity of anxiety as a human experience makes it difficult to identify pathological from normal anxiety, and this issue is only exacerbated in older adults, many of whom face significant life challenges. These issues include comorbid systemic

Table 12.2 Highlights of the DSM-5 diagnostic criteria for common anxiety disorders in older adults [10]

Generalized anxiety disorder	Specific phobia
Excessive anxiety/worry, on more days than not; duration > 6 months	Marked fear/anxiety about a specific object/situation; duration > 6 months
Plus three or more of: (1) restless, keyed up, on edge; (2) easily fatigued; (3) difficulty concentrating, mind going blank; (4) irritability; (5) muscle tension; (6) sleep disturbance	The phobic object/situation provokes immediate fear/anxiety, is actively avoided/endured with intense fear/anxiety that is out of proportion to the actual danger
Clinically significant distress/impairment in important areas of functioning; the disturbance is not better explained by another psychiatric disorder, physiological effects of a substance, or another medical condition	Clinically significant distress/impairment in important areas of functioning; the disturbance is not better explained by another psychiatric disorder

medical conditions that may limit their functional ability or life expectancy, as well as social losses due to bereavement or loss of independence.

12.1.4 The Interplay Between Anxiety and Depressive Disorders

Anxiety disorders are highly comorbid with depressive disorders in geriatric psychiatry [30]. These disorders have significant overlap in their symptomology, including impaired sleep, concentration, and energy levels, and share many of the same risk factors. In addition to this functional overlap, the genetic risks for generalized anxiety disorder largely overlap with those of major depressive disorder [31]. "Anxious misery" has been described as a potential dimension across the anxiety spectrum that may be involved in generalized anxiety disorder, major depressive disorder, and persistent depressive disorder (dysthymia) [32]. Therefore, it comes as no surprise that among those patients with late-life depressive disorder, comorbid anxiety symptoms are highly prevalent and contribute to the burden of symptoms [33]. In addition, anxious depression in older adults appears to represent a subtype of depression that is relatively treatment resistant, associated with an increased risk of neurocognitive decline and, perhaps most importantly, an increased risk for suicide [34–36].

Teaching Point
In late life, anxious depression may manifest in a treatment-resistant subset of patients that are at increased risk for neurocognitive decline and suicide, highlighting the importance for monitoring cognitive status and suicide risk in this population.

12.1.5 Etiology

Anxiety disorders, as is true of other psychiatric disorders, arise from a complex interplay of genes and the environment. The estimated heritability of generalized anxiety disorder is thought to be 0.42 [37, 38], which is comparatively less than schizophrenia and other genetically determined neuropsychiatric diseases (e.g., Huntington disease). While anxiety may not reach pathological levels until adulthood, or even late life, the behavioral manifestations of anxiety disorders are believed to demonstrate themselves in childhood and adolescence [39]. The genetics of anxiety disorders are thought to overlap with those of major depressive disorder via a complex polygenic interaction with the environment; importantly, these genetic risk factors change minimally with age [39, 40]. Late-life anxiety has been associated with the following risk factors: female sex, having several chronic systemic medical comorbidities, being single, lower education level, decreased subjective health, adverse early childhood events, stressful life events, physical impairment, and the personality trait of neuroticism (see Table 12.3) [30].

Table 12.3 Risk factors for late-life anxiety disorders [30]

Risk factors	Female sex
	Being single
	Low education level
	Personality trait of neuroticism
	Adverse early childhood events
	Stressful life events
	Multimorbidity
	Poor subjective health
	Physical impairment

Table 12.4 Common potential contributors to anxiety disorders

Category	Examples
Medications	Prescribed amphetamines, steroids, beta-agonists, thyroxine, levodopa
Substances	Illicit amphetamines (crack, crystal meth, cocaine), caffeine, alcohol (withdrawal)
Systemic medical conditions	*General*: pain, electrolyte imbalances, incontinence, physical disability, sensory impairment
	Neurologic: seizures, tumors, migraine, cognitive impairment
	Respiratory: COPD, asthma, hyperventilation, dyspnea, sleep apnea
	Endocrine: hyperthyroidism, tumors (e.g., pheochromocytoma) *Gastrointestinal*: constipation, diarrhea, abdominal pain *Cardiovascular:* anemia, angina, congestive heart failure, arrhythmias

12.1.6 Diagnostic Evaluation

As with all other psychiatric disorders, the diagnosis of late-life anxiety disorder requires a careful and comprehensive assessment of the patient, including a clinical history, physical examination, and laboratory investigations. The differential diagnosis for anxiety disorders is broad. One must consider both alternative as well as comorbid psychiatric and systemic medical diagnoses, in addition to medication or substance-induced interactions [41], a dilemma exacerbated in the geriatric population. Table 12.4 lists potential contributors to anxiety disorders. The clinical history should include a thorough review of the onset of anxiety symptoms and their relationship with cognitive impairment, as well as substance and prescribed medication use, since these play key factors in the differential diagnosis [14]. In addition, reviewing

previous medical records for information regarding previous treatment history and response may aid in developing an efficient and effective treatment plan [14]. Collateral information from family members or caregivers may aid in determining the degree and quality of the functional impacts of symptoms. Physical examination and laboratory investigation should be targeted based on the clinical presentation and differential diagnosis and should be used to eliminate the attribution of symptoms to systemic medical conditions. Consider baseline complete blood count, electrolytes (with extended panel), fasting lipid profile, thyroid-stimulating hormone, fasting glucose, and liver enzymes [41].

Teaching Point

The differential for anxiety disorder is broad and can result from and co-occur with a number of other psychiatric and systemic medical conditions, necessitating consideration of a broad differential diagnosis.

12.1.7 Treatment

After diagnosis, a treatment plan should be developed in collaboration with the patient. Care should be taken to provide the patient with psychoeducation about the disorder, placing emphasis on realistic goals, e.g., not to completely remove all anxiety symptoms, rather make the occurrence of anxiety feel tolerable and manageable, and thereby minimize suffering. In addition, education should include information regarding treatment efficacy, tolerability, aggravating factors, and signs of relapse [41]. Bibliotherapy may be used as an adjunct for patients who are cognitively capable and engaged in treatment [41]. Treatment options include psychological and pharmacological modalities; the choice of which option depends on availability, patient preference and engagement, cognitive ability, and clinician comfort [41]. Psychological treatment options include cognitive-behavioral therapy, behavioral activation, interpersonal therapy, and mindfulness-based therapies. Cognitive-behavioral therapy is a mainstay of psychological treatments, and all patients being treated with pharmacotherapy for an anxiety disorder should also be encouraged to face their fears via cognitive-behavioral therapy [41]. For specific phobias, psychological treatments, especially exposure-based therapies, are the primary treatment modality, and the role of pharmacotherapy is thought to be more limited [41].

A necessary first step is minimization of polypharmacy or the optimization of current medications and discontinuation of unnecessary and harmful medications including sedatives, anticholinergics, antihistaminergics, and over-the-counter medications [14] (see ▶ Chap. 5). First-line pharmacological options include selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs), and, in generalized anxiety disorder, buspirone may also be considered [41]. Mirtazapine may be effective particularly in cases with comorbid depressive disorder, poor appetite, and/or sleep disturbances [41]. Tricyclic antidepressants may also represent treatment options; reversible inhibitors of monoamine oxidase show some evidence of benefit but are generally poorly tolerated and considered less safe than SSRIs and SNRIs [41]. Anticonvulsant medications and atypical antipsychotics have demonstrated some evidence as being beneficial in anxiety disorders but are recommended as adjunctive or second- or third-line treatment options due to tolerability and limited evidence of benefit [41]. While benzodiazepines can provide short-term relief of symptoms, their use should be limited to cases of extreme suffering and, even then, should be used in a scheduled, time-limited fashion because benzodiazepines reinforce maladaptive coping behavior [14]. Moreover, the benefit-risk profile worsens among the geriatric population, and therefore treatment with benzodiazepines should be avoided in older adults [14, 41, 42]. Table 12.5 shows common pharmacotherapy options for generalized anxiety disorder [41, 42].

Table 12.5 Pharmacotherapy for generalized anxiety disorder in the general population [41, 42]

Treatment option	Medications
First-line treatment	SSRIs (fluoxetine, citalopram, escitalopram, sertraline) SNRIs (venlafaxine, duloxetine), pregabalin, mirtazapine
Second-line treatment	Agomelatine, quetiapine, buspirone, imipramine, clomipramine
Adjunctive treatment	Pregabalin, quetiapine, risperidone

12.2 Case Studies

This section utilizes case studies to illustrate the multiple challenges in recognition, diagnosis, and management of late-life anxiety disorders. Each case will be discussed in the form of questions and answers and conclude with a case analysis.

12.2.1 Case 1

Case 1 History

Mrs. A. is an 81-year-old retired female school teacher, who presented to an outpatient seniors' mental health clinic with her adult daughter after being referred for diagnostic clarification and treatment recommendations by her primary care physician. She has been diagnosed with a major depressive episode by her primary care physician who prescribed treatment with sertraline 2 weeks ago and recently increased her dosage from 25 mg to 50 mg daily.

Mrs. A. lives independently in her home with her pet cat. Sadly, her husband moved to a long-term care facility 2 years ago due to a severe major neurocognitive disorder. This has been a difficult transition for Mrs. A., as she had been with him for over 50 years, and she described in detail a meaningful and mutually supportive marital partnership before she took on the role of his primary caregiver due to his progressive illness. She laments not being able to provide care for her husband currently but also understands that he requires more care than she is able to provide at home. She continues to prepare her own meals but often does not cook because she does not like to stand, so instead she regularly uses a microwave oven to prepare frozen meals. She has never had difficulty using her microwave oven or any other appliances. On a recent Montreal Cognitive Assessment (MoCA), she scored 27 out of 30, losing points on attention and delayed recall.

She endorsed being worried about her husband, but said that she has not gone to visit her husband, or left the house very much at all over the past few months, and complained of lower back pain after a fall she suffered 6 months ago. She had a "mechanical fall" after she bought a new pair of slippers. At that time, she had visited the emergency department; hip and pelvic x-rays were both negative. Unfortunately, she has developed chronic neuropathic pain after the fall, for which her primary care physician has started nortriptyline 10 mg at bedtime. This has helped the pain as well as improved her ability to fall asleep. She has been continued on this medication due to the benefit for her neuropathic pain; concurrently, her primary care physician started sertraline for her suspected depressive episode, as well as monitored her cardiac status and vital signs for concerns of orthostatic hypotension.

In terms of past medical history, she has hypertension and diet-controlled type 2 diabetes mellitus. She has never been admitted to hospital for psychiatric illness, although she said that she was treated with psychotropic medications for depression in her 20s. She could not recall what medication she was prescribed but said that after about a year she felt better and stopped taking the medication on her own accord. She denied any suicidal ideation or self-harm behavior.

Case 1 Questions and Answers

Case 1 Questions

- Question 1. What additional information and investigations would you like to obtain in order to help further elucidate your diagnosis?
- Question 2. What is your differential diagnosis?
- Question 3. Describe a treatment plan utilizing the biopsychosocial model.
- Question 4. What other factors should be considered during long-term management?
- Question 5. Eight months later, during outpatient treatment, Mrs. A. has been seen in follow-up, and her dose of sertraline gradually increased. She endorses a remission of her symptoms for the past 2 months on a daily dose of 150 mg. She says that she would like to stop the antidepressant medication because she feels much better. What would you recommend?

Case 1 Answers

Case 1 Answer 1 (Question 1—What additional information and investigations would you like to obtain in order to help further elucidate your diagnosis?)

In order to get a better understanding of the ongoing difficulties that Mrs. A. faces, the clinician must better understand her current symptom profile. In addition, the assessment should be focused on assessing for other psychiatric comorbidities as well as concurrent systemic medical illnesses. She endorsed a low mood for the past 2 years after her husband moved to a long-term care facility; however, her mood has continued to decline over the past few months. Sleep disturbance is common, as she often awakes to go to the bathroom, and on most nights she is not able to fall back asleep. This issue has been worse since her fall 6 months ago, as she often worries about going to the bathroom throughout the night.

She endorses guilt about her inability to provide care for her husband, although she has insight that she could no longer provide the high level of care that he requires. She also endorses guilt about the burden that her difficulties have placed on her daughter. She denied any difficulties with concentration. She endorsed low energy over the past few months. She denied any suicidal ideation and feels that she still enjoys activities and social outings, but that this has been more limited over the past 6 months. She noted that she is fearful that she will fall and then will be completely unable to take care of herself. In order to cope with her fear, she endorsed avoiding activities that she feels will put herself at risk, including going for walks and gardening, both of which she used to greatly enjoy. She does consider herself to be a "worrier", and her primary worries are for her husband's health, her daughter's well-being, feeling like a burden to her daughter, a fear of falling and fear of her own health declining. She denied suffering from any panic attacks.

As a part of her work-up, cognitive testing is important as it helps to guide interventions and could also have significant diagnostic implications. She scored well on the MoCA and denied any issues with instrumental or basic activities of daily living. She denied any instances of getting lost when driving, leaving the stove on while not cooking, or having any difficulty remembering how to use the microwave oven or her television remote control. Mrs. A. does not smoke, and she drinks a glass of wine occasionally on special events. She has never had any issues with alcohol misuse in the past. She denied any illicit drug use. She drinks one cup of coffee a day in the morning.

In terms of her personal history, she was raised by both of her parents and described a happy childhood. This depressive episode that she suffered in her 20s occurred in response to her first marriage ending in divorce, as she described her first husband as emotionally and physically abusive. They married

when she was 19 years old. She remarried in her late 20s to her current husband, and this union produced her daughter. She described her husband as supportive prior to the development of his major neurocognitive disorder. She completed a high school education and then completed a teaching degree in college. She taught until she retired at the age of 70. In the last 5 years of her life, she has occupied her time by caregiving for her husband. Due to this she has had little time for socializing or engaging in meaningful activities for herself.

It may be useful to obtain further collateral information from family members. Older adults may minimize their difficulties, and it is not uncommon for psychological distress to manifest as persistent somatic complaints. Given that the patient came to the appointment with her daughter, obtaining consent to involve the daughter in the patient's care would be appropriate and worthwhile. A separate conversation with her daughter (after obtaining permission from the patient) did not yield any concerns with Mrs. A.'s cognitive abilities, although her daughter did express concerns about her mother's quality of life secondary to the degree of her isolation.

Physical examination including neurological examination was within normal limits. Routine laboratory investigations for complete blood count, electrolytes, creatinine, thyroid-stimulating hormone, vitamin B_{12}, and urinalysis were all within normal limits.

If possible, it would be helpful to obtain any information regarding past treatments and their relative effectiveness. Unfortunately, further information regarding her depressive episode in her 20s was not available. In terms of her current response to treatment, she denied any significant changes in her mood and anxiety since her dose of sertraline was increased to 50 mg daily a week ago. She does feel that nortriptyline has improved her sleep pattern as she has experienced a decreased latency in the time to fall asleep and has remained asleep for more hours consecutively.

Case 1 Answer 2 (Question 2—What is your differential diagnosis?)

As stated previously, diagnosis should include a comprehensive medical work-up including physical examination and laboratory studies. An assessment of cognitive function is helpful to guide diagnosis, to obtain a baseline for later comparison, as well as to potentially guide treatment. In addition, anxiety is thought to be toxic to the brain [43], associated with cognitive decline [30], and leads to an increased risk of developing a major neurocognitive disorder [9, 30]. Rating scales may be used as adjunctive tools to aid in clinical assessment. Scales designed for older adults, including the Geriatric Anxiety Inventory [44] and the Geriatric Anxiety Scale [45], can help quantify the symptoms and assign a severity score for anxiety symptoms. Differential diagnosis should include consideration of the following:

A2.1. *Major depressive disorder*. Mrs. A. is suffering from some depressive symptoms including low mood, excessive guilt, low energy, and sleep disturbance. She denied anhedonia, although she has been avoiding activities. She endorses some criteria for a major depressive episode; however, these symptoms developed in the context of major life stressors, namely, her spouse having to move to a long-term care facility. In addition, it is also prudent to consider components of a grief reaction as well as the role transition related to the loss of her partner. Importantly, the significant decline in her functioning appears to be related to the physical and psychological effects of her fall.

A2.2. *Specific phobia*. Fear of falling is a specific phobia that primarily affects the geriatric population [19, 46]. The prevalence of fear of falling among community-dwelling older adults ranged between 20.8% and 85% [47]. Interestingly, a review of studies suggested that over 50% of older adults with fear of falling did not actually suffer a fall themselves [47]. Risk factors for fear of falling include older age, female sex, and previous falls [46]. Mrs. A. experienced a significant impairment in her functioning after her fall as she withdrew from important activities in her life like cooking and social activities.

A2.3. *Generalized anxiety disorder*. In addition to the worry about her falling, Mrs. A. also endorsed worry about her husband but denied other generalized worry. She is witnessing her husband's experiences of physical and cognitive decline, and therefore some degree of worrying about her husband is within normal limits.

Case 1 Answer 3 (Question 3—Describe a treatment plan utilizing the biopsychosocial model.)

Treatment should include a thorough review of the presumptive diagnoses and their interactions with systemic medical comorbidities. All the prescribed medications should be carefully reviewed, and a comprehensive consideration of potential side effects should be undertaken. The Beers criteria for potentially inappropriate medication use in older adults may be a helpful tool [48]. (See ▶ Chap. 5.)

Providing psychoeducation is a necessary and an important first step in the treatment of late-life anxiety disorders and should include a discussion of the impact of anxiety on quality of life. In terms of biological treatment, the patient is already receiving first-line pharmacological treatment as she has been started on sertraline, a selective serotonin reuptake inhibitor (SSRI). The dose of sertraline should be optimized based on effect and tolerability. Early follow-up after the initiation of treatment should be ensured in order to monitor for response, adherence, and/or side effects. Should the initial medication not lead to a resolution of symptoms, then the medication can be further augmented. There is some preliminary evidence to suggest that pregabalin may be an effective augmentation strategy for geriatric patients with comorbid depressive and anxiety disorders [49]. Benzodiazepines should be avoided, and if prescribed they should be used with caution in the geriatric population due to their poor safety profile, development of tolerance, and misuse potential leading to substance use disorder [13, 14, 41, 42].

Table 12.6 Management of late-life anxiety disorders in older adults

Comprehensive assessment	Laboratory studies Physical examination Review of current medications; minimize polypharmacy Review of previous diagnoses, treatments, and treatment responses Screening for other systemic medical conditions (e.g., hyperthyroidism) Cognitive testing
Psychoeducation	Include caregivers and family members as appropriate Provide written materials as necessary, including bibliotherapy Discuss a patient-centered care plan and offer both psychosocial and pharmacotherapy-based interventions
Treatment	Consider both psychotherapy (cognitive-behavioral therapy, behavioral activation, interpersonal therapy, and mindfulness-based approaches) and pharmacotherapy (e.g., selective serotonin reuptake inhibitors and other antidepressants as first line; buspirone can be considered for generalized anxiety disorder; benzodiazepines should be avoided) Psychotherapy may be less effective in older adults due to high incidence of cognitive impairment; may require modification of psychotherapy protocol
Follow-up	Monitor for treatment response, adherence, tolerability, and side effects If needed, consider augmentation strategies with either medication or psychotherapy Monitor cognition If necessary, consult experts for further guidance

Teaching Point
Use of benzodiazepines among the geriatric population should be judicious, if at all, due to a poor safety profile.

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Psychological treatments include cognitive-behavioral therapy, behavioral activation, and mindfulness-based therapy [13, 14, 41, 50, 51]. Given the loss of the spousal role, connecting the patient with grief services may be a welcome resource. Geriatric day programs may be a way to improve the quality of life and increase meaningful activities throughout the day, thereby decreasing social isolation. The management of late-life anxiety disorders is summarized in Table 12.6.

Case 1 Answer 4 (Question 4—What other factors should be considered during long-term management?)

Further follow-up should monitor for full resolution of mood and anxiety symptoms. Response to medications should be monitored, and if treatment is not effective, then ineffective medications should be weaned and discontinued. As Mrs. A. is being treated with an SSRI, monitoring of serum sodium should be performed as there is a risk of developing the syndrome of inappropriate antidiuretic hormone (SIADH) with euvolemic hyponatremia, which often presents with delirium [52]. A baseline cognitive status as measured with standard cognitive assessment instruments (e.g., MoCA), with periodic monitoring, is recommended, given that anxiety disorders in late life are associated with an increased risk of development of a major neurocognitive disorder [9, 53, 54]. In this case, we are reassured by Mrs. A.'s relatively normal MoCA as well as denial of any memory impairment from both the patient and her daughter.

Case 1 Answer 5 (Question 5—Eight months later during outpatient treatment, Mrs. A. has been seen in follow-up, and her dose of sertraline gradually increased. She endorses a remission of her symptoms for the past 2 months on a daily dose of 150 mg. She says that she would like to stop the antidepressant medication because she feels much better. What would you recommend?)

It is important to fully understand exactly why Mrs. A. would like to discontinue treatment in order to engage her in a discussion as to the costs and benefits of ongoing treatment. It may also be useful to engage with family if the patient feels that family support is helpful. As longer-term treatment is associated with continued symptom improvement and the prevention of relapse, treatment should be continued for at least 12 months for most patients prior to weaning off of medication, assuming that she maintains a complete remission of symptoms [14, 41, 42].

Case 1 Analysis Mrs. A.'s diagnosis is most consistent with a specific phobia, the fear of falling. This case highlights the importance of identifying an anxiety disorder as the physical impacts of the fall did lead to a significant impact on functioning. She had some significant mood symptoms which come close to meeting criteria for a major depressive episode, but this is also in the context of major stressors. The fact that the patient has a chronic illness, type 2 diabetes mellitus, also increases the risk of developing an anxiety disorder [55, 56]. She was started on sertraline and responded well but will continue to face challenges moving forward as she and her spouse continue to age and will also continue to decline.

Teaching Point
Fear of falling represents a specific anxiety syndrome that affects older adults and can lead to a significant impairment if left unrecognized.

12.2.2 Case 2

Case 2 History

Mr. B. is a 77-year-old male who lives at home with his wife. The couple has an adult daughter who is supportive. He is retired, and prior to retirement he worked at various marketing firms. He denied any formal psychiatric history although he described himself as a "lifelong worrier". He does believe that he has always been able to cope with his worry appropriately. He believes his worrying has been a motivating factor that has led to his successful career. His medical history is significant for chronic obstructive pulmonary disease (COPD), hypertension, and dyslipidemia. He has been admitted to hospital a week ago with an episode of dyspnea, generalized malaise, and a productive cough. He was found positive for *Streptococcus pneumoniae* infection, a community-acquired pneumonia that was adequately treated in hospital with intravenous followed by subsequent step-down to oral antibiotics, as well as corticosteroid inhalers. He continues to describe intermittent episodes of shortness of breath and stated that he does not feel comfortable with discharge to his home. The admitting general medical team did not find any reversible causes for his ongoing episodes of shortness of breath. He continued to smoke a ½ pack of cigarettes per day, although he stopped smoking during his admission to hospital. He drinks 1–2 beers per day on the weekends. He does not use any illicit drugs. The consultation liaison psychiatry team was asked to assess the patient for diagnostic clarification of his anxiety and to provide treatment recommendations. His current list of medications includes atorvastatin 40 mg daily, hydrochlorothiazide 25 mg daily, and ramipril 10 mg daily. He is not currently being treated with any psychotropic medications.

Case 2 Questions and Answers

Case 2 Questions

- Question 1. How would you differentiate between shortness of breath secondary to panic disorder as opposed to COPD?
- Question 2. How common are anxiety disorders among patients with COPD?
- Question 3. How can an untreated anxiety disorder impact outcomes in COPD?
- Question 4. What pharmacological treatment would you recommend for this patient?

Case 2 Answers

Case 2 Answer 1 (Question 1—How would you differentiate between shortness of breath secondary to panic attack as opposed to COPD?)

Differentiating among causes of shortness of breath in the geriatric population can be particularly challenging due to the complex interplay of systemic medical and psychiatric comorbidities. Worsening of shortness of breath on exertion, especially when paired with oxygen desaturation, is more suggestive of systemic medical causes, whereas subjective shortness of breath related to stressful events with no corresponding change in oxygen saturation is more consistent with a psychiatric presentation, especially anxiety disorder [57]. Often there are multiple etiologies that overlap. New onset of panic disorder late in life is thought to be uncommon, but cases have been documented [22, 24]. A thorough history in combination with physical exam and laboratory findings can help delineate which symptoms are related purely to psychological distress. If it is believed a patient is experiencing panic attacks, it is important to determine the patient's understanding of the behavior and for the presence of anticipatory anxiety and avoidance which are required for the diagnosis of panic disorder.

Case 2 Answer 2 (Question 2—How common are anxiety disorders among patients with COPD?)

For patients that carry a diagnosis of COPD, anxiety and depressive disorders are among the most common and least often identified and treated comorbidities [58]. COPD that is associated with comorbid anxiety disorder is associated with poorer clinical outcomes [59]. The prevalence of comorbid anxiety disorders among patients diagnosed with COPD varies between 10% and 51% depending on the clinical study [57].

Case 2 Answer 3 (Question 3—How can an untreated anxiety disorder impact outcomes in COPD?)

COPD leads to an increased risk of development of comorbid anxiety disorders as described in *Case 2 Answer 2*. Dyspnea, one of the cardinal symptoms in COPD, is a potent cause of anxiety, and the severity of dyspnea in COPD is associated with depressive and anxiety disorders [60]. To further complicate matters, some COPD treatments, including beta-agonists, may increase the symptomatic experience of anxiety and panic, highlighting the possible significant contribution of shortness of breath due to anxiety and panic as opposed to airway obstruction per se [61]. Among patients with COPD, anxiety has been associated with increased dyspnea [59], increased risk of COPD exacerbations including hospitalizations [60], and greater disability [61–64], highlighting the importance of both recognition and treatment of anxiety disorders in this population.

Teaching Point

Anxiety disorders and COPD share presenting complaints and commonly coexist, and diagnosis of either or both can have significant treatment implications.

Case 2 Answer 4 (Question 4—What pharmacological treatment would you recommend for this patient?)

Whether or not to initiate pharmacological treatment should be based on each patient's degree of symptom severity and impact on functioning weighed against the potential

costs of medication. Ideally, pharmacological interventions should be combined with psychological and social interventions for patients with moderate-to-severe symptoms, while, for patients with only mild symptoms, an initial psychosocial approach should be utilized [65]. Benzodiazepines should generally be avoided due to the increased risks of falls, potential for respiratory depression, and risk of developing dependence [14, 41, 65]. This risk should be weighed against the benefit of providing some immediate relief and should be reserved only for the most severely distressed patients and even then should be considered a time-limited treatment [42]. Given this patient's level of distress, a trial of an SSRI would be a first-line pharmacologic treatment option. Pharmacological treatment should be combined with psychoeducation and psychosocial intervention, with cognitive-behavioral therapy having the strongest evidence base in effective treatment of anxiety disorders in patients with COPD [66]. For patients with COPD who are undergoing pulmonary rehabilitation, this serves as an ideal setting for the incorporation of psychosocial treatments [57].

Case 2 Analysis COPD and anxiety disorders are known to coexist [57] and have some overlapping symptomology causing difficulty in discerning which disease may be contributing to a patient's suffering [59]. Among patients with COPD, anxiety is associated with greater hospitalizations and disability [60–64]. However, an understanding of the cause of distress is critical as it can impact treatment; for example, beta-agonists may aid in airway obstruction but worsen anxiety [61]. SSRIs are first-line pharmacologic options [65], while cognitive-behavioral therapy has the strongest evidence among psychotherapeutic treatments [66]. Pulmonary rehabilitation settings are ideal to implement psychological treatment in the care of patients with COPD and anxiety [57].

12.3 Key Points: Late-Life Anxiety Disorders

- Anxiety is a normal human emotion, but pathological anxiety is costly. It can lead to a diminished quality of life and is related to many other medical diseases, including cardiovascular diseases.
- Late-life anxiety disorders are challenging to detect because they are intimately associated with aging, medical comorbidity, loss of independence, and symptom minimization; nonetheless, they remain common phenomena, and early recognition is imperative in order to minimize the burden of suffering in the geriatric population.
- In late life, generalized anxiety disorder is the most common anxiety disorder, whereas panic disorder is less common.
- Fear of falling represents a specific phobia that differentially affects older adults.
- Anxious depression may manifest in a treatment-resistant subset of patients who are at increased risk for neurocognitive decline and suicide.
- Management should focus on a comprehensive assessment, providing psychoeducation and a holistic treatment approach including social, psychological, and pharmacological interventions.
- Benzodiazepine use should be avoided in this population.

12.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. How are late-life anxiety and cognitive impairment related?

A. Anxiety is a risk factor for the development of major neurocognitive disorders.
B. Chronic anxiety in older adults may lead to hypothalamic-pituitary-adrenal (HPA) axis hyperactivity.
C. Anxiety may develop as a result of cognitive decline.
D. Increased cortisol is thought to mediate some of the negative consequences of chronic anxiety.
E. All of the above.

Answer: E

Anxiety is known to be a risk factor for the development of major neurocognitive disorders [27]; therefore, answer A is correct. Chronic anxiety in older adults is thought to lead to HPA-axis hyperactivity and increased cortisol levels resulting in negative consequences on memory and executive function [62], making answers B and D correct. Cognitive decline may lead to increased anxiety [27] (answer C) further complicating the relationship between anxiety and cognitive impairment.

MCQ 2. How may the presentation of anxiety differ in older compared to younger adults?

A. Younger adults are more likely to have somatic complaints.
B. Older adults are more likely to have systemic medical issues.
C. Presentations in older adults are more likely to be complicated by cognitive impairment.
D. A and B
E. B and C

Answer: E

Older adults are thought to present with more somatic complaints [14] making answer A false.

MCQ 3. Mrs. C. is an 83-year-old female that you are following for generalized anxiety disorder. She is treated with the SSRI, citalopram, 20 mg daily. In addition, she has a past medical history of congestive heart failure and is treated with the diuretic, furosemide, 40 mg daily. Mrs. C. presents to your clinic with her son who is concerned that over the past few days, his mother has been

complaining of head and muscle aches and seems disoriented. What would you recommend?

A. Tell Mrs. C. she may have a viral infection and suggest she follows up with her primary care physician if her symptoms do not resolve in a week.
B. Give Mrs. C. a letter explaining the situation and ensure that she goes to the emergency department as she may have an electrolyte imbalance that could require urgent but monitored correction.
C. Suggest that Mrs. C. come back to your clinic in 2 weeks for follow-up if symptoms do not improve with supportive management.
D. Send Mrs. C. and her daughter for outpatient bloodwork including a complete blood count, electrolytes, and creatinine that will be forwarded to you. You will arrange follow-up by contacting her directly should there be reason for concern.

Answer: B

The combination of a diuretic, SSRI, and her history of congestive heart failure puts Mrs. C. at risk for developing an electrolyte imbalance (in particular, hyponatremia), and this may be causing her symptoms; thus, statement B is correct. Mrs. C. should receive urgent medical attention to prevent any further reversible causes to her symptoms, which makes statements A, C, and D incorrect.

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Obsessive-Compulsive and Related Disorders in Older Age

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13.1 Background

13.1.1 Definitions and Clinical Description

Obsessive-compulsive and related disorders differ from developmentally normative preoccupations and rituals by being excessive or persisting beyond developmentally appropriate periods. The distinction between the presence of subclinical symptoms and clinical disorder requires assessment of a number of factors, including an individual's level of distress and impairment in functioning [1].

The *Diagnostic and Statistical Manual of Mental Disorders* (DSM) has been an accepted method of promoting standardization in diagnosis of psychiatric conditions. Several important changes were made in creating the DSM-fifth edition (DSM-5) for the obsessive-compulsive and related disorders. Firstly, obsessive-compulsive disorder and related disorders were separated from anxiety disorders to reflect increasing evidence of these disorders' relatedness to one another and to distinguish them from anxiety disorders. Secondly, hoarding and excoriation (skin-picking) disorders are now two new disorders in DSM-5. These are critical changes that may bring more awareness to all of these disorders as distinct from other anxiety disorders and of their significant impact on quality of life for people. It is still recognized that there are close relationships among obsessive-compulsive disorders and anxiety disorders; therefore, the chapters are sequential in DSM-5. Thirdly, some new specifiers were added into individual diagnoses (marked with * in text). Here most noted diagnosis, prevalence estimates, risk, and prognosis are derived from DSM-5.

The obsessive-compulsive and related disorders include the following:

- Obsessive-Compulsive Disorder (OCD)*
- Body Dysmorphic Disorder
- Hoarding Disorder*
- Trichotillomania (Hair-Pulling Disorder)*
- Excoriation (Skin-Picking) Disorder*
- Substance/Medication-induced Obsessive-Compulsive and Related Disorder
- Obsessive-Compulsive and Related Disorder Due to Another Medical Condition
- Other Specified Obsessive-Compulsive and Related Disorders*
- Unspecified Obsessive-Compulsive and Related Disorders

Obsessive-Compulsive Disorder (OCD) OCD is delineated by individuals suffering from obsessions and/or compulsions that the individual feels driven to complete rigidly. *Obsessions* are intrusive, unwanted, recurrent, and persistent thoughts, urges, or images. *Compulsions* are rigidly applied repetitive behaviors or mental acts that individuals perform in response to an obsession and can often follow rules which are strictly adhered to. For highlights of key DSM-5 diagnostic criteria, please refer to Table 13.1, including marked changes which include updated range of insight specifiers and the added specifier if OCD is tic-related.

Table 13.1 Obsessive-Compulsive Disorder (OCD) [1]

DSM-5 criteria: diagnostic highlights
Key characteristics:
Presence of obsessions, compulsions, or both
Obsessions/compulsions are time-consuming (>1 hour/day) or cause significant distress or impairment
Specifiers:
Level of insight: good/fair, poor, absent/delusional
If it is tic-related
Differential diagnosis:
Symptoms are not secondary to or better explained by other medical conditions or other psychiatric disorders
Not to be confused with obsessive-compulsive personality disorder (OCPD)

Prevalence Prevalence of OCD is 1.2% in the USA with similar values internationally. Males are more commonly affected in childhood, whereas females are affected at higher rates in adulthood.

Differential Diagnosis Obsessions in OCD show a spectrum of severity which may even reach delusional proportions, making it similar to delusional disorder. OCD can be differentiated from delusional disorder by the presence of repetitive compulsions or rituals intended to reduce the distress associated with the obsession. Obsessive-compulsive personality disorder can share features with OCD, particularly preoccupation with order. Individuals with obsessive-compulsive personality disorder show rigidity and inflexibility in multiple domains of their life and do not typically have the specific rituals associated with OCD. They react with annoyance rather than anxiety when they are not able to indulge their obsessions/compulsions.

Disease Course Onset is typically gradual, and duration is typically chronic, with a waxing and waning course. Its severity can also be graded based on its impact to quality of life, with high levels of social and occupational impairment. Avoidance is a significant issue as it can affect the patient's engagement with loved ones or even the ability to take medications or engage in treatment (e.g., fear that medications may be contaminated). Health consequences can occur such as skin excoriation from excessive hand-washing and when combined with other medical problems may trigger infections or non-healing wounds.

Risk and Prognosis Factors Despite 50% of the cases having been reported to have had pediatric onset, the prognosis for adult-onset OCD is poorer than pediatric-onset OCD. Little research is done specifically in older adult populations. Exposure to physical or sexual trauma and/or stressful traumatic/stressful events in childhood has been associated with increased risk of developing OCD. Having a first-degree adult relative with OCD doubles the risk of an individual

developing OCD. If the first-degree adult relative developed OCD as a child, an individual's risk increases tenfold. Twin studies suggest a strong genetic component to the heritability of OCD. Concordance rates in monozygotic twins range from 80% to 87%; in dizygotic twins, concordance is from 47% to 50% [2, 3]. Suicidal ideation is thought to occur in up to half of individuals with OCD with suicide attempts in one-quarter of the individuals with OCD. Psychiatric comorbidities, including major depressive disorder, increase suicide risk.

Body Dysmorphic Disorder Body dysmorphic disorder is a preoccupation with one or more potential defects or flaws an individual perceives in their physical appearance making him/her believe that he/she looks ugly. These defects or flaws are slightly or not observable by others; however, the individual's concern ranges from "not right" to "hideous" or "monster-like." These preoccupations classically involve the skin, hair, or nose but can focus on any area of the body. Some people focus on certain anatomic details including scars, wrinkles, and asymmetry of body areas. The preoccupations are defined as intrusive and time-consuming (affecting daily life). Excessive or repetitive behaviors or mental acts are performed with this disorder in response to the preoccupation which are not pleasurable to the individual and may also increase anxiety or dysphoria. These preoccupations are known to cause significant distress and/or impairment in daily functioning (including social or occupational areas). Oftentimes, these individuals do not present to a psychiatrist for treatment but rather to another medical/surgical specialist (especially dermatology and plastic surgery) seeking improvement in perceived physical flaws. For highlights of DSM-5 diagnostic criteria, please refer to ◘ Table 13.2.

Prevalence Point prevalence is 2.4% in the USA independent of sex and postulated to be 1.7–18% outside of the USA (e.g., Germany). Presentation is highest among dermatologic patients (9–15%); then cosmetic surgery patients (7–8% in the USA, larger in international cosmetic surgery patients (3–16%)); 8% among orthodontia patients; and 10% in patients presenting for maxillofacial surgery.

Differential Diagnosis Unfortunately, geriatric patients are more likely to have actual medical disease, particularly malignant or nonmalignant tumors which may create a real focus for their attention. Clinicians should be cautious about dismissing a person's concerns without conducting an appropriate physical examination. Body dysmorphic disorder can be confused with illness anxiety disorder (new to DSM-5, similar to hypochondriasis in DSM-IV) or somatic symptom disorder (also new in DSM-5, similar to somatoform disorder in DSM-IV). However, persons with body dysmorphic disorder will show disproportionate concern with their appearance, whereas individuals with illness anxiety disorder are preoccupied with the *significance or etiology* (usually fearing an ominous causative illness) of the perceived physical flaw, not necessarily its appearance, per se. Individuals with somatic symptom disorder are concerned about symptoms. Due to the rituals associated with body dysmorphic disorder, it is diagnostically similar to OCD but is specific to concerns about appearance and rituals associated with seeking reassurance or mitigating flaws in appearance. Concerns specifically with body weight should be evaluated as related to an eating disorder before being attributed to body dysmorphic disorder.

Disease Course Mean age of onset is 16–17 years with most common age of onset at 12–13 years. Two-thirds of the patients present before 18 years old. Those with onset before 18 years old are associated with more comorbidity and higher suicide risk. Twenty percent of youths with body dysmorphic disorder drop out of school secondary to symptoms associated with body dysmorphic disorder, and this can significantly affect their quality of life and future livelihood at ages above 50 years old. Missed school or work and being late to school or work illustrate how maintaining employment is challenging with struggling with active symptoms. Specific data on the older adults with this disorder is limited, as younger age groups are more frequently studied.

Risk and Prognosis Factors Body dysmorphic disorder is associated with high rates of childhood abuse and neglect. Its prevalence is also elevated in individuals who have first-degree relatives that suffer from OCD.

◘ Table 13.2 Body dysmorphic disorder [1]

DSM-5 criteria: diagnostic highlights
Key characteristics:
Individual has preoccupation with one or more perceived physical appearance flaws or defects that are not observable or appear slight to others
At one or more points, the individual has performed repetitive behaviors or mental acts in response to appearance concerns
Preoccupations are associated with significant distress
Specifiers:
Level of insight: good/fair, poor, absent/delusional
If it is with *muscle dysmorphia*
Differential diagnosis:
Symptoms are not secondary to or better explained by other medical conditions or other psychiatric disorders including body/fat-related issues in eating disorders

Teaching Point

There are iatrogenic harms incurred by older adult patients with body dysmorphic disorder seeking cosmetic or unnecessary procedures. Higher intraoperative risk, delayed wound healing due to age or medical comorbidity, and poor post-procedure self-care due to diminished ability with activities of daily living and social isolation can lead to greater morbidity and mortality than with younger patients.

Table 13.3 Hoarding disorder [1]

DSM-5 criteria: diagnostic highlights
Key characteristics:
Accumulation of possessions resulting from difficulty discarding clutter in active living areas to the point of congestion and substantially compromises their intended use
Behaviors cause significant functional impairment or distress
Specifiers:
Level of insight: good/fair, poor, absent/delusional
If it is with excessive acquisition or animal hoarding
Differential diagnosis:
Symptoms are not secondary to or better explained by other conditions/disorders (e.g., brain injury, cerebrovascular disease, genetic syndromes)

Hoarding Disorder* Hoarding disorder is defined as a persistent difficulty discarding (or parting with) possessions. This behavior is independent of the value of the possessions, and the behavior is associated with harmful effects. Harmful effects can include but are not limited to financial, social, emotional, physical, or even legal consequences. While many people collect items or possessions, hoarding is distinguished as accumulating large quantities of possessions that can fill up or clutter active living areas of home or workplaces to an extreme that their intended use is not possible. **DSM-5 changes:* Hoarding disorder is now recognized in DSM-5 as a distinct disorder when in earlier editions hoarding was considered part of OCD or obsessive-compulsive personality disorder, anxiety disorder not otherwise specified, or without diagnosis. The creation of a unique diagnosis in DSM-5 was intended to increase public awareness, improve identification of cases, and promote research or development of treatments for hoarding disorder. For highlights of DSM-5 diagnostic criteria, please refer to Table 13.3. DSM-5 recommends assessing if there are characteristics consistent with excessive acquisition.

Prevalence Point prevalence in the USA and Europe is 2–6% though it is found to be a universal phenomenon. It normally affects both sexes; however, some studies suggest greater prevalence in men, but clinical samples are predominantly women, and it is noted that women may display more excessive acquisition and buying behaviors. Symptoms of hoarding are three times more prevalent in older adults (55–94 years) than in younger adults (34–44 years).

Differential Diagnosis Hoarding disorder is frequently comorbid with OCD, but OCD could be mistaken for hoarding disorder. If the person's collecting behavior (compulsion) is intended to ward off some imagined eventuality (obsession), the behavior may more accurately be attributed to OCD. Collectors may run the spectrum from hobbyist to "eccentric" to hoarding, so it is important to assess the impact on the person's *level of function* related to their collecting or collections—how much does their behavior or collections themselves interfere with their lives? Do the collections place an undue financial burden? Are the collections stored and catalogued, or are they kept haphazardly around the dwelling? Most collectors will keep their items in easily found places and sorted and organized, whereas hoarders do not, nor do hoarders typically collect specific or valuable items. Major neurocognitive disorder may result in behavior similar to hoarding due to cognitive difficulties remembering what the individual already has at home, but major neurocognitive disorder may also be comorbid with hoarding disorder. Diogenes syndrome (the vast majority of whom are geriatric) has been used to describe patients who hoard, live in squalor, have no shame associated with their circumstances or behavior, and engage in self-neglect, to the point of rejecting help.

Disease Course Hoarding classically begins early in life but can often persist and become significantly problematic in adulthood. Most research participants are around 50 years old with limited studies in older adults. Severity of hoarding increases with each decade of life. Symptoms are considered chronic with a waxing and waning course. Some who hoard may not appear distressed; others can suffer significant social or occupational impairment or distress. The behavior of accumulation can distress others including family members or landlords. Severe cases have history of legal evictions or are in the process of eviction when they present clinically. Clutter impairs daily function significantly, ranging from navigating their home safely; having water or electricity disconnected due to broken appliances that cannot be reached or repaired; affecting cooking, cleaning, or even personal hygiene; or the ability to maintain or reach an area to sleep. Of note, a subtype of hoarding involves accumulation of a large number of animals in excess of individual's ability to maintain the animals' minimal standards of care, nutrition, and safety. While less common, it should be considered as a future area of study in older adults who are more socially isolated and may be more vulnerable to the accumulation of animals as surrogate family and companionship. There is also greater likelihood that the animal hoarding behavior will impact their self-care, maintenance of hygienic living conditions, or potentially lead to adverse outcome such as evictions or severe health complications.

Risk and Prognosis Factors It should be noted that a strong familial pattern of presentation given 50% of those with hoarding disorder has a relative that hoards. Twin studies indicate that 50% of variability in hoarding behaviors can be associated with cumulative genetic factors.

Trichotillomania (Hair-Pulling) Disorder Trichotillomania (hair-pulling) disorder is defined as pulling out one's own hair recurrently on any part or region of the body where hair is present. The most common sites are scalp, eyebrows, and eyelashes. Hair-pulling behavior can vary over time ranging from episodic to time of day but can continue for hours. For behavior to qualify for the disorder, it must be associated with hair loss.

Table 13.4 Trichotillomania (hairpulling disorder) [1]

DSM-5 criteria: diagnostic highlights
Key characteristics:
Hair loss as a result of pulling out one's own hair chronically
The individual attempts to stop or reduce hairpulling
Behavior causes significant impairment or distress
Differential diagnosis:
Dermatologic condition, OCD, body dysmorphic disorder, alopecia due to medical condition or iatrogenic condition

Table 13.5 Excoriation (skin-picking) disorder [1]

DSM-5 criteria: diagnostic highlights
Key characteristics:
Self-induced skin-picking that is repeated and causes skin lesions
The individual attempts to stop or reduce skin-picking
Differential diagnosis:
Dermatologic condition, delusional parasitosis/substance-induced psychosis

For key DSM-5 diagnostic criteria, please refer to Table 13.4. **DSM-5 changes:* It should be noted that the descriptor "hair-pulling" was added to increase awareness of the disorder's definition as it was found that there is lack of familiarity with the term *trichotillomania* within clinicians.

Prevalence Trichotillomania affects 1% of the general population of adults and adolescents at any given time. Females are affected more than males at an approximate rate of 10:1. Prevalence is similar across cultures.

Differential Diagnosis Care should be taken to distinguish hair pulling from normative hair removal for cosmetic purposes. Alopecia may be differentiated from trichotillomania by the compulsion to actively remove hair in the latter. Skin disorders such as eczema or psoriasis may cause scratching in areas of hair growth, but the individual's goal is to relive itching rather than hair removal, and one can usually see evidence of scaling or plaques from the skin disease. Thyroid disorders may cause hair loss or increased turnover of hair, though would be a rare cause of trichotillomania. Hair pulling that is done for sexual gratification or done to others does not meet criteria for trichotillomania.

Disease Course Onset of symptoms occurs early in life, and most individuals admit to hair-pulling associated with significant distress and impairment in social or occupational realms. Onset of behavior can coincide with onset of puberty and have a waxing and waning course postulated to worsen with hormone changes or menstrual cycles. The minority of patients remit without future relapse in their life span. Descriptions of older adult onset and progression of the disorder in later life are limited to case reports—there is little research about trichotillomania in older adults, and more research is needed in this area.

Risk and Prognosis Factors Evidence supports that trichotillomania has increased occurrence in individuals who have first-degree relatives with OCD, indicating genetic vulnerability.

Excoriation (Skin-Picking) Disorder* Excoriation (skin-picking) disorder is defined by recurrent skin-picking resulting in lesions. To qualify for this disorder, individuals who pick must have repeated attempts to stop or decrease skin-picking with marked impairment in social, occupational, or other important functional areas of daily living. These symptoms are not best defined by another psychiatric disorder. For key DSM-5 diagnostic criteria, please refer to Table 13.5. **DSM-5 changes:* It was included in DSM-5 after literature reviews revealed its prevalence. It is thought to be a clinically significant, specific diagnosis and is associated with multiple medical issues including infections, skin lesions, scarring, and physical disfigurement. These may be harder to treat in the older adults who may have many chronic medical problems, be slower to heal, and have more significant complications.

Prevalence Lifetime prevalence is estimated to be 1.4% or higher. Initial information suggests three-quarters of the affected individuals are women, but prevalence may vary across cultures.

Differential Diagnosis Excoriation disorder may be difficult to discern from a skin condition such as eczema or psoriasis as all three conditions result in skin lesions. However, individuals with skin-picking disorder do not start out with skin lesions. The skin lesions are secondary to their excoriation behavior and are not generally associated with itching or other sensations from the underlying skin. This condition should also be distinguished from delusional parasitosis, sometimes associated with psychostimulant (particularly methamphetamine) use. In delusional parasitosis, the picking is driven by a belief that there are insects or other "bugs" under the skin. Acute or subacute onset of symptoms may indicate delirium or substance withdrawal. Sudden onset of symptoms in medically ill patients associated with waxing and waning level of mental status should cause clinicians to investigate medical causes of delirium, such as infection, hypoxia, or encephalopathy. If associated with autonomic hyperactivity and suspected or reported alcohol or benzodiazepine use, withdrawal should be ruled out. Older individuals with suspected skin-picking disorder should be examined for evidence of skin cancer as well.

Disease Course Age of onset and presentation can be variable. Onset commonly occurs with onset of puberty (similar to trichotillomania). Typically, it follows a chronic course but can be variable (waxing and waning) and can be episodic.

Skin-picking can be associated with intense emotions, boredom, or minor skin irritation. There may be tension associated with resisting urges to pick skin followed by pleasure, relief, or gratification after picking skin or scabs have occurred. Skin-picking typically does not occur in the presence of others, and only some individuals disclose their behaviors to others. Skin-picking can be associated with missed school or work as excoriation behaviors can last one hour or longer. Picking also can be associated with tissue damage and scarring, repeated infection requiring antibiotics, or even surgery. This can be particularly concerning in older adults with multiple medical illnesses with higher risks of complications. It is suspected that skin-picking may have histopathologic distinguishing characteristics, but data is limited.

Risk and Prognosis Factors Similar to many disorders covered in this chapter, there is increased risk in individuals who have a first-degree relative with OCD compared to the general population. We have highlighted the most common disorders in this chapter, and the reader is referred to DSM-5 diagnostic manual for more details on disorders not covered in depth here including substance/medication-induced obsessive-compulsive and related disorder, obsessive-compulsive and related disorder due to another medical condition, other specified obsessive-compulsive and related disorders (new diagnosis in DSM-5), and unspecified obsessive-compulsive and related disorder.

Teaching Point

While DSM is helpful for initial diagnosis, it is important to bear in mind that some cases may not fit classic DSM criteria for diagnosis due to various reasons including cultural explanations of illness. It is important therefore to consider DSM as a helpful guide rather than rigid criteria and offer potential treatment when pertinent in geriatric individuals if there is potential to improve quality of life.

13.1.2 Epidemiology

While anxiety disorders seem to decline in prevalence in the older adult population, anxiety remains a common psychiatric complaint among adults over the age of 65 [4]. In studies conducted on the general population in the USA, Canada, and Europe, researchers have found rates ranging from 3.5 to 14.2% [5]. Of the obsessive-compulsive and related disorders, OCD is the most commonly encountered and diagnosed disease, with prevalence estimates of about 1%, decreased compared with younger adults, with a slightly increased prevalence in women [5]. No studies have found differences among racial or ethnic groups related to obsessive-compulsive and related disorders, though this may be due to its low prevalence. OCD is highly comorbid with schizophrenia, with approximately 12.1% of the patients with schizophrenia also meeting criteria for OCD over their lifetime and 25% experiencing obsessive-compulsive symptoms [6].

Hoarding disorder typically appears before age 65 but tends to worsen with age, with middle-aged and geriatric people presenting with more severe symptoms. Thus, patients may not present with symptoms of hoarding behavior until later life, when their habits present clinically or socially relevant impairments in function [7]. This is particularly important as despite affecting only 2–5% of the population, these behaviors can be severe, including life-threatening or severe health hazards. In older adults it can be more of a concern for fall or fire hazards, not only for themselves but also for neighbors.

13.1.3 Etiology

Anxiety disorders have been postulated to involve the dysregulation of noradrenergic, serotonergic, and GABA-ergic neurotransmitters. The locus ceruleus remains the brain's primary source of noradrenergic neurons, and normal aging leads to a significant reduction in its cells that leads to a reduction of noradrenaline and monoamine oxidase levels in the brain, thus postulated to reduce the risk for development of anxiety disorders in this population [8–10]. New-onset hoarding has also been noted as incident to damage to the medial prefrontal and orbitofrontal cortex in patients who had no prior history, so head trauma may explain new-onset symptoms in patients with no history of hoarding behavior [11].

Some researchers have noted associations with new-onset OCD among people with schizophrenia treated with second-generation atypical antipsychotics such as clozapine and olanzapine, postulated to be due to the drugs' anti-serotonergic effects at the $5HT_{2A}$ receptor level [12]. As these are medications which may be used in later life due to previous treatment failures or behavioral problems related to other disorders, clinicians should be aware of the possible iatrogenic effect.

There is an environmental risk factor for early-onset OCD (which may persist in adulthood and geriatric age) in childhood streptococcal infection which leads to abrupt onset of obsessive-compulsive symptoms and co-occurring tics. It is considered a pediatric autoimmune neuropsychiatric disorder associated with streptococcal infection (PANDAS) which can result in relapsing and remitting OCD and OCD-related symptoms associated with recurrent streptococcal infections, though there has been no report of this persisting into older age.

13.1.4 Diagnostic Evaluation

For all of the OCD-related disorders, diagnosis is clinical, thus, primarily based on interview. Physical exam and diagnostic studies should be conducted as indicated, particularly when the history does not strongly support the diagnosis.

Rating scales, such as the 10-item Yale-Brown Obsessive Compulsive Scale (Y-BOCS), are useful for assessment of severity and response to treatment in OCD. The Saving Inventory-Revised (SI-R) is a diagnostic instrument that can

even help discern hoarding behavior from other obsessive-compulsive disorders [13]. The Clutter Image Rating (CIR) has been validated in older populations as an assessment tool for the severity of hoarding behavior and allows clinicians to assess severity of clutter via objective rating of images from the individual's home [14]. The Massachusetts General Hospital Hairpulling Scale (MGH-HPS) and the NIMH Trichotillomania Severity Scale (NIMH-TSS) are two widely used measures of trichotillomania severity, though neither have been studied specifically in the geriatric population.

Clinical History Taking

Geriatric patients with obsessive-compulsive and related symptoms should be interviewed both individually and with a collateral data source, when available. Those with OCD or trichotillomania should have insight into the illogical nature of their behavior and thoughts but may minimize the severity or frequency of both, whereas those with hoarding disorder may not view their habits as problematic at all. Remember that struggling with these disorders may be very distressing for the individual, associated with embarrassment or guilt, and may also be associated with significant functional impairment in daily living and quality of life. Family or friends may offer less biased observations of how impairing or problematic the behaviors are, including having to provide frequent reassurance about particular obsessions. A history should include duration, onset of symptoms, frequency, and associated illogical thoughts or rituals that the person feels compelled to execute. Consider asking about childhood trauma, neglect, major stressors, as well as education and employment history (recall 20% of youths with body dysmorphic disorder report dropping out of school as a result of struggling with body dysmorphic disorder symptoms). (See ► Chap. 14.)

Teaching Point

Establishing rapport with the patient is critical; creating safety for self-disclosure is important. Do not forget that avoidance is a key tenet found in many of these disorders, including avoiding disclosure or masking of symptoms—this underscores the importance to pay attention to nonverbal cues and signs. Note changes in posture (such as pulling on clothing to cover areas of excoriation) or eye contact when discussing sensitive topics.

Questions to Ask for OCD

Screening for OCD can be complex. To effectively screen, it is important to recall that patients are hesitant to disclose information about habits, obsessions, or compulsions for various reasons including shame, fear, and embarrassment. Therefore, it is critical to establish rapport and trust when exploring these topics. They may have put significant effort into masking these symptoms. It is important to be mindful of asking about symptoms in a nonjudgmental way. Normalizing statements when interviewing can be useful.

» I ask all patients I meet for the first time a number of questions including the following: Do you have any specific habits, or activities you do repeatedly on a daily basis? Sometimes people have specific fears or worries about certain topics including fear of infection or contamination, or fear of someone breaking into a home or harming them. Do you experience any of these or other fears/concerns? Do your fears/worries ever make you feel compelled to complete certain tasks or activities? How do you feel if you don't complete these tasks/activities?

Some common screening questions include exploring if an individual has specific fears, habits they repeat, or any rituals. It can be helpful to ask specifically if they have common fears including of contamination or infection and if they have frequent hand-washing or other types of cleaning. Separating your questions related to obsessions *or* compulsions can also be helpful.

» Do you ever experience specific fears, worries or have concerns that you can't get out of your mind? Do these thoughts ever prevent you from completing tasks or affect your daily tasks? Do these thoughts or fears ever affect your interaction with others or socially?

Note that, if individuals fear leaving home and become isolated there, they may be very hesitant to disclose it to their clinician. When patients answer affirmatively for any of the above, it is often helpful to explore more details and quantify the thoughts or habits or ritual activities.

» How often do you complete this (habit/ritual)? How long does it take you? Does it disrupt any daily routines? Does this activity affect you getting to places on time (for example: locking doors or checking locks associated with getting late to appointments outside of the home)? What happens if you are interrupted while completing this task? Does the activity ever affect you physically (hand-washing resulting in chafed or bleeding hands)?

Questions to Ask for Hoarding

Teaching Point

Self-disclosure may be significantly limited about symptoms, or behavior may not be perceived as problematic; therefore, responses to questions about the patient's dwelling, home safety, and stability (history of eviction or pending eviction notice) can be very informative.

» Have family members or friends commented that you have too much stuff or that you need to throw things away that you don't feel comfortable discarding? Have you ever been forced to move because you were told that your home was too cluttered or unsafe?

At times governmental agencies or social services such as Adult Protective Services may need to be consulted due to concerning living conditions. Interventions may range from

assistance with obtaining treatment, in-home support for cleaning/decluttering, or condemnation and relocation due to unsafe home environment. It is important to remember that the objective for most of these agencies is to maintain maximal independence and continued self-sufficiency for older and disabled individuals. Often, clinicians can call Adult Protective Services to describe a concerning situation without obligation to disclose information about the individual unless the agency deems it necessary. Individual states have differing statutes regarding mandated reporting. Clinicians should familiarize themselves with their local laws.

Physical Examination

As OCD, trichotillomania, excoriation disorder, and hoarding disorder are clinical diagnoses; physical exam findings may be minimal. Clinicians should conduct a thorough neurological exam, looking for lateralizing and localizing signs that may indicate brain injury, but this is a rare cause of OCD or related disorders. Relevant physical findings related to OCD, trichotillomania, or skin-picking generally relate to the compulsive behavior and can indicate or confirm severity (e.g., excoriation of hands from excessive hand-washing, bald patches including eyebrows and eyelashes from hairpulling, cellulitis, or scarring from skin-picking). It is also important to consider how individuals may mask findings including putting on hair wraps or gloves or engage in behaviors on areas that are normally clothed (pulling out toenails instead of finger nails).

Laboratory Examination

There are no conclusive findings of EEG, MRI or CT, or other diagnostics that will confirm diagnoses of OCD and related disorders. As with other psychiatric conditions, clinicians are recommended to check a sensitive thyroid-stimulating hormone (TSH) to rule out systemic medical contribution or cause of the symptoms, but these conditions are rarely the result of thyroid abnormalities.

Medical Risk and Comorbidity

OCD and related disorders have high comorbidity with depression (nearly 25%), alcohol use, generalized anxiety disorder, and agoraphobia. Interestingly though, alcohol use in the general older adult population is associated with *lower* rates of anxiety. Hoarding is described commonly with OCD but may occur independently as well. Anxiety disorders are seen frequently in individuals with coronary artery disease, but there are no studies of the subset of patients with OCD and related disorders and cardiac diseases. Major or mild neurocognitive disorder does not seem to be a risk factor for any anxiety disorders except for perhaps in hoarding disorder, where it may also present a complicating factor with regard to housing placement [5].

13.1.5 Treatment

Non-pharmacological Treatment

For most patients suffering from OCD, cognitive behavioral therapy (CBT) is considered first-line treatment. It is considered first line for all degrees of severity of OCD. Exposure and response prevention is considered the most essential component of CBT in OCD treatment. It involves the psychotherapist supporting the individual to have progressive prolonged exposure to triggers and supporting efforts in resisting compulsion responses. Other psychotherapies including psychoanalytic psychotherapy have limited efficacy in OCD or OCD-related disorders (Please refer to ► Chap. 8).

Literature and study data are limited for efficacy using CBT in older adults specifically for OCD or OCD-related disorders. However, it is known that response rates of CBT are lower in "late-life" samples compared with younger adults for generalized anxiety disorder and characteristics of generalized anxiety disorder overlap in some areas with OCD and OCD-related disorders. Designation of what is considered onset of late-life also varies among studies from 60 years and older to other study data with mean age 66.9 years [15–18]. For example, only 40% of the late-life individuals studied in a primary care setting responded to CBT interventions for generalized anxiety disorder compared with 56% in younger individuals [15, 17]. Often, one barrier to treatment is location as some older adults live in rural areas where therapy is not readily accessible in person. One study of over 2000 patients found that telephone-delivered CBT was more effective than telephone-delivered nondirective supportive psychotherapy in this population living in rural settings [19].

Group treatment is thought to have benefit in treating older adults. It encourages interaction and promotes self-disclosure which may increase the efficacy of CBT in older adults [20]. Group treatment may also reduce social isolation for older adults which can be a significant support for those whose OCD or OCD-related disorder has isolated them from family or loved ones.

Teaching Point

Older adults may benefit from incorporating learning aids (e.g., acronyms) and memory enhancers (e.g., homework reminders, alarms, weekly review of techniques) to compensate for short- and long-term memory deficits if present. They may have improved response with slower-paced CBT sessions and fewer homework assignments and being open to adapt the process for each individual.

Treatment of OCD is thought to be more efficacious using CBT rather than other psychosocial interventions. Studies suggest that CBT that involves exposure and response prevention is more effective than antidepressant treatment. SSRI treatment is considered a reasonable alternative to CBT if CBT is not available or if patient is unable or unwilling to engage in psychotherapy.

Pharmacological Treatment

No medications have received regulatory approval for treatment of OCD or related disorders specifically in the older adults, so studies have concentrated on medications

indicated for OCD or anxiety disorders in younger adults. Furthermore, no medications have received indication for treatment of OCD related disorders (outside of OCD itself), including trichotillomania or hoarding disorder. Clinicians have focused on treatments that are indicated or have been shown to be effective for OCD. Clomipramine (a tricyclic antidepressant (TCA)) and fluoxetine, fluvoxamine, paroxetine, and sertraline (selective serotonin reuptake inhibitors (SSRIs)) are all approved by the US Food and Drug Administration (FDA) and Health Canada for treatment of OCD in adults but may pose unique risks in the older adult population. For example, reductions in hepatic blood flow associated with aging leads to delayed clearance of drugs metabolized by CYP3A4 such as alprazolam, triazolam, sertraline, and mirtazapine [21]. (See ▶ Chap. 5.)

Due to the increased prevalence of psychiatric and systemic medical comorbidities and polypharmacy involved in treating geriatric patients, clinicians should use caution with medications known to inhibit the cytochrome P450 enzyme system, such as fluoxetine, fluvoxamine, and paroxetine (see ◘ Table 13.6). In particular, fluvoxamine causes inhibition of multiple important enzymes involved in the metabolism of medications and is not recommended as a first-line treatment in older adults. Clomipramine, while considered a serotonergic reuptake inhibitor (SRI), still retains properties of TCAs that include anticholinergic, antihistaminergic, and alpha-1 blockade, as well as cardiac conduction delays, so should be avoided as well. SSRIs have been associated with increased risk of gastrointestinal and intra/postoperative bleeding due to blockade of serotonin transporters in platelets. Platelet activation and aggregation (clotting) are stimulated by serotonin release from the platelets, but the platelets are dependent on the extracellular transport of serotonin into the platelets, thus, inhibited from initiating the clotting cascade in the presence of SSRIs/SRIs.

Venlafaxine, a serotonin-norepinephrine reuptake inhibitor (SNRI), has been used in OCD and related disorders with evidence of success in small, non-placebo-controlled studies. It is associated with mild elevations in blood pressure, so patients with preexisting hypertension should be monitored closely for worsening of blood pressure. Venlafaxine, even in its extended-release (daily) formulation, has a short half-life and is associated with a significant discontinuation syndrome if stopped abruptly.

The accepted school of thought regarding medication treatment in the older adults is "start low, go slow." As with other medications used in geriatric populations, clinicians are encouraged to start with one-quarter to one-half of the usual starting doses for younger adults. However, as described in treatment of other anxiety disorders, pharmacological treatment may require higher doses than those used for depression and a longer treatment trial (10–12 weeks) to assess response. (See ▶ Chap. 12.)

Since 2011, the FDA and Health Canada issued new warnings with the SSRI citalopram, restricting the dosing to 40 mg or less in most adults (20 mg or less in patients over 60 years of age), and revealed that citalopram was found to be associated with prolongation of QTc and increased risk of development of torsade de pointes. Patients with underlying heart conditions such as congenital long QT syndrome or those predisposed to low potassium and/or magnesium are at particular risk [22]. Benzodiazepines should be avoided due to risks of cognitive and physical impairment. TCAs (besides clomipramine) have no proven benefit in the treatment of OCD and related disorders. Antipsychotics may be needed for extreme cases of OCD and OCD-related disorders, particularly as they approach or cross over to delusional beliefs. However, it is important to keep in mind that there are increased risks associated with atypical antipsychotics

◘ **Table 13.6** Potent CYP inhibitors and their substrates

Enzyme	SSRI inhibiting enzyme	Other medications affected
1A2	Fluvoxamine	Alosetron, caffeine, clopidogrel, clozapine, duloxetine, melatonin, ramelteon, tasimelteon, theophylline, tizanidine
2C9	Fluoxetine Fluvoxamine	Celecoxib, glimepiride, phenytoin, tolbutamide, warfarin
2C19	Fluvoxamine	Diazepam, lansoprazole, omeprazole, rabeprazole, voriconazole
2D6	Fluoxetine Paroxetine	Atomoxetine, amitriptyline, desipramine, dextromethorphan, eliglustat, encainide, imipramine, metoprolol, nebivolol, nortriptyline, perphenazine, propafenone, propranolol, tolterodine, tramadol, trimipramine, venlafaxine
3A4	Fluvoxamine	Alfentanil, alprazolam, aprepitant, atorvastatin, avanafil, budesonide, buspirone, colchicine, conivaptan, darifenacin, darunavir, dasatinib, dronedarone, ebastine, eliglustat, eletriptan, eplerenone, everolimus, felodipine, ibrutinib, indinavir, lomitapide, lovastatin, lurasidone, maraviroc, midazolam, naloxegol, nisoldipine, pimozide, quetiapine, rilpivirine, rivaroxaban, sildenafil, tadalafil, ticagrelor, tolvaptan

From ▶ http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm (Accessed 8 Nov. 2016)

in geriatric patients related to increased risks of cerebrovascular events and death. Older adult patients are also more susceptible to extrapyramidal symptoms, including tardive dyskinesia. Of the antipsychotics, haloperidol, risperidone, and aripiprazole seem to produce the most benefit in OCD and trichotillomania. Antipsychotics should only be used as an augmenting agent after a trial of at least 3 months of an SSRI at maximally tolerated dose [23].

Teaching Point
It is important to consider how genotypes may predispose patients to be more sensitive to medications and side effects related to the cytochrome P450 system. This may include delayed metabolism or increased metabolism through certain enzymes. These genetic differences may be more common in ethnic minority patients. Genetic testing may be helpful to assess or predict individual response or tolerability of drugs affected by these factors. Cultural factors such as diet or use of herbal/traditional remedies may cause interactions with conventional-prescribed medications as well.

Combining Treatments Randomized control trials in which CBT is added to SSRI treatment show that augmentation of SSRI with CBT has been more effective in those who have a partial response to SSRIs [24, 25]. Another study demonstrated that individuals with partial response to SSRIs had improved efficacy when combined with CBT exposure and response prevention than augmentation with risperidone or placebo [26]. It is important to remember that CBT is first-line treatment for OCD or OCD-related disorders when available and the patient is a good candidate for CBT.

Alternate Treatments

Deep brain stimulation is an alternate treatment hypothesized to benefit patients with severe OCD; however, its efficacy has not been established. Implantation is an invasive surgical procedure. It may have limited benefit in older adults who have significant medical illness or comorbidities that make surgical procedures contraindicated or higher bleeding risk (increased risk of cerebrovascular accidents). Most studies of efficacy using deep brain stimulation for OCD review adults below age 63 with decreases in Y-BOCS score by 7–31 points with treatment over a variable course ranging 3–36 months. Noted complications during studies include intracerebral hemorrhage and infections [27, 28]. Surgical alternatives include treatments like neurosurgical ablation but are invasive and considered higher risk for those with surgical contraindications or medical comorbidities, which is a concern with many older adults.

Transcranial magnetic stimulation is a noninvasive alternate consideration for treatment of refractory OCD involving placing a coil against the scalp and generating a magnetic field which induces an electrical current to depolarize neurons in the cerebral cortex. It involves multiple daily treatments, is still considered an experimental treatment for OCD, and is only indicated for treatment-resistant major depressive disorder.

Putting It All Together: "How Do I Pick the Right Treatment for My Patient?"

It can be difficult to select the right treatment for patients, especially older adults, but it can be helpful to focus on targeting which interventions will most likely be effective in improving quality of life and daily functioning. Often, involving social workers or a team approach is helpful to explore resources for the patient. Clinicians managing these individuals are faced with many questions such as "Are they able to engage in CBT? Would they benefit from group therapy? Do they have access or transportation to therapy or groups? Is it safe clinically to start an SSRI?"

Teaching Point
It is critical to focus interventions on improving quality of life and daily functioning of each older adult suffering from OCD or OCD-related disorders.

13.2 Case Studies

This section emphasizes two case studies intended to highlight how a geriatric patient with the featured disorder may present clinically along with important considerations in their work-up and management.

13.2.1 Case 1

Case 1 History

Mr. D. is a 71-year-old Chinese man who recently retired from an affluent information technology company as a senior managing accountant. He presents to his primary care clinic on the urging of his wife for increasing irritability and possible depression. As his primary care physician, you have seen him only once before for a brief medication refill visit after his previous physician retired. He reveals that he has been feeling more sad lately and intermittently tearful in the past few months but that it is centered around financial concerns since his retirement. He is home throughout the day, worried about how to pay bills, fearing that he is unable to support his family since he was previously the sole breadwinner in the home. He endorses struggling to find activities that fulfill him and is feeling bored. He rarely leaves the home, and when his children or grandchildren come to visit, he retreats to his bedroom to watch the news on TV and monitor his bank accounts on the computer. He continues to enjoy watching politics and news channels and has transferred his passion for accounting to monitoring bank account numbers and calling computer technical support companies to fix computers or programs on his devices for himself and for his

friends. His ability to focus on tasks and memory is intact. He has fair energy in the daytime, but he and his wife endorse that he is often late or misses events outside of the home due to struggling to be ready to leave on time. He denies any suicidal ideation or past suicide attempts. He denies any changes in appetite or weight and has not noted any problems with restlessness or decreased movement.

He receives treatment for hypertension with lisinopril 10 mg daily, diabetes mellitus with metformin 1000 mg twice daily, hyperlipidemia taking simvastatin 40 mg daily at bedtime, and hypothyroidism with levothyroxine 50 mcg daily. Because his father suffered severe diabetic complications, including below-the-knee amputation, he is meticulous about taking medications consistently. Mr. D. is also very regimented about the timing of his meals throughout the day to regulate sugar control; however, he also refuses to eat outside of the home, as he is worried it will disturb his control of blood sugar. He has no history of substance use, including alcohol, as he is concerned about the effects on his blood sugar. He has never smoked. He was born in the USA, but his parents were immigrants. He is married with three children and eight grandchildren.

At today's appointment his vital signs are within normal limits with temperature 98.7 °F (37 °C), blood pressure 124/74 mmHg, heart rate 70 beats/minute, respiratory rate 12 breaths/minute, and blood sugar 93 mg/dL (5.2 mmol/L), but he endorses pain (6/10 point scale) with walking. Given his diabetes mellitus, you want to conduct a physical exam of his heart and lungs and assessment of lower extremities including feet. Heart and lung exams are unremarkable, but when he removes his sneakers and pulls up his pants, you note that his skin is red, with hair loss, and appears visibly irritated, with tenderness to palpitation along skin surface from below the knee down to toes, but no induration or increased warmth. The skin areas appear to be scrubbed, and there is a slight, 5-mm-shallow ulceration on the anterior surface of his right tibia without exudate. Distal pulses are 2+ bilaterally in both feet (dorsal pedis and posterior tibial artery pulses). He is oriented to person, place, date, and situation. He names the last three presidents in his country and is able to calculate serial sevens without any difficulty.

Mr. D. immediately becomes very anxious and embarrassed, stating that he has been very fearful of ending up like his father who had below-the-knee amputation due to poor sugar control with complications. His father became an amputee at 75 years old, and Mr. D. feels that it is only a matter of time until the same thing happens to him. He is in the bathroom for 1.5 hours every morning and again before bedtime, examining his legs and feet. He wakes up early so his wife is less likely to notice. He worries about having fungal infections on his lower extremities (as he read that diabetics are at increased risk when he researched this topic on the internet) so he has been cleaning his legs daily with multiple antifungal creams and ointments as well as lemon juice. The cleaning and treatments started 10 years ago as once per week but have progressed to daily and longer durations since retiring. He has tried to stop the urge to treat his legs but has been unsuccessful due to very high anxiety when he tries to skip his examination or treatment routine. He has not told his wife about his legs and hides them in socks and shoes at home but realizes that he needs support as his skin is very irritated.

To evaluate his diabetes mellitus and look for occult evidence of cellulitis, you order a basic metabolic panel, hemoglobin A1C, lipid panel, complete blood count (CBC) with differential, and C-reactive protein (CRP). To rule out thyroid over- or under-supplementation as the cause of his OCD symptoms, you get an ultrasensitive thyroid-stimulating hormone (TSH).

You counsel him that you suspect that he has OCD and discuss potential treatments including psychotherapy, which he declines, citing struggles to leave the home and time constraints. After reviewing with him the potential risks, benefits, and side effects, he agrees to start citalopram 10 mg once a day. He is also encouraged to cleanse with fragrance-free hypoallergenic soaps only once daily followed by fragrance-free hypoallergenic moisturizers. To support him for his urges, you allow him to continue examining his legs and feet and offer to review a log of his findings in the next visit so you can both decide on treatment together. You make an appointment to see him in 2 weeks.

You also offer a psychiatry referral, but he declines, this time citing transportation issues and that he did not grow up "needing that stuff … my family didn't need, use or believe in that—we prayed." He describes that he is from an Asian minority background where prayer is favored over Western interventions including psychotherapy for behaviors.

Mr. D. presents to clinic 2 weeks later and states that he was tolerating citalopram for 7 days but in the second week is having a "bad reaction" to the citalopram, described as diarrhea, headaches, and full-body muscle aches, and he feels more anxious and restless. Vitals today reveal a blood pressure of 145/85 mmHg, heart rate of 102 beats/minute, and temperature of 100.1 °F (37.8 °C) with physical exam revealing slightly less irritated legs and reddened skin surface, but no obvious signs of infection. In reviewing his log, he spends 1 hour twice daily on his inspections but has stopped the cleanses with antifungals. He still cleans extensively with hypoallergenic soap once a day for up to 20 minutes at a time. Laboratory results are remarkable for normal glucose, but hemoglobin A1C is 6.4%; otherwise, basic metabolic panel, CBC, TSH, lipid panel, and CRP are unremarkable.

On review you ask him about other medications, over-the-counter medications, or herbals, and he apologetically reveals that in the last visit he did not have time to tell you that he was in pain (on his feet) and has been sleeping only 4–5 hours per night with some daytime fatigue and early-morning awakening, so he talked to his close friend who is a physician and started him on amitriptyline 50 mg at bedtime 7 days ago. He endorsed that his sleep and pain issues improved as a result of starting amitriptyline. Five years ago he had taken valerian root for sleep but denies current use.

Today, given his tachycardia and concurrent use of a tricyclic antidepressant, you order a 12-lead electrocardio-

gram (ECG). Six months prior, it had been unremarkable with a QTc of 408 milliseconds. Today's ECG reveals a heart rate of 108 beats/minute with sinus tachycardia and QTc of 452 milliseconds.

You counsel Mr. D. on the risks of combining medications without advice from a medical professional. He is amenable to stopping citalopram and amitriptyline today. As he appears well, with no neurological or motor signs, you feel comfortable with conservative management. After a few days of washout from citalopram and amitriptyline, he is amenable to starting sertraline 25 mg at bedtime and gabapentin 100 mg at bedtime for his peripheral neuropathy.

He continues to engage in care and follow-up with appointments for the next 4 months. You work with him to titrate sertraline to 150 mg daily with positive improvement in sleep and anxiety. He feels less compelled to examine his legs and feet, now engaging in the behavior for 35–45 minutes per day, and has some success resisting urges to clean at all approximately two times per week. He reveals that he is tired making "so many changes in my life," but agrees to continue because he values your recommendation as a physician.

You schedule him to follow-up again in 4 weeks, but he is a no-show. He does not return clinic calls over the next 2 weeks. You are concerned that he may have stopped treatment or that his dermatologic leg condition may have worsened. Given his past reactions, you are worried that he may feel ashamed about a relapse in his behavior. You consult your clinic colleagues on the case, the clinical director and the social worker. The clinic manager supports the social worker scheduling and completing a home visit to the patient.

After visiting the patient at home, the social worker states that the patient was very grateful for her coming to see him. He reports stopping sertraline immediately after his last appointment due to "wanting to be healthy on my own … I don't want to be dependent on medications to control what I should be able to do on my own." In the past 6 weeks since stopping medications, he notes increased worrying about his skin again and has been examining them more. He also restarted cleansing them with antifungal creams. He revealed to the social worker that he struggled with interpersonal relationships as a child; he loved his father, but his father was emotionally and physically abusive to his mother, himself, and siblings. He noted that even as a child he began to wash his hands more frequently when stressed. He ended his visit with her ambivalent about restarting sertraline but agreed that he would consider rescheduling with you.

After 4 additional months, he presents to your clinic for follow-up. He has not restarted sertraline but endorses severe pain in both lower extremities below the knee. On exam he is found to be febrile and has irritated skin from cleansing and open wounds on his anterior shins with evidence of cellulitis. He receives aggressive antibiotics and wound care treatment in the hospital, but due to difficulty with dressing changes, he is sent to a skilled nursing facility for 3 weeks as his wounds heal. As he is transitioned to home, he agrees to engage in an intensive outpatient psychiatry program, focusing on CBT and exposure and response prevention for his OCD. Your social worker arranges medical transportation for him to and from the treatment program. Ongoing treatment also included family meetings and psychoeducation for his wife and children to collaboratively support Mr. D. in his recovery.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What is your primary psychiatric diagnosis?

? Question 2. What potentially fatal drug interaction can occur with commonly used antidepressants?

Case 1 Answers

Case 1 Answer 1 (Question 1—What is your primary psychiatric diagnosis?)

Mr. D. meets criteria for OCD. He is unreasonably concerned (obsessed) with having a fungal infection and experiences these thoughts as unwelcome but has been unsuccessful in suppressing them. He undergoes rituals of inspecting and cleaning his legs and feet that are time-consuming and resulting in harm to his skin. He has insight into the problem and has been hiding it from his wife. He also shows evidence of obsessive-compulsive personality disorder, with rigid rules governing what and when he eats, even to the detriment of his health when he is outside of the home. His difficulty with sleep appears to have been due to pain, but he does not meet criteria for major depressive disorder at this time as his energy, appetite, and concentration are fine, and he does not have complaints about psychomotor agitation, or retardation, or thoughts about suicide or death. He describes feeling bored, having difficulty finding fulfillment, and becoming tearful, but this may be explained by his transition from work to retirement and is best categorized as an adjustment disorder with depressed and anxious mood. Adjustment disorders, depending on their severity, do not require pharmacological intervention by themselves.

Case 1 Answer 2 (Question 2—What potentially fatal drug interaction can occur with commonly used antidepressants?)

Serotonin syndrome is a condition of excess serotonin, usually attributable to use of SSRIs in combination with other drugs, such as tricyclics, triptans, tramadol, or meperidine. It is characterized by symptoms and signs of elevated temperature, diarrhea, tachycardia, muscle soreness or rigidity, hyperreflexia/clonus, ataxia, confusion, or even stupor and seizures. The care for serotonin syndrome involves immediate discontinuation of the offending agent(s) and supportive care, including intravenous fluids if necessary. In extreme cases, an anti-serotonergic agent such as cyproheptadine may be used. In addition, you are concerned about his cardiac conduction given the drug agency regulations of citalopram dosing and use with older adults (over 60 years old).

Case 1 Analysis Mr. D.'s presentation is an example of a complicated case of OCD in which the presentation is masked or obscured by comorbidities including likely obsessive-compulsive personality disorder as well as multiple medical problems.

What distinguishes OCD from obsessive-compulsive personality disorder is that OCD is associated with distressing urges and compulsions with repetitive thoughts, fears, or urges, whereas obsessive-compulsive personality disorder has more pervasive patterns of perfectionism and rigid controls without distressing urges or repetitive compulsions. In Mr. D.'s case, he meets criteria for OCD and possibly obsessive-compulsive personality disorder, but we are focusing treatment primarily on OCD here. (Please refer to ▶ Chap. 25, for specific information on obsessive-compulsive personality disorder.)

Treatment for OCD is challenging as there is prominent avoidance which delays the presentation further and limits the patient's ability to engage in interventions. In older adults, psychotherapy is still the first-line treatment, but one must also weigh if that individual has access to or is able to engage in therapy (transport, cognitive issues, openness to therapy, or stigma of psychiatric illness). Mr. D. manifested resistance to the idea of therapy based on familial and possible cultural views of psychiatric illness and therapy. Many ethnic minority cultures view those with psychiatric disorders as far more stigmatized than even modern Western society, and discussion of the problems with a therapist is considered taboo as it shares private information outside of the family. These same patients may be less likely to continue medications due to misconceptions about the continued need or duration of treatment (particularly people from countries where health care was episodic or only for acute conditions).

Teaching Point

Clinicians should investigate the health literacy of their patients and educate them on the indications for duration of treatment and prognosis of their condition with and without treatment.

At times SSRIs are appropriate first alternates or adjunct treatment. Individual psychotherapy has also been known to be more effective when combined with group therapy or memory aid tools (refer to ▶ section Non-pharmacological Treatment). In addition, team approach and collaborative support are even more important in treating older adults. Teams can pool potential resources including transportation, as well as provide psychoeducation to family and friends, which can increase support to isolated individuals suffering from OCD. This case also illustrates an extreme adverse clinical outcome due to medical complications to skin overcleansing. Building rapport with patients is critical to support them on this waxing and waning course.

13.2.2 Case 2

Case 2 History

Ms. H. is a 72-year-old Caucasian woman who presents via ambulance to the emergency room following a fall in her home. She reports to the emergency physician that she tripped in her living room and injured her hip but was able to call for an ambulance. The ambulance personnel report that upon their arrival, they discovered Ms. H. on the floor, surrounded by piles of what appeared to be old newspapers, magazines, and other papers such that they were unable to get a gurney into the home and had to carry Ms. H. out on a backboard. Because emergency services were activated, the fire department was on scene and declared the home uninhabitable, so Ms. H. cannot return upon her hospital discharge. An x-ray confirms that her left femur is fractured and she is given some morphine for pain control, but she remains lucid and coherent. Her past medical history is significant for hypertension, for which she is not taking any medication. She is single, never married, and denies any drug use. She is concerned about the fire department's decision about her home and insists that her home is a little "cluttered," but certainly not anything that should be considered problematic. She refers to the papers as her "collections." The emergency physician contacts social work and psychiatry services, while orthopedics decides if she needs surgery.

Ms. H. reports that she saves magazines and newspapers in case she wants the articles in them someday. She has been doing this since she was a teenager, and her mother, who had grown up during the Great Depression, had taught her to "waste not, want not." She states that it was a pile of magazines that had toppled over that caused her to slip and fall. Over the last several years, she has fallen because of similar slips, but she has never gotten hurt this severely before. She believes that she can just straighten up her piles and this should prevent future incidents.

There are no rituals or obsessive thoughts associated with Ms. H.'s collections. She does not exhibit any paranoia or false beliefs about her collections beyond a vague belief that they may come in handy "someday." She scores 30 out of 30 points on a Montreal Cognitive Assessment (MoCA).

Mrs. H. last saw her primary care physician 3 years ago and was told that she had hypertension and should lose some weight. Her physician told her that she no longer needed annual gynecological exams or mammograms, so she just stopped going to see him. On physical exam, she is noted to be hypertensive with a blood pressure of 150/90 mm Hg, heart rate of 72 beats/minute, respiratory rate of 14/minute, normal temperature, and body mass index of 40.5 kg/m^2 (obesity) and has no acute distress. Examination of her thyroid is normal, heart and lung sounds are normal, and neurological exam is negative, although motor exam of the left leg is limited due to pain and immobilization.

Ms. H. is taken to the operating room for internal fixation of her femur fracture. She gives permission for the hospital social worker to contact her sister, Ms. S. Upon hearing about her sister's accident, Ms. S. expresses distress but is not surprise about the conditions of the home. She reports that she has not been to the house in several years as Ms. H. had told her that she was not welcome back after the last time she visited and commented on the amount of clutter in the home. As a result, the only times she has seen Ms. H. have been at

family functions at other people's homes. She would like to help her sister but fears her reaction if she were to clean the home for her.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. What else do you need to know as the consulting psychiatrist to determine if she has a psychiatric disorder such as hoarding disorder?

? Question 2. Are there any other comorbid psychiatric problems or major neurocognitive disorder that may better explain her behavior?

? Question 3. What medical examination and work-up should be completed before ruling in a diagnosis of hoarding disorder?

? Question 4. What commonly comorbid geriatric conditions are likely to have the most clinical impact on an individual with hoarding disorder?

Case 2 Answers

Case 2 Answer 1 (Question 1—What else do you need to know as the consulting psychiatrist to determine if she has a psychiatric disorder such as hoarding disorder?)

Further history and ideally collateral descriptive reports or pictures of what the home is like would be helpful. Many individuals with hoarding disorder will minimize the severity of the problem. Questions to ask that help to discern whether her "collections" meet the criteria for hoarding disorder include asking what she collects and why and what would happen if the objects were discarded. Hoarding behavior is more commonly seen in women, who are often single and have never been married. They may have a family history of hoarding or "collecting" behavior. Hoarding behavior usually starts in earlier age, though can develop de novo in older adulthood, but in either case, the onset and severity are typically gradual, often without anyone who lives outside the home even noticing. Adults with hoarding disorder have some awareness that others may view their behavior or collections as abnormal and may avoid inviting people into their homes as a result. They may maintain a job, though if they have a personal workspace, that area may be perceived by others as cluttered and messy. It is often not until the person retires or develops reduced mobility that others may become aware of their hoarding behavior. Friends or family often attempt interventions without success as the person with hoarding disorder refuses to get rid of their belongings unless forced to. The objects hoarded may be specific or general, but the most commonly hoarded objects are newspapers, magazines, clothes, boxes, and household goods. A specific type of hoarding disorder, animal hoarding (Noah's syndrome), often involves cats or dogs, which presents a health hazard as the individual develops the inability to care for and clean up after the animals. News stories abound with reports of homes found with feces and bodies of deceased animals of which the person with hoarding disorder was unable to take care or simply could not find due to the disarray of their home. Patients with less severe circumstances are still at risk as it may only be a matter of time until their collections reach the proportions where their ability to safely ambulate is compromised or conditions reach a point where they are interfering with health and safety (e.g., windows/doors for evacuation are blocked by piles). A new housing situation may temporarily relieve the concern, but the individual (without treatment) is likely to resume the old behavior. The fire department's condemnation of Ms. H.'s home obviates the need to obtain further information from collateral sources as to the severity of the hoarding behavior, but in other cases, it may be necessary to get information from friends, family, and social services who can give a firsthand account of the conditions of the home. Adult Protective Services and social services can also render a decision about the safety and person's ability to return to the home.

Case 2 Answer 2 (Question 2—Are there any other comorbid psychiatric problems or major neurocognitive disorder that may better explain her behavior?)

To differentiate from other potential psychiatric disorders such as OCD or delusional disorder, it will be helpful to determine if Ms. H. has any specific obsessions or rituals associated with her "clutter" or any fixed, false beliefs regarding her collections. However, OCD is highly comorbid with hoarding disorder, and the presence of OCD does not rule out hoarding disorder. People with pure hoarding disorder compared with OCD have little insight into the problematic nature of their behavior. In contrast to patients with schizophrenia or delusional disorder, however, there are no false beliefs that would be viewed as delusional regarding the reasons they need to keep things. In fact, many of those with hoarding disorder may not be able to state a specific reason to hold onto their belongings, except that they may need them in the future. Getting rid of the objects or the thought of someone else getting rid of the objects fills the patient with hoarding disorder with anxiety; thus, they do not eliminate the excessive objects and resist others' attempts to do so. Social service agencies such as Adult Protective Services may have to seek alternative living arrangements for someone with hoarding disorder whose home has become unlivable. Only about 25% of the people with hoarding disorder have some form of major neurocognitive disorder, though this should be evaluated as well, since the presence of both neurocognitive disorder and hoarding disorder may further complicate the social disposition of the individual and dictate the higher level of support needs, including possible assisted living or skilled nursing services.

Teaching Point
Individuals with hoarding disorder can be distinguished from those with OCD or delusional disorder by their lack of insight into the severity of their behavior as well as an absence of bizarre reasons why objects need to be collected.

Case 2 Answer 3 (Question 3—What medical examination and work-up should be completed before ruling in a diagnosis of hoarding disorder?)

It is highly unlikely that the degree of severity of Ms. H.'s piles has occurred in a short period of time, and her own history corresponds with a lifetime of accumulation. However, in a patient with new-onset behavior, secondary causes of hoarding disorder should be investigated, including CT or MRI of the brain without contrast for tumor or metastasis, rapid plasma reagin for neurosyphilis, and TSH for hypo/hyperthyroidism. Physical exam should focus on neurologic deficits, musculoskeletal function, palpation of the thyroid, and signs of malignancy such as lymphadenopathy, breast lumps, abdominal masses, and prostatic nodularity in male patients. Age-appropriate cancer screening, including low-dose chest CT in patients with 30 pack year or greater history of smoking, should be performed [29]. In patients with history of lifetime hoarding behavior, physical and laboratory findings are rarely contributory to the diagnosis or management, but appropriate management of comorbid medical conditions is always warranted as these may affect the patient's quality of life and mobility status.

Common comorbid medical conditions with hoarding disorder include hypertension, obesity, seizures, sleep apnea, diabetes mellitus, and arthritis. These medical comorbidities may increase the risk of injury, which is often how someone with hoarding disorder comes to clinical attention as people with hoarding disorder attend visits with a primary care physician far less often than age-matched controls [30].

Case 2 Answer 4 (Question 4—What commonly comorbid geriatric conditions are likely to have the most clinical impact on an individual with hoarding disorder?)

Arthritis affects about half of the people over the age of 65 [31]. Many forms of arthritis are likely to affect the patient's mobility around a cluttered home. Similarly, visual impairment can increase the likelihood of accidents with increased objects on the floor and reduced space in which to ambulate. Interventions to optimize mobility through physical or occupational therapy, assistive devices such as canes and walkers, visual aids such as glasses and appropriate lighting, pain control, and addressing the safety of the physical environment are vital to mitigating the morbidity or even mortality which can occur in patients with hoarding disorder.

For unknown reasons, patients with hoarding disorder are more likely to have seizures than those without [32]. Seizures present a particularly dangerous condition for those with hoarding disorder as they put them at increased risk for falls and injury (and possible inability to obtain help due to difficulty navigating the space).

While major neurocognitive disorder is found in approximately 25% of the patients with hoarding disorder, 22.6% of the patients with major neurocognitive disorder also show hoarding behavior [33]. Diogenes syndrome has been found in 36% of the patients with frontotemporal neurocognitive disorder, and hoarding behavior is described in 57% of the patients with this type of neurocognitive disorder [34, 35]. Studies have also found problems with executive function compared with age-matched controls in subjects with hoarding disorder [36]. Major neurocognitive disorder or subclinical problems with executive function may result in higher risk of fires and self-neglect.

Teaching Point
Comorbid medical conditions that affect mobility such as arthritis, visual impairment, epilepsy, and major neurocognitive disorder need to be appropriately managed as they place the person with hoarding disorder at greater risk for injury or even death.

Case 2 Analysis Ms. H. presented to the emergency room with a physical complaint rather than a psychiatric one, although her broken hip could be viewed as an indirect consequence of her hoarding behavior. She was unable to provide a logical rationale for her hoarding but lacked insight into the severity and problematic nature of her actions. Medical and psychiatric work-up for other conditions (beyond hypertension and obesity) was negative. Her history of hoarding began in early life but has become more severe with time. Her sister has not even been in her home in several years and is reluctant to get involved due to Ms. H.'s reactions to her concerns in the past. The fire department's condemnation of the home precludes her from returning without some intervention. There are companies who specialize in cleaning the homes of people with hoarding, preserving what is still usable and useful while discarding what is excessive. It is doubtful that Ms. H. would be capable (physically or mentally) to discard enough of the clutter to make the home safe, but Ms. S. could employ such a company to avoid blame from the patient about deciding what to keep. The home will need to conduct an inspection to determine that the home then passes for livability. Adult Protective Services can be involved to monitor the home periodically for re-accumulation of dangerous levels of objects. The patient should be encouraged by clinicians and family to attend appointments with a therapist and psychiatrist for treatment of her underlying psychological disorder.

People with hoarding disorder rarely complain of psychiatric distress and instead present late in life when their behavior has escalated to such a point that it interferes with their physical function, not uncommonly due to a physical injury. The more fragile physical health of geriatric patients makes them more vulnerable to falls, other injuries, and fires associated with the excessive clutter of their homes.

Hoarding disorder may be with or without OCD, but people with hoarding disorder lack insight into the severity or problematic nature of their collections. Clinicians should rule out psychotic disorder, major neurocognitive disorder, or thyroid conditions before diagnosing hoarding disorder. Treatment team members should include family members, social service agencies, and medical as well as psychiatric clinicians.

13.3 Key Points: Obsessive-Compulsive and Related Disorders in Older Age

- OCD and OCD-related disorders are typically chronic disorders in the older adults. They will often mask or underreport symptoms due to shame or embarrassment. Timely diagnosis and treatment rely on rapport and establishment of trust. Clinicians must stay attuned to clues of hidden behavior such as excoriations or areas of the body missing hair.
- The iatrogenic harms produced by cosmetic procedures must be considered in geriatric patients with body dysmorphic disorder due to medical comorbidity, slower healing, and increased intraoperative risk.
- The creation of a unique diagnosis in DSM-5 of hoarding disorder was intended to increase public awareness, improve identification of cases, and promote research or development of treatments for hoarding disorder. Hoarding disorder can have a disproportionately severe effect on not only the geriatric patient with this condition but also society due to health and safety of their community as their behavior may promote unsanitary conditions or fire hazards.

13.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ1. Which treatment method is considered first-line in older adult patients suffering from OCD or OCD-related disorders?

A. Treatment with a selective serotonin reuptake inhibitor (SSRI) at relatively high doses
B. Psychoanalytic psychotherapy
C. Treatment with an atypical antipsychotic
D. Cognitive behavioral therapy (CBT) with exposure and response prevention
E. Transcranial magnetic stimulation

Answer: D

While CBT with exposure and response prevention is the first-line treatment for all adult patients with OCD and OCD-related disorders, it is important to factor in barriers to effective CBT including transportation and cognitive impairment. Shorter assignments and combining with memory tools can promote better response. Remember that self-disclosure can be challenging in older adults, but studies show that combining CBT individually with group therapy promotes better engagement and self-disclosure as well as becoming a potential source of support for the patient. SSRIs and other pharmacotherapies are effective when CBT is not an ideal option. Another consideration, if CBT has only partial response, is combining CBT with SSRI or other appropriate pharmacotherapies. Transcranial magnetic stimulation is more frequently studied in depressed patients but can be an option for those suffering with refractory symptoms or patients in whom medical or psychotherapeutic interventions may be contraindicated due to medical disease or intellectual disability. Psychoanalytic psychotherapy is not indicated for OCD as it does not effectively target the behavioral patterns with response prevention as well as CBT with exposure and response prevention. Atypical antipsychotics have not been shown to be effective in OCD or OCD-related disorders in monotherapy and thus would not be indicated as first-line therapy. Therefore, the correct answer is D.

MCQ2. Which of the following most accurately describes key diagnostic criteria for OCD and OCD-related disorders?

In OCD and OCD-related disorders:

1. The individual suffers from intrusive urges to complete tasks they feel compelled to do in addressing an underlying fear.
2. The behaviors are associated with significant impairment in social, occupational, or other critical areas of daily function.
3. The daily behaviors are soothing to the individual and help decrease initial fears.
4. There are both genetic risk factors and comorbidities including anxiety or depressive disorders.

A. One of the above statements is true.
B. Two of the above statements are true.
C. Three of the above statements are true.
D. All statements are valid and true for the diagnoses in this category.

Answer: C

Individuals suffering from OCD and OCD-related disorders suffer from obsessions and compulsions focused on addressing underlying fears. These behaviors are associated with significant impairment affecting their daily quality of life and overall function. There are significant genetic and comorbid risk factors to consider. These behaviors and obsessions are distressing rather than soothing.

MCQ3. Which of the following screening tools may be most effective for OCD in older adults?

A. Beck Depression Inventory
B. Yale-Brown Obsessive Compulsive Scale
C. Clutter Image Rating
D. Saving Inventory-Revised

Answer: B

The Beck Depression Inventory is not specific to OCD and OCD-related disorders but rather helpful for depressive disorders and is commonly used in many treatment settings and is more well known. The Clutter Image Rating and Saving Inventory-Revised are better used for those suffering from hoarding disorder rather than OCD. Yale-Brown Obsessive Compulsive Scale is a screening tool commonly used for OCD in general population including older adults; therefore, the statement B is correct.

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Trauma- and Stressor-Related Disorders in Late Life

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14.1 Background

14.1.1 Trauma: Generalities and Definitions

Many people who are victims or witnesses of traumatic events (e.g., accidental death, assault, natural disaster) display posttraumatic stress reactions shortly afterward. In the acute phase, some can meet diagnostic criteria for acute stress disorder. Others will present with adjustment disorder or other specified trauma- and stressor-related disorder (including persistent complex bereavement disorder), both of which are classified in the trauma- and stressor-related disorders category in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), along with acute stress disorder and posttraumatic stress disorder (PTSD).

However, most people recover from their initial distress (e.g., acute stress disorder lasts from 3 days to 1 month following exposure to a traumatic event). This chapter addresses the clinical entity that becomes more intense, sustained, severe, and disabling after and in reaction to traumatic event(s).

It is important to keep in mind that older adults, besides constituting a highly heterogeneous group, have specific developmental issues and cohort perspectives. Yet, most studies of PTSD involve younger populations or specific groups (like combat veterans). As we are learning more about trauma, the public awareness will be increased, more people will seek treatment, and the approaches will be subsequently adapted to the needs of the older population. Meanwhile, we have to rely on the data available and remind ourselves that this is a dynamic, evolving, and complex field.

The conceptualization of this clinical entity currently known as PTSD has undergone various transformations since its first descriptions among soldiers over a century ago ("shell shock" in WWI, "gross stress reaction" in DSM-II). The term PTSD was for the first time included in DSM-III. For 35 years, PTSD was defined as an anxiety disorder. But with the complexity of the syndrome, often consisting of symptoms from various categories (anxiety, depressive, dissociative, neurovegetative, cognitive, perceptual), it seems appropriate for it to now have its own category in DSM-5: trauma- and stressor-related disorders.

Another specific characteristic of acute stress disorder and PTSD is that there is no other mental health diagnosis in which the causation is directly linked to the diagnosis [1]. Exposure to a major event perceived as overwhelming (to the point of creating intense reactions, like terror) and for which the person was unprepared is a prerequisite for the diagnosis.

Trauma (from the German word *Traum*, meaning "dream") does not necessarily lead to PTSD (see ▶ Sect. 14.1.2). The subjective experience of trauma (e.g., its meaning) and subsequent expression of symptoms vary considerably and will likely interact in regulating its long-term impact [1]. PTSD is defined as persistent difficulty processing previously experienced extreme life-threatening situations, such as combat violence, natural disasters, assault, or critical illness [2].

van der Kolk said, "Trauma has nothing whatsoever to do with cognition. It has to do with your body being reset to interpret the world as a dangerous place" [3]. Traumatic experiences are not processed by the higher centers of the brain but are held in implicit memory, also called "procedural" or "sensorimotor" memory, and then expressed through the body [4]. Therefore, the way to treat psychological trauma would be through the body. Also, in many cases, it was the patients' bodies that were grossly violated and these same bodies that have failed them (legs had not run quickly enough, voices had not screamed loudly enough) [3], a phenomenon also described as "inescapable shock" [5]. The nucleus of *neurosis* is *physioneurosis* [5]. The root of what would eventually be called PTSD lays in our bodies, which has treatment implications.

A consciously attended trigger (supraliminal stimulus) may result in defensive response recognizable by the patient (active avoidance of an unpleasant situation). A subliminal trigger (subconsciously perceived threat) would elicit unexplainable symptoms because of the missing link between stress and conscious response. Supraliminal stimulus correlates with decreased neural activity in the medial prefrontal cortex and increased activity in the pregenual anterior cingulate cortex, limbic regions, and posterior regions related to traumatic memory recall. A subliminal stimulus relies on an innate alarm system consisting of the brainstem, the amygdala, pulvinar, and frontotemporal cortex [6].

In summary, a trigger is a stimulus, either external (e.g., spouse's angry voice) or internal (e.g., tachycardia), that elicits an intense physiological, emotional, cognitive, or behavioral response (e.g., avoidance, panic, drug use), sometimes without the person's awareness of the link between the trigger and the reaction. It constitutes a reminder of a past trauma but bypasses conscious awareness, as if to make the person believe that it is happening again, hence the autonomic response (e.g., tachycardia, shortness of breath, hyperhidrosis) often associated with it (see ◘ Fig. 14.1). Certain historical events can trigger trauma-based reactions in older patients (see ◘ Tables 14.1 and 14.2).

14.1.2 Epidemiology

Trauma is frequent and its levels of exposure are high in the USA (40–90%) [7]. Only a small number of people will eventually develop PTSD (lifetime prevalence of 7–12%), which is, however, far more frequent than schizophrenia (1%), for instance. Yet, this is most likely an underestimate because many people with PTSD tend to not seek care (see ◘ Table 14.3 on barriers to care).

A larger number of Vietnam era veterans have sought care for PTSD during the more recent wars in the Middle East, presumably in part as a consequence of transitions in their life associated with aging [1]. A cross-sectional study revealed

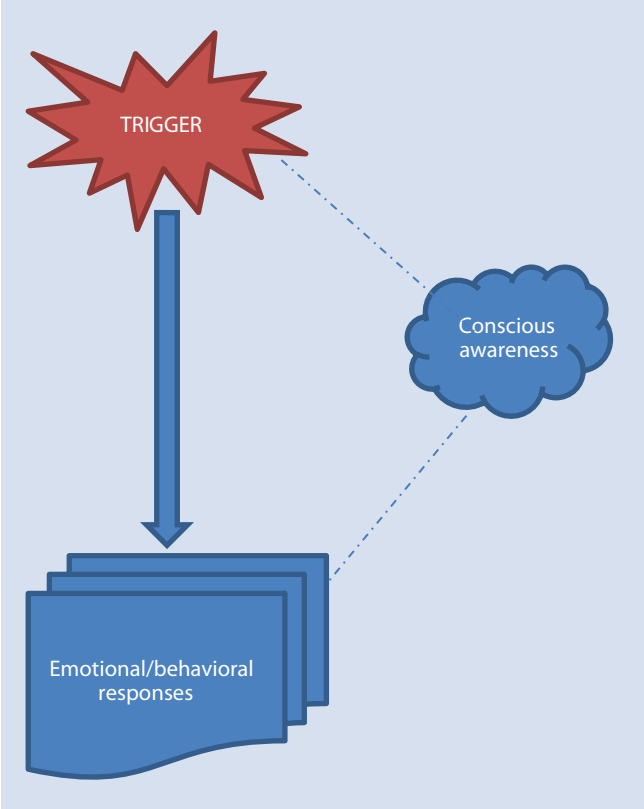

Fig. 14.1 Bypassing of awareness in trigger-induced responses

Table 14.1 Triggers of traumatic responses

Environmental triggers	Interpersonal triggers	Patient as their own trigger
Institutions (involuntary hold)	Argument with relative	Musculoskeletal pain from war wounds
News, movies, documentaries	Confrontation with perceived authority	Korean frostbite: neuropathy
Calendar (see Table 14.2)	Abandonment	Agent orange: diabetic neuropathy
Worried about military offspring	Intrusive medical procedure	Phantom limb pain
Weapon accessibility		Residual shrapnel
		Tinnitus
		Developing frailty, unable to defend self

Table 14.2 Potentially traumatic anniversaries for older population

Examples of anniversaries of events as triggers
Bombing of Pearl Harbor *Dec. 7, 1941*
Iwo Jima (battle started *Feb. 19, 1945*, US flag raised *Feb. 23*)
D-Day *Jun. 6, 1944*
Battle of the Bulge *Dec. 16, 1944–Jan. 25, 1945*
Tet offensive *Jan. 30, 1968*
Beirut barracks bombing *Oct. 23, 1983*
Terrorist attacks on New York and Washington, *Sept. 11, 2001*

Table 14.3 Potential myths and barriers to treatment in older adults [11, 12]

Myths	Other barriers
Only "crazy" people seek mental health treatment	Older patients who do not seek help
Psychological problems indicate moral weakness	Unaware of resources
Psychotherapy constitutes an invasion of privacy	General health conditions affecting mobility
Adults do not need to ask for help	Social isolation
Psychotherapy has no relevance	Lack of transportation
	Difficulty speaking the language
	Decreased self-efficacy

that the lifetime prevalence of PTSD in combat theater veterans aged at least 60 was about 17% (versus 5.5% among non-theater veterans) [8]. To the general public, PTSD is a condition most typically associated with war [9]. But PTSD from any trauma has affected 17 million individuals in the USA, even more than PTSD from war combat (1.4 million). Women are twice as likely as men to develop PTSD. Before the DSM-5 era, most evidence pointed to an overall decline in the prevalence of anxiety disorders with aging, and epidemiological research on PTSD in this population has been limited. With the expanded criteria of PTSD in the DSM-5, we would hope such an improvement would generate a more accurate set of data. But since the implementation of DSM-5 is fairly recent, such data remain scarce, and it is yet unclear how these changes affect the diagnosis of PTSD. A Canadian study found a 6-month prevalence of posttraumatic stress syndrome of 11% in a sample of older adults [10].

A multicenter, prospective cohort study by Patel et al. assessed preexisting PTSD and included veterans and civilians from mixed medical and surgical intensive care populations [2]. Their ages ranged from 46 to 74 years old. The authors demonstrated that the cumulative incidence of PTSD associated with the intensive care unit experience was 6–12% in the year after hospital discharge. Approximately two in five survivors developed clinically significant PTSD symptoms of avoidance or hyperarousal, demonstrating that patients without full spectrum PTSD can still have clinically significant symptoms [2].

Teaching Point

One of the first tasks for scientifically informed clinicians is to assess their older patients for traumatic exposure and its effects. Such screening is particularly important for high-risk groups (see Table 14.4) such as veterans, Holocaust survivors, refugees or immigrants, those identified in rape crisis centers or older abuse contexts, victims of torture, survivors of major physical trauma, and those who present with anxiety disorders [11].

Table 14.4 Groups at high risk of remote or recent exposure to trauma

Remote past	Recent past	Remote or current
Veterans	Admission to rape crisis center	Anxiety disorders
Holocaust survivors	Elder abuse	
Prisoners of war	Refugees	
Refugees	Immigrants from war zones	
Immigrants	Torture victims	
	Accident/physical trauma victims	
	Illness victims	

14.1.3 Etiology

Genetic and epigenetic factors, female sex, a history of childhood maltreatment, prior psychiatric disorders, and increased severity of trauma all increase the likelihood of developing PTSD [12]. Prior level of psychiatric symptoms and severity of the stressor, but not age, predicted the development of PTSD symptoms following a natural disaster [13]. As suggested by a number of studies, PTSD is the result of a complex interplay of genetics, environmental factors, and epigenetic regulation. Besides women, combat veterans, and ethnic minorities, other populations at high risk of victimization include sexual minorities (25% had been threatened with violence, and 16% had been assaulted) [11].

Some environmental factors that seem to have a role in the development of an altered response to traumatic events are: (i) the type and intensity of trauma, (ii) exposure to trauma (or direct exposure, such as being present, having witnessed or experienced the traumatic situation, as opposed to vicarious trauma, or secondary traumatization, which can occur after hearing about a traumatic event), and (iii) living in unsafe neighborhoods. Individual susceptibility to PTSD mediated by genetic factors may also exist. The estimated genetic contribution is between 30% and 40%. Peritraumatic dissociation in children who experienced acute medical injury is a strong predictor of PTSD later in life. Predictive factors of the development of PTSD in veterans include premorbid neurotic personality traits, genetic factors, chaotic childhood, prior exposure to trauma, lack of social support following trauma, and exposure to reactivating stressors [13].

Some of the lasting effects caused by environmental factors are likely mediated by epigenetic changes (they do not affect the sequence of the DNA but its accessibility to transcription factors or effects mediated by noncoding RNA that shape the transcriptional response of affected tissues) [14]. Epigenetic changes can occur at multiple stages throughout life, including in adulthood [14]. Increasing evidence suggests that parental vulnerability to PTSD can be transmitted to the next generation [15].

Teaching Point

Although environmental factors do not affect the genetic code itself, they can alter gene function by epigenetic changes such as DNA methylation, histone modification, or noncoding RNAs.

The neurobiology of PTSD in older adults has received limited empirical attention. Prolonged stress or exposure to glucocorticoids can have an adverse effect on cortical function, which may contribute to memory impairment. The number of locus ceruleus cells decreases with aging, as does the level of norepinephrine response to noradrenergic agonists. This decline in noradrenergic function may help to explain why older patients with PTSD have a decline in symptoms or why they are less likely than the young ones to develop PTSD after trauma [13].

Histories of PTSD and depressive disorder are strong markers for intensive care-related PTSD risk [2]. This is particularly relevant for older populations, since the numerous medical conditions and complications might make them more likely to experience a critical illness.

14.1.4 Phenomenology

Clinical presentation of trauma-related distress in older adults appears to be less intense than in younger populations [11]. Stress inoculation is one of the hypotheses; with advancing age, people are more likely to have been exposed to stressful situations, which in turn might have enhanced resiliency factors [16]. In comparison of older and younger adult earthquake survivors, although overall PTSD severity was comparable, older adults exhibited relatively higher arousal and lower intrusive symptoms. Dissociation may be less persistent over time [11]. Some authors have found that symptoms of PTSD are similar across age groups: reexperiencing, avoidance, and hyperarousal [13].

It is quite normal to experience acute symptoms consistent with PTSD immediately after a traumatic event [12]. Most research related to trauma in adults have focused on short-term to medium-term mental health problems, mainly PTSD [17]. For a long time, it has been argued that a diagnosis of PTSD did not capture some of the enduring problems experienced

by adults following the exposure to major trauma, and in that sense, the DSM-5 represents a significant improvement because the criteria have expanded in terms of the alterations of mood, cognition, and behavior. Therefore, some patients might present with sub-syndromal PTSD, and once identified, it can prompt the clinician to do a more thorough evaluation and develop a deeper understanding while screening for past traumatic experiences and any episode meeting full criteria for PTSD. Knowing that trauma- or any stressor-related disorder has been part of the patient's trajectory will align the interventions more optimally.

The type of disorder (mental or physical) likely to develop following traumatic events is influenced by age at the time of trauma. Early trauma (before age 13) among girls confers higher risk for the later development of depressive disorder versus PTSD, whereas trauma during puberty confers higher risk of developing an anxiety disorder. Plus, the brain response is likely to vary depending on the type of trauma (automobile accident versus intimate partner violence or repeated child abuse). An adverse childhood experience is a difficult situation that occurs before age 18 and affects various systems. Some authors suggested the following definition for adverse childhood experience: acute or chronic stressful events which may be biological or psychological in nature, occurring during childhood and resulting in a biological and/or psychological stress response [18]. A higher proportion of women than men in the age group 50 years and older experienced adverse childhood experiences. The study of adverse childhood experience brought to light a foundational concept in medicine: childhood maltreatment and family dysfunction have a powerful long-term influence on health, both physical and mental [19].

Child neglect is the most common form of childhood adversity [20]. There is a dose-response relationship between the number of adverse childhood experiences a person has endured and the subsequent health-related and social problems. For instance, cardiac diseases, COPD, diabetes mellitus, and obesity were common physical problems in traumatized patients. Beyond a certain number of adverse childhood experiences (six and more), life expectancy is reduced by 10 years. Depressive and bipolar disorders, anxiety disorders, PTSD, substance use disorders, personality disorders, and health-risk behaviors (intimate partner violence, sexual promiscuity) have also been identified.

The separation between mind and body is no longer useful as trauma (either psychological or physical) affects the whole person (see ▶ Chap. 26), and the mechanism by which adverse childhood experiences predispose to such outcomes might be mediated by the interconnectivity among genetics, epigenetic factors, stress-related hormonal systems (HPA axis), and immune parameters [21]. Toxic stress in childhood affects the developing architecture of the brain, subsequent disorganization in brain systems, and can cause chronic difficulties in mood regulation or even executive functioning with lifelong consequences for mental health [21].

Adverse childhood experiences lead to an increased risk factor for suicidal ideation and suicide attempts throughout the life span. Interpersonal trauma seems to be worse than natural disaster [18]. Such developmental trauma, by interfering with the emergence of trust, can impact attachment relationships throughout life, whereas stress from a natural disaster (which also occurs less frequently) can be addressed more easily by using social support. Automobile and industrial accidents, for instance, are more circumscribed. Interpersonal violence, on the other hand, is more complicated and multifaceted. Its negative psychological and social impact is much more likely to generalize beyond the incident context, so experiences with human brutality and sadism are more likely to negatively affect core beliefs that otherwise sustain the well-being [22]. We need connection with others to heal, and it is harder to do so when it is a human being who has perpetrated abuse, for instance, when the survivor is constantly confronted with the initial shock and confusion. "How could another human being, just like you or I, commit such horrific acts …." Therefore, for some victims, it takes longer to develop trust in people.

Teaching Point

Adverse childhood experiences are more common among women. Physical abuse was associated with non-substance-related psychiatric disorders in women and substance use disorders in men [21] (see ◘ Table 14.5). Older adults' increasing rates of substance misuse is often attributed to a more permissive culture of substance use among the baby boomers. The relationship between adverse childhood experiences and the subsequent development of substance misuse may be partially mediated by PTSD and depressive (and possibly bipolar) and anxiety disorders from adverse childhood experiences.

The DSM-5 cluster "B" diagnostic criterion for PTSD, or reexperiencing (intrusive memories, or so-called flashbacks, and nightmares), is perhaps the primary or pathognomonic symptom of PTSD [7]. Such intrusive, trauma-related memories differ from other memories in that they are experienced as mainly sensoriperceptual and include emotional details of the trauma [23]. Reexperiencing has been linked to a biological marker, the activity of dopamine beta-hydroxylase [1]. More anxious arousal has been noted in older adults. It is possible that it is due to a loss of executive modulation of hypervigilance and startle symptoms [24].

◘ **Table 14.5** Manifestations correlated with specific adverse childhood experiences in men

Adverse childhood experience	Clinical disorder
Physical abuse	Major depressive disorder Anxiety disorder Alcohol use disorder
Sexual abuse	Drug use disorder
Emotional neglect	Anxiety disorder PTSD
Parental divorce/ separation	Drug use disorder/nicotine use disorder Major depressive disorder

Acute psychological traumatization activates the HPA axis, but over time PTSD is associated with suppression of this axis, characterized by reduced cortisol production under resting conditions [13]. The most replicated biomarker in PTSD is an HPA axis finding of low plasma cortisol and increased glucocorticoid receptor sensitivity, a finding opposite of that in major depressive disorder [1].

Several brain imaging studies have shown abnormalities in the hippocampus, a part of the brain that has a major role in regulating stress response. But these are nonspecific and have also been found in people with major depressive disorder and borderline personality disorder [11]. Reduced motivation to seek reward and decreased pleasure from reward consumption have both been observed in PTSD [9].

Teaching Point
Given the biological and clinical complexity of PTSD, no single biomarker of disease has been identified.

Trauma victims are alienated from their bodies by a cascade of events that begins with the amygdala (sometimes viewed as the alarm system and that becomes hypersensitive after trauma). Various brain structures are involved. There is an altered cerebellar-limbic-thalamo-cortical network that acts as an innate alarm system in PTSD [6]. The structural connections of the cerebellum to the midbrain and limbic system demonstrate its involvement in emotion regulation.

Dissociation, in the form of depersonalization (looking at oneself as if "from above") or derealization (the world is experienced as "non-familiar") means "taking leave" of one's body, so much so that often the person cannot describe his/her own physical sensations. Dissociation is also a way to protect the ego from unpleasant sensations by blocking their access to awareness. Numbing and detachment, other manifestations of dissociation, often seen in military PTSD cohorts, emergency service workers, and sexual trauma survivors, have a well-characterized neurobiology [1]. A consequence of those mechanisms is memory lapses; the mind is disconnected and does not experience the situation, therefore cannot remember it. Also, the mechanism of dissociation cements the traumatic memories in the part of the brain that normally stores behavioral knowledge. The trauma "leaks out" when reminders surface or when one's guard is down, and it is only accessible through the traces it leaves in the body or unconscious memory [3].

With older adults sometimes reporting memory problems, it can be challenging to distinguish these disorders from dissociative manifestations of PTSD, and some patients may have both illnesses comorbidly. Not to mention that PTSD is accompanied by altered memories of the traumatic incident itself as well as for non-trauma-related events [23]. Verbal memory is more consistently impaired than non-verbal memory [25]. Executive functions and emotional regulation factors are directly involved when people try to access specific memories. In patients with PTSD, the capacity to access specific memories depends less on executive function and more on emotional regulation factors [23]. Memory decline may be accelerated in PTSD. On the other hand, major or mild neurocognitive disorder might contribute to late-emergent PTSD in older individuals [24].

Two of the most common and distressing symptoms of PTSD are insomnia and nightmares, reported by 70% and 52% to 96%, respectively. These two symptoms are also the most widespread among Auschwitz survivors [13]. Poor childhood attachment may continue to influence sleep through poor adulthood attachment [26]. Hypervigilance, intense distress at reminders of the trauma, numbing, poor concentration, and affective instability were also very common. Recurrent nightmares can persist for several decades [12].

Hypocortisolism was correlated with avoidance symptoms [13]. In comparison with other PTSD symptoms, avoidance is associated with functional impairment and disability after a systemic medical illness, as patients often ignore significant health demands, given that they are reminders of the inciting medical event. For instance, PTSD anchored to a cardiovascular event might result in nonadherence to cardiac medications.

Many Holocaust survivors display alexithymia, a reliance on logic and minute details, and an inability to soothe themselves [13]. Holocaust survivors are more likely than other older persons to report anxiety and depressive symptoms.

Teaching Point
The subjective experience of trauma and subsequent expression of symptoms vary considerably (see ◘ Fig. 14.2) [1]. It is a heterogeneous disorder in which there is interplay among several neurobiological systems. Many different theoretical models have been used to guide treatments.

Changes in PTSD diagnostic criteria in DSM-5 continue to result in high comorbidity of PTSD and major depressive disorder; half of the people with PTSD also meet diagnostic criteria for major depressive disorder [1]. Is major depressive disorder really a distinct, comorbid disorder, or is it due to the fact that five symptoms from the DSM-5 criteria D and E for PTSD overlap with criteria for major depressive disorder? (See ◘ Table 14.6). Moreover, are some cases of major depressive disorder, in fact, primarily residual PTSD? It is important to note that major depressive disorder is more frequent than PTSD in women who have suffered early childhood trauma. Maybe the key lies in the glucocorticoid receptor sensitivity. Patients presenting with major depressive disorder should be screened for childhood abuse because, if present, they will likely need more intensive treatment.

Fig. 14.2 Various manifestations of trauma besides PTSD

Table 14.6 DSM-5 criteria D and E of PTSD (shared with major depressive disorder, in bold and underlined)

Criteria D Negative alterations in cognitions and mood (2 or more)	Criteria E Marked alterations in arousal and reactivity (2 or more)
Inability to remember an important aspect of the trauma (due to dissociative amnesia, and *not* due to substances or head injury)	Irritable behavior and angry outbursts (with little or no provocation) typically expressed as verbal or physical aggression toward people or objects
Persistent and exaggerated negative beliefs or expectations about oneself, others, or the world ("I am bad" or "the world is completely dangerous)	Reckless or self-destructive behavior
Persistent, distorted cognitions about the cause or consequence of the trauma (the individual blames himself/herself or others)	Hypervigilance
Persistent negative emotional state (e.g., fear, anger, shame, guilt)	Exaggerated startle response
Markedly diminished interest or participation in significant activities	**Problems with concentration**
Feelings of detachment/estrangement from others	**Sleep disturbance**
Persistent inability to experience positive emotions (happiness, satisfaction, or love)	

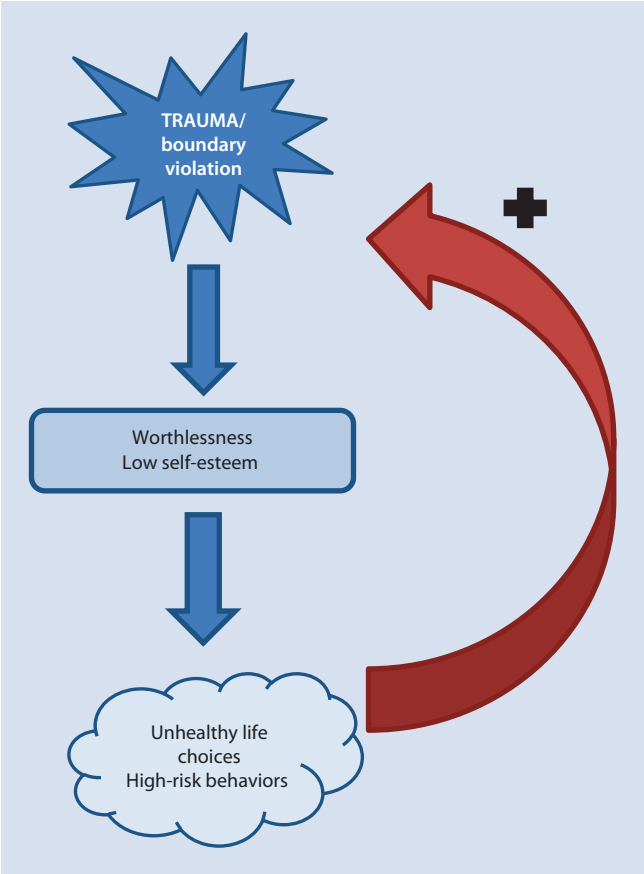

Fig. 14.3 The vicious cycle of re-traumatization

Table 14.7 Four-factor model of PTSD

Domains	Manifestations
Reexperiencing	Flashbacks Nightmares
Effortful avoidance	Isolation Shrinking of interests
Negative mood/cognition	Hopelessness, worthlessness
Hyperarousal	Insomnia Irritability (Older population: agitation)

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It seems like trauma-induced weight loss (e.g., during captivity) is predictive of long-term compromise in cognitive performance. More specifically, captivity weight loss was associated with impaired learning and memory performance, whereas PTSD was associated with attention, mental tracking, and executive function deficits [11].

Another salient characteristic of trauma victims is low self-esteem and sense of worthlessness, especially when trauma occurs in early life. Children who are mistreated internalize the message that they are not worthwhile, hence leading to the abuse or neglect, and they tend to replicate this paradigm throughout their lives by mistreating themselves via poor health behaviors and/or by selecting abusive relationships, which in turn lead to an increased risk of re-traumatization (see Fig. 14.3). The four-factor model of PTSD lists four domains (reexperiencing, avoidance, negativity, and hyperarousal) and clinical manifestations associated with each (see Table 14.7).

Older adults who are experiencing negative effects of unresolved trauma may present with somatic complaints or other clinical needs. They might be using (or have used) substances to cope with the distress. Therefore, alcoholism, opioid addiction, or dysregulated eating behavior can be manifestations of unresolved trauma. The losses, physical changes, and decreased socialization often associated with aging may reactivate PTSD symptoms [13]. Also, old age is a period where one establishes self-coherence and self-continuity, a difficult task for people whose lives have been dramatically altered in midcourse by severe trauma. Following a hurricane, older adults not only reported fewer symptoms of PTSD, major depressive disorder, and generalized anxiety disorder than younger adults, but also their psychological reactions were more closely connected to economic repercussions of disasters, maybe because of their fixed incomes [11].

PTSD-Related Accelerated Cellular Aging

Stress is associated with neuroimmunological dysregulation and inflammation. Chronic inflammation increases risk for diseases of aging [18]. In a Danish population study, PTSD was associated with increased incidence of myocardial infarction, stroke, and venous thromboembolism [27]. This association might be mediated by health behaviors. In a study by Schnurr and Spiro [11], both combat exposure and PTSD seem related to poorer self-reported physical health. PTSD had a direct effect on health [11]. Sexual assault history was associated with an increased risk of arthritis and breast cancer in older women and thyroid disease in older men [11]. In a large population study, it was found that the odds of having cancer before age 50 increased twofold among women who had two or more adverse childhood experiences [18].

In a large study of US veterans, PTSD was associated with a 50% increased risk of new-onset heart failure over the course of 8 years. PTSD is causally implicated in cardiovascular disease. Higher levels of childhood abuse and neglect are associated with a higher likelihood of cardiovascular disease in adulthood. In a longitudinal study, the likelihood of chronic cerebral infarction was nearly threefold higher in those with moderately high levels of emotional neglect in childhood than in those with moderately low levels [20]. Emotional neglect may contribute to poor self-care, and it is possible that aspects of physical health underlie the association.

PTSD is also linked to increased prevalence of metabolic syndrome, which is defined by central obesity, elevated blood sugar, dyslipidemia, and hypertension. It is associated with: (i) increased inflammation, (ii) type 2 diabetes mellitus, and (iii) premature mortality. Forty percent of people with PTSD met the criteria for metabolic syndrome, which is nearly double the prevalence compared to a control population [27]. PTSD-related metabolic syndrome was also associated with

bilateral reductions in cerebral cortical thickness. According to some studies, PTSD was associated with shortened telomere length [27]. Also, greater lifetime PTSD severity was associated with advanced DNA methylation age compared to chronological age. Exercise may lead to both symptom improvement and beneficial changes in the biological pathways affected by PTSD and that are crucial for cardiometabolic health [27].

Teaching Point

Psychological stress- and trauma-related psychiatric symptoms may accelerate the aging process at the genomic level. These epigenetic alterations may give rise to premature cardiometabolic and other age-related health problems, including neuronal decline (such as increased cell death and decreased neurogenesis) [27].

Differences in Combat and Civilian PTSD

Considerable trauma research and discussion occurs around two groups: soldiers/veterans and victims of violent crime (e.g., rape). The groups and the precipitating traumas are quite different. The treatment response to both psychotherapy and medication is typically lower in veteran groups than others diagnosed with PTSD.

There is also a distinction between certain groups within the combat population. WWII and prisoners of Korean war have higher rates of PTSD, depressive disorder, and generalized anxiety disorder than do non-prisoners of war and combat veterans four or more decades later [13]. One in ten older US veterans experiences a clinically significant exacerbation of PTSD symptoms in late life. Executive dysfunction may contribute to such a risk [24]. Thirty percent of veterans would no longer meet criteria for PTSD because they do not actively avoid (something that soldiers often overcome due to their very nature), and persistent avoidance represents cluster C for PTSD criteria [1]. Guilt and shame seem to interfere with recovery in veterans with PTSD, but they are not elements of the diagnostic criteria.

The primary symptoms in prisoners of war seem to be intrusive memories, anxiety, and hyperarousal. They may appear asymptomatic due to their high level of psychosocial functioning. But they can present with cognitive impairment secondary to nutritional deficiencies from food deprivation at the time of imprisonment [13].

Since most studies have examined veterans, we have to be cautious in overgeneralizing findings to the general population. For instance, there might be a higher incidence of associated brain injury in veterans, giving rise to a specific subset of symptoms (cognitive impairment).

Course

Most studies do not follow survivors longitudinally in old age. Some former prisoners of war are continuously troubled; others have waxing and waning symptoms across the lifespan, and still others remain symptom-free. Other investigations with this population indicate immediate and intense symptom onset shortly after the trauma, followed by a gradual decline for several decades, and resurgence later in life. The prevalence of late-emergent PTSD has ranged from 11% to 34% (early abatement of symptoms followed by exacerbations decades later). Factors contributing to this include chronic physical illness, cognitive decline, retirement, reduced social support and loss of a spouse, war-related triggers, and an increased propensity to reminisce about past traumatic events. A small proportion (2%) had a rare, long-delayed onset in which PTSD symptoms initially presented more than two decades following stress exposure. We can also refer to such a delayed onset as tardive PTSD. Prisoners of war have been shown to have a higher prevalence of delayed-onset PTSD than non-prisoners of war veterans [24]. Studies of WWII prisoners of war reported rates of PTSD ranging from 48% to 60% immediately after the war and from 29% to 48% 40 years later [13]. Onset or worsening of PTSD many years after WWII has been observed when veterans were exposed to symbolic representations of wartime trauma or losses (retirement, deteriorating health, death).

Possible factors mediating the evolution of symptoms over the life course include occurrence of other stressful events, cognitive appraisal of trauma, and coping strategies. Reactivation of symptoms may in part be due to aging-related events. Losses can elicit traumatic thoughts of death, physical injury, and lack of control. Also, coping strategies can become compromised in older adult trauma survivors by challenges associated with aging. An older adult with decreased mobility who used to exercise to cope with reexperiencing symptoms might experience more symptoms when not distracted by other social/productive activity. Institutionalization, especially when the older adult had little or no control over the decision, may also initiate or re-activate trauma-related symptoms. Moreover, cognitively impaired older adults with losses in recent short-term memory may find that long-term memory for traumatic events that occurred in earlier times comes to the forefront [11]. Table 14.8 lists some protective factors that have been found to possibly prevent the development of PTSD or attenuate its duration or severity.

Table 14.8 Protective factors mediating the development of PTSD

Population in general	Holocaust survivors
Stress inoculation	Good physical health
Certain personality traits (e.g., low as opposed to high neuroticism)	Financial security
Good psychosocial support	Being married, social support
High education level	
High socioeconomic status	

There are two models regarding the effect of traumatic exposure in older adults. There might be an inoculating effect from specific type of trauma (e.g., natural disaster), meaning that such a stressor might in fact promote resilience. These survivors have a less distressed response to subsequent stressors, whether similar to or different from the initial trauma. The second model, which supports the "vulnerability perspective," seems to apply to survivors of more severe trauma, maybe because of the interpersonal nature, such as is the case for Holocaust survivors or combat veterans.

But age, in and of itself, is not a risk factor for the development of PTSD. Premorbid personality (such as high level of neuroticism) and personal and family psychiatric history are likely risk factors. Other risk factors in male military veterans included adolescent psychological difficulties, age at time of entry into military service, degree of combat exposure, societal and familial responses and support post conflict, and prisoner of war status [11].

Even after controlling for known risk factors for suicide (such as poor social support), trauma seems to be an independent factor associated with suicidal ideation [11]. Sexual abuse is associated with heightened risk for suicidal behavior. It is suggested that the relationship between childhood sexual abuse and suicidal behavior extends beyond adolescence and young adulthood into older adulthood [28].

Treatment-seeking older adult crime victims are often multi-traumatized and experience moderate to severe levels of psychopathology, such as PTSD, depressive disorder, and panic disorder [11]. Childhood adversity is associated with an increased risk of adult homelessness, and in turn, homelessness is a risk factor for the development and worsening of psychiatric illnesses [29]. The functional status in this population is worse than those 20 years older in the general population. In conclusion, trauma affects the whole person. When the coping mechanisms are overwhelmed and there is no resolution, it becomes the organizing principle of the person's life.

14.1.5 Prevention and Treatment Approaches

General Principles

Prevention of all types of trauma would be ideal but this is not an attainable goal. Hence, once trauma occurs, it is important to detect its impact and prevent complications by mobilizing individual and social resources. A comprehensive assessment is crucial before initiating interventions. Table 14.9 lists the proposed elements of the evaluation of a geriatric patient who has suffered trauma.

One potentially important factor that promotes recovery is general self-efficacy, which Bandura has broadly defined as an individual's perceived ability to achieve a desired outcome [30]. Self-efficacy may foster recovery from stress reactions because persons with high levels of self-efficacy use more active and adaptive coping strategies and do not succumb to catastrophizing or other dysfunctional thought patterns.

Table 14.9 Comprehensive assessment of the older patient who has experienced trauma

Comprehensive assessment	
Meaning	Patient's view on how the trauma has affected him/her
Complete history	Developmental, medical, psychiatric
Clinical exam	Physical, psychiatric (including cognitive)
Social support/ functioning	Activities of daily living

General self-efficacy is highly stable, with trait-like qualities, and may be linked to genetic predispositions. However, traumatic events may alter psychological traits that are normally stable. General self-efficacy is moderately to strongly negatively related to posttraumatic stress reactions. In a longitudinal study by Nygaard et al., social support was significantly related to less severe posttraumatic stress reactions and higher scores on the scale that measured general perceived self-efficacy [30]. The positive effect of self-efficacy in promoting coping seems to be time limited, with the strongest effects occurring during the first months post-disaster.

Normalization with psychoeducation is an important element of early intervention. The usual reaction following a traumatic event is a normal one that leads to recovery. Such a process should not be disrupted. Psychological first aid lists some useful guidelines [16]. Safety, comfort, and connection to resources are the main components. It also includes providing information about possible stress reactions and recommended coping (e.g., avoid alcohol or substance use, resources for how to access clinical assistance). But people cope with stress in different ways. The interventions have to be culturally sensitive and developmentally appropriate [31]. Older people are more likely than younger persons to list religion as a coping mechanism for stress [13].

College education was associated with reduced odds of major depressive disorder and drug/nicotine use, which underscores the important role of educational attainment and associated socioeconomic resources in mitigating the impact of early life stressors, moderating health risk behaviors, and buffering the effects of adverse childhood experiences. Marital status and income were found to mediate the association between early life stressors and depressive disorder in late life [22].

Myths that older cohorts might entertain constitute potential barriers to treatment (see Table 14.3). Therefore, the treatment should begin with a preparatory introduction to treatment during which incorrect assumptions can be discussed and roles and expectations clarified. Providing mental health treatment to older adults requires flexibility and adjustments at many levels (see section on procedural adaptations in ▶ Chap. 8). Weintraub and Ruskin wrote that older adults require more time than the young to work through the traumatic event [13].

Table 14.10 Factors guiding the type of psychotherapy for PTSD

Factors for psychotherapy	Comorbid disorders
	Severity and timing of the problem (e.g., acute versus chronic)
	Cognitive functioning
	Existing skills
	Patient preference
	Motivation
	Ethnicity and culture
	History of previous psychiatric treatment and response

During the acute phase, the National Institute for Health and Care Excellence (NICE) recommends a "watchful waiting" for the first month after the traumatic experience [12]. Plus, in the early phase, traumatized individuals might be too distraught and consumed by other pressing needs to engage in psychotherapy. Repeated monitoring of symptoms can hasten recovery in some [22]. The monitoring could be conducted via various telehealth methods (see ► Chap. 35). Until the need for a specific psychotherapeutic intervention becomes clear, optimizing social support and minimizing external stressors and demands in the early period after a traumatic event is recommended. The narrative part of the assessment is crucial. Phenomenology needs to precede diagnosis and treatment [32].

Once a diagnosis of traumatic reaction is confirmed, the goal of treatment is to resolve the "body-mind" disconnect. Psychotherapy is the first-line treatment for PTSD. The choice of an optimal form of psychotherapy for an older adult should be based on a variety of factors (see Table 14.10). But regardless of the technique, it should always be done in a trauma-informed manner. Supportive listening, following the person's pace, not forcing disclosure and providing education about trauma and its effects, and validating the difficult emotions are essential components (see ► Chaps. 8 and ► 26).

Psychotherapeutic and Other Non-pharmacological Interventions

Talk Therapy

Some studies suggest that individual psychological debriefing might exacerbate PTSD symptoms in some people [31]. Debriefing is not recommended because it may be deleterious to listen to the trauma narratives of others or to discuss one's own with a group of strangers in the early period after a shared traumatic event (maybe by enhancing encoding of traumatic memories). It is also possible that debriefing tends to divert people from the use of natural coping mechanisms by inducing them to become preoccupied with their experiences and status as victims, thereby degrading their psychological self-efficacy.

Once the therapeutic alliance is established and the patient has agreed to proceed with treatment, we must help our patients tolerate their own bodily sensations when they are triggered, to help them process the trauma and manage the responses to potential subliminal trauma-related triggers (see Tables 14.1 and 14.2 for examples of triggers). It is important to recognize, tolerate, and label somatic states in order to link them to emotions. Then, we should identify the contexts that provoke the emotions [33]. Defusion is a technique used in various approaches to deactivate the responses linked to triggers or prevent escalation of symptoms (see ► Chap. 8).

The strongest evidence of efficacy for early interventions, as for later ones, is for multisession cognitive behavioral therapy (CBT) techniques in the first month after trauma for people with an elevated risk for PTSD (see ► Chap. 8). Cognitive processing therapy is a subcategory. Study findings by Nygaard et al. support the idea that core beliefs about the ability to master challenging environmental demands promote resilience to adversity and effective coping [30]. For mixed-sex accident and assault survivors, CBT reduced avoidance behaviors, but it had little impact on other PTSD symptoms and co-occurring depressive disorder [22].

Exposure therapy is a form of CBT that is the opposite of avoidance behaviors and hence targets them. Exposure therapy consists of repeated exposure to images or memories associated with the traumatic events. Because the physical health of older adults is often compromised and direct trauma processing can produce strong physiological effects, such as changes in heart rate and respiration that may exacerbate existing health conditions, there have been questions about the benefit of exposure involving disclosure of trauma material in this population [11]. But relying on clinical judgment and careful assessment of risks and benefits should guide the decision as to whether or not this is an appropriate intervention.

Life review therapy, also called narrative storytelling, is a form of exposure (via narration) and may be a good option for patients who need to examine past trauma. It involves reworking of previously experienced conflicts to gain a better understanding and acceptance of one's past.

Cloitre et al. developed a phase-based treatment for PTSD in which skills training in affect and interpersonal regulation (STAIR) precedes standardized exposure therapy with the hypothesis that improvements of day-to-day competencies might enhance efficacy of, and protect against potential adverse consequences of, subsequent trauma processing [12]. STAIR is derived from dialectical behavioral therapy (DBT) (see ► Chap. 8).

Teaching Point

There is evidence that exposure therapy could be efficacious, tolerable, and safe, even for those with high levels of trauma-related dissociation.

If psychotherapy is not contraindicated, it may be important to start as soon as possible after the traumatic event in order to not reinforce the avoidance features of PTSD. Shared decision-making, a defining characteristic of trauma-informed care, should be emphasized.

Trauma-focused therapies, including exposure therapy and cognitive therapy, are evidence based. For instance, CBT and imagery rehearsal (exposure, relaxation, and re-scripting therapy) should be considered first-line treatments for PTSD-related insomnia and nightmares [14]. There is insufficient evidence to recommend *eye movement desensitization and reprocessing* (EMDR). One manualized psychoeducational treatment program for older combat veterans developed at a VA center involves therapy education, PTSD education, life review, stress management, building of social support, anger management, working through grief and loss, and forgiveness [11].

One intervention that has been effective for depressed older adults is interpersonal psychotherapy [11] (see ▶ Chap. 8). Given the relationship between social support and the development and maintenance of PTSD, the potential application for this therapy to older trauma survivors appears relevant.

Mindfulness-based stress reduction appeared to have a modest advantage over present-centered therapy [12]. It might be efficacious for simultaneously improving both neurocognitive and PTSD symptoms. Two recent meta-analyses provided some evidence that hypnotherapy could produce large effect sizes in the treatment of adults with PTSD [12].

Group psychotherapy is effective in older war veterans and Holocaust survivors. It aims to normalize the symptoms of PTSD, depathologize treatment, and encourage persistence in treatment.

14

Body-Based Therapies

If talking does not seem to help (in some cases, it made things worse, per van der Kolk [5]), body-oriented interventions such as yoga, tapping, dance, karate, and mindful practices may be helpful [6]. Body-based therapies (e.g., somatic experiencing, sensorimotor psychotherapy) focus on retraining the higher brain to regulate subcortical disturbances (e.g., amygdala hyperactivity) [12]. By acknowledging traumatic sensorimotor memories and their associated emotions that may not easily be expressed in words and helping people to find feelings of safety in their bodies, body-based therapies may be more acceptable and may allow patients to process material that otherwise would not be accessed or tolerated. Acupuncture, emotional freedom therapy, mantra-based meditation, and yoga are largely theoretically grounded in mind-body philosophies [12]. Also, physical therapy should be an integral aspect of the multidisciplinary management of PTSD. Because of the specific challenges and circumstances associated with old age, therapeutic approaches should be designed to increase locus of control, perceived self-efficacy, and positive reappraisal.

A study evaluating electroconvulsive therapy (ECT) for PTSD with comorbid depressive disorder found that ECT was associated with decreased PTSD and depressive symptoms as well as reduced cardiac-related mortality over the course of an 8-year follow-up [27]. See ◘ Table 14.11 for a summary of non-pharmacological approaches.

◘ **Table 14.11** Psychotherapeutic approaches for PTSD

Cognitive behavioral therapies	Body-based therapies
Cognitive behavioral therapy	Somatic experiencing
Exposure	Mindfulness, defusion
Narrative	Yoga
Psychoeducation, defusion	

Pharmacological Interventions

As stated earlier, psychotherapy is preferred over medication as the initial intervention for PTSD. Plus, it is possible that the severity of PTSD correlates with poorer response to medication [13]. We should consider medications if there are comorbidities (e.g., depressive disorder, psychotic disorder), lack of access to psychotherapy, failed attempts at psychotherapy, and the personal preference of the patient [12]. Although older adults with PTSD are typically given the same medications as prescribed for younger adults, a general rule of thumb in delivering safe and effective pharmacotherapy is to start at a lower dose (often half the dose recommended in the pharmacology guides) and titrate more cautiously and slowly. In the general adult population, two selective serotonin reuptake inhibitors (SSRIs), paroxetine and sertraline, have been shown to be efficacious in the treatment of PTSD and have been recommended as first-line treatments [11]. Since paroxetine has anticholinergic side effects, sertraline is considered safer and is well tolerated by older adults. Serotonin-norepinephrine reuptake inhibitors (SNRIs) are also a good option. Trials should be conducted for at least 12 weeks. The goal is symptomatic relief. To prevent relapse, pharmacotherapy should be continued after symptoms improve, although the optimal length of treatment is unknown.

Prazosin is effective for nightmares and generally well tolerated; it can be titrated up to 13 mg daily [12]. To minimize potential dizziness, the initial dose should be 1 mg qPM, then titrate slowly. The physician should adjust the doses of other antihypertensives.

PTSD is associated with increased noradrenergic tone, raising interest in the use of alpha-2 receptor agonists (e.g., clonidine, guanfacine). Clonidine is less specific and more sedating. For those patients with PTSD-related hyperarousal, antidepressant targeting norepinephrine reuptake inhibition may induce anxiolysis, calm the sympathetic nervous system, and limit future cardiovascular consequences [2].

Patel et al. wrote that antipsychotics, particularly of the atypical classes (second and third generation) may decrease rates of intrusive symptoms [2]. Atypical (second and third

generation) antipsychotics often have an expanded usage for various indications, including emotional regulation, anxiolysis, and antidepressant augmentation. It is not excluded that their mechanism for decreasing intrusive symptoms is indirect, for instance, by addressing other PTSD-related symptoms (mood dysregulation, fear, avoidance, negative outlook of the world).

Teaching Point
The literature does not support the use of benzodiazepines in PTSD. Temazepam and alprazolam may actually *worsen* PTSD outcomes [12]. In addition to the well-known risks of addiction and exacerbation of depressive symptoms, they increase the risk of falls and cognitive impairment in older adults.

14.2 Case Studies

The following cases studies have been used to help the reader integrate some of the theoretical concepts of trauma- and stressor-related disorders into clinical strategies for patient care.

14.2.1 Case 1

Case 1 History

You are the psychiatrist from the consultation-liaison service in a general hospital. You are paged for an 81-year-old man, Mr. M. who is in the intensive care unit (ICU). He was very agitated once he woke up in the ICU. He was admitted to critical care service a few days ago, and episodic agitation was noted, especially if his meal tray was late. It became concerning to staff when he escalated in an anger outburst at the nurse. His medical team thought it was delirium. After rushing to the unit and discussing with the team, you learn that his medical history is notable for tuberculosis, pancreatitis, prostate surgery, and occult blood in stool (for which he refused the colonoscopy). A quick glance at his chart tells you that pre-admission, he was taking a diuretic, a statin, and diazepam for many years (prescribed by his primary care physician at the time for insomnia and for "the nerves"). Your exam relies mostly on the chart and collateral information from the son because he is guarded and reluctant to answer your questions.

You meet with Mr. M. He had a medical injury as a child, but he does not remember many details. He used to drink a six-pack of beers daily because of chronic insomnia. His wife, who was very supportive and loving, died a few months ago from surgical complication. He gasps and swallows his tears as he is telling you this. She used to remind him to take his medications. "She made me a better man." He also mentions that he is more forgetful, asking "am I senile?" Otherwise, he says there is not much else interesting to say about himself, "I am pretty much a loner, you know." He tried to kill himself before meeting his wife. It was in the context of job loss and transient homelessness. "I was in a lot of pain back then, from combat injuries, you know." He was using opioids. He says he took what the doctor gave him for pain but it was never enough. Suddenly he becomes irritable and he ends the conversation, saying you are asking too many questions. "How is this gonna help me!"

You meet with his son who says that Mr. M. had a farm accident as a child, their father's tractor backed up on him (he was severely injured) and his younger brother, who died. Mr. M. suffered from guilt and had some flashbacks of the tragedy for a long time after that. Mr. M.'s father dove into a deep episode of depressive disorder while the patient was hospitalized for his major injuries.

Mr. M.'s son says that his older half-siblings no longer talk to their father because he had major anger outbursts as they grew up. "They think he's a freak, a crazy eccentric." He never really talks to them about his combat experience. You also learn he had been prisoner of war during the Vietnam War. The patient has two older daughters who take psychotropics (one is on lithium, the other is on paroxetine). He was very harsh with them for no apparent reason. He had started drinking heavily after a family celebration on a Fourth of July, shortly after coming back from the war. "He couldn't stand the fireworks on such celebrations, he appeared so frightened." He never sought help, because he believes you have to "pull yourself up by your bootstraps." "It takes a strong moral character to survive war, then the streets and bad neighborhoods." For a long time, he was afraid a doctor would not believe him or would think he was crazy that he would be locked up in a facility. He was incarcerated once, after being involved in a fight when he was homeless, he stabbed a man who stole his food and pointed a gun at him. He calmed down a little bit after meeting his second wife. But his son felt that he was regressing since the admission, "now he believes the patient next door stole his food, this is nonsense, the poor guy is in a coma!"

His most recent investigations and laboratory results included the following: vitals with blood pressure if 160/85 mmHg, ECG with ancient myocardial infarction, chest X-ray with moderate cardiac enlargement, effusion, and no apical or lobar lesions. Brain imaging showed that, other than some decrease in cortical thickness, there were normal age-related changes. A complete blood count showed a mild anemia, white blood count was normal, and platelet count was low. He had refused the colonoscopy. Renal panel and electrolytes came back normal. Urinalysis was normal. Liver panel showed elevated ALT. He had a high glucose, with HbA1c of 5.9%.

On exam, he was disheveled and he looked older than stated age. His face was pale and he presented abdominal obesity and some digital clubbing. There was a hand tremor and his voice was also shaky. He avoided eye contact but rather scanned the room, and every time there was a beeping sound, his eyes went to the corresponding machine. He was overall guarded and reluctant to disclose information. His affect was restricted and a little fearful. His speech was limited to short

sentences, with no spontaneous narrative which made the interview rather challenging and very "checklist-like." His thought process was vague, and at times fragmented. He had some paranoid thinking and the recurrent themes seemed to revolve around food. His insight seemed poor based on his limited self-awareness. Judgment was affected by hypervigilance and paranoia. Montreal Cognitive Assessment (MoCA) was not done because he was uncooperative.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What is your differential diagnosis of this patient's agitation?

Question 2. What are your recommendations to the medical team?

Question 3. What should be the treatment plan after discharge?

Case 1 Answers

Case 1 Answer 1 (Question 1—What is the differential diagnosis of this patient's agitation?)

First, we have to zoom out and make a differential diagnosis of agitation. Because of his advanced age, delirium should be on the top of the list. Because of his current substance use, alcohol withdrawal would also be ruled out. Because of historical use of opioid medications, opioid withdrawal should be ruled out. After logging in on the website for the prescription drug monitoring program in your area, you entered Mr. M.'s identifying information to generate a report of all the medications that he filled over the past 12 months. This controlled substance and utilization review system (also called CURES) did not reveal any evidence of overuse or "prescription shopping." However, there was a monthly fill of diazepam, 30 tablets (for a total of 12 prescriptions over the past year), and at a high dose (30 mg) for his age, yet without evidence of using more than prescribed. Neurocognitive disorder is also in the differential. As we know, some patients with major neurocognitive disorder have behavioral disturbances when triggered by environmental cues (see ▶ Sect. 14.1).

The agitation can also be an expression of hyperarousal. If that is the case, we are thinking about PTSD reactivation (from trauma in childhood and/or war-related trauma). It might not be easy to distinguish between a reactivation versus a new-onset war-related PTSD, or both. He has a history of significant traumatic events; in childhood, he witnessed the accidental death of his brother, while at the same time suffering injuries himself. He reported intrusive symptoms after those events. As an adult, he experienced war-related trauma. He witnessed civilians being killed and he was also a victim during his captivity as a prisoner of war. The focus around food could be explained by food deprivation that likely happened then as a form of torture. The hospital setting and the delay in getting his food could be triggering factors that reactivate trauma-based reactions. More generally, all those events could have contributed to interfere with the development or consolidation of sense of normal trust in life and in other people.

Another manifestation of unresolved trauma could be the refusal of the colonoscopy. The elements are insufficient to determine why but we might speculate that this invasive procedure could be perceived as highly threatening, especially if he suffered sexual trauma (as a prisoner of war).

A history of PTSD and depressive disorder are strong markers for ICU-related PTSD risk. Maybe he had premorbid PTSD or depressive disorder. Personality factors could also account for anger expression problems (see ▶ Chap. 25). Given his eccentric character and avoidance of socialization, "I'm a loner," and anger outbursts, a paranoid personality can be in the differential. Antisocial personality disorder is unlikely; there was an account of one criminal act, which was potentially triggered, and there was no pattern of rule violations. Bipolar disorder appears less likely (no grandiosity, no functional impairment to the point of necessitating psychiatric admission). However, some unspecified depressive disorder, unresolved grief or persistent complex bereavement should be on the differential list. On a general medical standpoint, metabolic syndrome and malignancy (occult blood in stool) should be evaluated.

Case 1 (Continued)

The next day, once transferred out of ICU, you visited to monitor his clinical evolution. He is calmer and apologized for having been rude. He felt "imprisoned" in the ICU with all the tubes, "being alone in the dark."

He also tells you that he now feels sad. He has had down periods. Recently, his first grandchild was born a few weeks before the admission, and he was unable to experience joy. He is forgetful, but MoCA is 25 out of 30 today. Evaluation highlights some evidence of executive dysfunction.

Case 1 Answer 2 (Question 2—What are your recommendations to the medical team?)

As another diagnostic layer, he might be presenting ICU-related PTSD. Being in such a setting not only has reactivated memories of captivity but might have also created an additional traumatic experience in itself (his critical illness, the uncertainty about his condition). His difficulty breathing, if it led to fear of fatal suffocation, might have been traumatic. It is also possible that he had transient delirium with visual hallucinations, which, in and of itself, can be traumatic (see ▶ Chap. 26). Additionally, he was already in a more fragile condition from grieving his wife, which could have reactivated a sense of vulnerability, or a fear of death.

His depressive symptoms and executive dysfunction could be from PTSD, major depressive disorder, and/or alcohol and chronic benzodiazepine use. Persistent complex bereavement disorder is another possibility. The distinction between depressive disorder and residual PTSD is not easy, since their diagnostic criteria overlap (see ◘ Table 14.6). Early neurocognitive disorder is also on the differential, and following the evolution (through serial cognitive testing)

would be informative. Before initiating new medications, it is important to assess the indication and risk-benefit ratio of the current agents in light of the new hypothesis. On a pharmacological level, since the evidence for treating PTSD argues against using benzodiazepines (see ► section Pharmacological Interventions), we should taper and stop diazepam. For flashbacks, we can start prazosin at 1 mg at bedtime and titrate as needed (in some cases, up to 13 mg per day). It is important to monitor vital signs and hypotension. If there are significant depressive symptoms, anxiety, and suicidal ideation, an SSRI or SNRI should be considered. For continued insomnia, we could consider mirtazapine or trazodone.

As a general guideline, it is always good to identify and address myths/barriers to treatment and provide psychoeducation. Suicide precautions should be implemented, since combat veterans are more at risk of committing suicide. You also proposed to do psychoeducation about trauma, PTSD, the etiology, manifestations, and recommended treatments. For instance, it might help alleviate his guilt toward not experiencing joy about the birth of his grandchild by explaining that emotional detachment is a common manifestation of PTSD. In order to protect themselves, victims of trauma tend to dissociate from painful reminders and emotions, but it has the unfortunate consequence of depriving them of joyful moments also.

In psychotherapy, you help identifying triggers such as the ICU setting (which reminded him of captivity), heart failure and impending sense of death (which reminded him of his wife's passing), and his new grandchild, named after his young brother who died (which triggered some painful memories).

Your resident, who just learned about adverse childhood experiences, wonders if his alcohol consumption and cardiovascular disease would be long-term consequences of difficult upbringing. She realized how complex trauma is, and how it affects the whole person. You agree with her and feel stimulated by the fruitful discussion. As you are noticing Mr. M.'s seemingly more depressed presentation today, you share with her that you wonder if the following experience applies to him: the self-observation and losses that typically accompany aging lead to reactivation of shame, depressive symptoms, and despair [13].

Case 1 Answer 3 (Question 3—What would be the treatment plan after discharge?)

After providing extensive psychoeducation about trauma, reassurance through some kind of normalization (it is frequent; it can have a significant impact on life, but there is hope once we can identify the issue), you explain the specific recommendations and that medication works best in combination with psychotherapy (such as mindful awareness, exposure, life review, Alcoholics Anonymous, anger management). Throughout the ongoing assessment and monitoring process, a trauma-sensitive and informed approach is essential (see ► Chap. 26). Once the therapeutic alliance is established, rule out sexual trauma (which could explain his colonoscopy refusal). If that is the case, prepare him for invasive procedures with gradual exposure. Processing guilt feelings, such as hopelessness, could be part of a cognitive or grief counseling approach. During the war, he was very affected by the death of civilians. He also felt hopeless about his brother's death, and in therapy you could explore survivor guilt. Also, he has metabolic syndrome. Lifestyle modification through a holistic approach is key.

Case 1 Analysis Because of his chronic mood dysregulation, you proposed psychotherapy. He was not interested at first, saying that he was not that "mental." He preferred a medication and you started sertraline 25 mg daily. You titrated it to 50 mg daily. Since he was relying on his wife for the medication adherence, you emphasize his forced independence and his ability to identify barriers to treatments as an opportunity to develop a feeling of self-efficacy (see ► section General Principles under "Prevention and Treatment Approaches"). As you monitored his evolution, he became a little bit more open with the idea of psychotherapy, after the other patient sharing his room, who was decades younger, told him his story and how life-saving therapy had been for him. He just had nightmares occasionally when he was under severe stress.

Exposure therapy helped the patient once he was discharged. His primary care physician provided interpersonal therapy to help with processing his grief (of his wife, of his brother, of his youth) and to help with his current relationships with his children. During that process, he realized he was unable to attach to his new grandson because his birth had triggered overwhelming guilt from the patient not having been able to connect with his own children. At the time of their birth, he was often intoxicated with alcohol and he deeply regrets to not have been there for them all those years.

14.2.2 Case 2

Case 2 History

You are a senior psychiatry resident starting an elective rotation at a community mental health clinic that serves a publicly insured population. There you meet Mrs. S., a 73-year-old woman, who has been coming to this clinic for the past 7 years and was a patient for the previous resident rotating at the clinic. Mrs. S. presents with depressed mood more days than not, crying spells, poor appetite, poor memory and concentration, lack of energy, loss of interest in things she used to enjoy, such as going out with her grandchildren, and broken sleep with recurrent nightmares. She also thinks she sees shadows sometimes and hears voices talking but she is not sure if they talk about her. She feels vaguely that people judge her. She denies suicidal or homicidal ideation and current alcohol or drug abuse.

Her current medications include escitalopram 10 mg daily and aripiprazole 5 mg daily. The patient started these medications 5 months ago. Your asking about her medications prompts Mrs. S. to comment "I've tried so many meds! They seem to work for a while but they all stop working."

While reviewing her chart, you realize that her last visit with the resident was more than 3 months ago, longer than the customary 4–6 weeks between appointments. You asked Mrs. S. about the gap in services, and she explains to you that she did not get to say goodbye to the resident, because she canceled the last appointment due to her being ill that day. When you ask Mrs. S. what she was hoping to get out of the visit, she tells you, "I wanted to make sure you were as nice as the other doctor, that's all."

Mrs. S. is retired and lives with her third husband, who is 11 years her junior, employed, and moderately supportive (e.g., drives her to health care appointments). She acknowledges a conflictual relationship ("we've been back and forth") over the years. She has a daughter from her first marriage, with whom she keeps in close touch despite frequent arguments.

Mrs. S.'s chart indicates that she has a primary care nurse practitioner who treats her for hypertension, asthma, and chronic neck pain, back, and knees due to osteoarthritis. Reviewing her chart, you also learn that Mrs. S. has a surgical history including colon surgery for a volvulus and bilateral hip replacement. In addition, the first hip replacement was complicated by nerve damage that caused a left foot drop. She has no known drug allergies. Besides her psychiatric medications, she also takes tramadol, baclofen, and lisinopril and uses a couple of inhalers, unknown doses.

On exam, Mrs. S. is a petite, frail Caucasian woman who looks older than her age, walks with a cane, cooperative, polite, and displays good eye contact. Her voice is soft and thought process is linear, with some circumstantiality. Her affect is restricted in range, congruent and tearful at times. Her mood is "sad" and her thought content includes vague visual and auditory hallucinations and some paranoid ideation. The main themes during the visit are her feelings of hopelessness over a life characterized by victimization and adversities. She complains repeatedly of memory impairment, but she is alert and oriented to time, place, and person. She was off by a couple of days regarding the date of the month but she knows today's day of the week. No formal cognitive testing was conducted at this visit.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What is your differential diagnosis at this point to explain the poor response to antidepressant treatment?

Question 2. What are evidence-based approaches to treat PTSD?

Question 3. What is the role of screening for intimate partner violence in primary care and psychiatric settings?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is your differential diagnosis at this point to explain the poor response to antidepressant treatment?)

The presence of nightmares and poor sleep should alert you to the possibility of trauma exposure and the diagnosis of PTSD. It has long been recognized that PTSD is frequently overlooked in psychiatric outpatient settings when symptoms of PTSD are not the presenting complaint [34]. Moreover, patients with psychotic depressive disorder in one study were nearly four times more likely to have PTSD (57.9% vs. 15.7%) [35], an additional finding that is relevant to this case. To date, five meta-analyses of individual or multiple forms of childhood maltreatment have found an association of trauma exposure with poor depressive disorder outcomes, including treatment resistance [36]. These results are echoed by a multiple-phase, multi-site, real-world effectiveness study of three antidepressants conducted in five countries with outpatients seeking treatment for major depressive disorder. This study found the lowest remission rates associated with interpersonal types of childhood adversities (i.e., abuse and neglect) that occurred during the very early period of 4–7 years of age, and not overall exposure to traumatic events [37].

Another explanation of Mrs. S.'s poor antidepressant response is bipolar depressive episode in the context of bipolar II disorder, a diagnosis that is often missed, especially among patients reporting "soft" signs of bipolar disorder [38]. A third diagnosis to consider is complicated grief, a condition that is prevalent in older adults [39], often preceded by major depressive disorder [40], frequently under-recognized and which responds better to grief-based therapies rather than antidepressants alone [41] (see ▶ Chap. 8). Last, it would be important to rule out a medical cause for the persistent depressive symptoms, such as hypothyroidism.

Case 2 (Continued)

You consider that an inquiry into exposure to traumatic events in a depressed patient whom you just met in the midst of change of providers may worsen her condition significantly and threaten your chances of establishing a therapeutic alliance and decide on a conservative approach. You conduct an inquiry into lifetime presence of "soft" bipolar disorder signs and rule out bipolar disorder and order a thyroid-stimulating hormone test, although your review of symptoms does not reveal the presence of a general medical condition that could explain her depressive disorder, including hypothyroidism. You educate Mrs. S. on the need to make sure that her lack of improvement with her antidepressant regimen is not due to a systemic medical illness and both agree to meet again in 4 weeks.

At follow-up, Mrs. S. is essentially unchanged and the thyroid test you ordered shows a level within the normal range. During this visit you have time to review her past psychiatric history and corroborate information that you found in the chart. Mrs. S. first received treatment for depressive disorder at age 40 in the context of intimate partner violence during her first marriage. At age 60, she was admitted for the only psychiatric hospitalization in her life after an overdose on medications, which did not require inpatient care at a general hospital. She had a previous suicide attempt, also by overdose in her late teens. Because of partial response, over

the course of her depressive illness, she was treated successively with bupropion, mirtazapine, and sertraline, and to augment antidepressants, she has tried lithium and aripiprazole. To treat comorbid anxious symptoms and insomnia, she has also tried clonazepam and zolpidem.

In the distant past, Mrs. S. admits to having abused alcohol for short periods of time. She also tried marijuana and hallucinogens in her 20s. She denied a family history of psychiatric illness, adding "my parents didn't believe in psychiatric medications."

Since you only have 30 minutes for this follow-up visit, you decide to administer the shortest possible screening for PTSD, the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) [42]. Mrs. S. answered "Yes" to the five questions pertaining to the past month. These include nightmares about traumatic events or thinking about those events when she did not want to; trying hard not to think about the events or going out of her way to avoid situations that reminded her of the events; being constantly on guard, watchful, or easily startled; feeling numb or detached from people, activities, or her surroundings; and feeling guilty or unable to stop blaming herself for the events. Although you explained to Mrs. S. that she only needed to answer "Yes" or "No" and that there was no need (or time) to go into details of the traumatic events, Mrs. S. surprised you with a revelation after asking her about feelings of guilt. Her only son had died in a motor vehicle accident at age 23, "we were so close," she explained as she began to cry silently. Although not recorded in the chart, this information seems germane to understanding her depressive symptoms, as Mrs. S. regrets to this day an altercation she and her son had the day before his death. You express your sympathy, adding "I cannot begin to imagine what that loss might have been for you." Mrs. S. leaves your office trying to compose herself and agrees to follow your recommendation to increase the dose of escitalopram to 20 mg daily and meet again in a month. Mrs. S. declines your offer to increase aripiprazole to 10 mg daily, since she experienced nausea when she started taking the medication.

Case 2 Answer 2 (Question 2—What are evidence-based approaches to treat PTSD?)

Some clinical practice guidelines value equally medications and trauma-focused psychotherapies (e.g., US Veteran's Affairs/Department of Defense, American Psychiatric Association, and International Society for Traumatic Stress Studies), while others (e.g., National Institute for Clinical Excellence in Australia and World Health Organization) consider trauma-focused psychotherapies as preferable to medications when available [43]. To settle this controversy, the most comprehensive set of meta-analyses comparing psychotherapy and medication efficacy for PTSD to date found that trauma-focused therapies were superior to medications by every measure considered. Trauma-focused therapies included were cognitive processing therapy, eye movement desensitization reprocessing (EMDR) therapy, imaginal exposure, prolonged exposure, prolonged exposure with cognitive restructuring, stress inoculation training, and trauma-focused cognitive behavioral therapy [43]. For individuals too avoidant or autonomically activated to engage in trauma-focused therapies, sertraline, venlafaxine or nefazodone appear to offer the most robust responses, also indicating that not all serotonergic or serotonergic-noradrenergic medications are alike [43]. This set of meta-analyses considered studies of prazosin as an adjunctive pharmacotherapy only (with large effects from a single research group), but one systematic review [44] and one meta-analysis [45] of prazosin monotherapy for PTSD found significant decreases in nightmares, avoidance, and hypervigilance across studies.

Case 2 (Continued)

When Mrs. S. returns a month later, you are pleasantly surprised that she seems more cheerful and tells you that "the medication must be working," because her mood has improved and she expressed gratitude "for the therapy last time." You know you did not do intensive therapy—just empathic listening—but decide not to challenge this expression of positive transference (you have been attending a seminar on supportive psychotherapy and this technique is fresh in your mind—see ▶ Chap. 8). Her PTSD symptoms, however, continue unabated.

You consider that Mrs. S.'s condition has somewhat improved and your budding therapeutic alliance may allow the exploration of her trauma history (neither that history nor the diagnosis of PTSD are documented in her chart). You learn that Mrs. S. was told that her father found her mother in bed with another man when she was 2 years old, so they divorced and never saw her mother again until she was in her teens. Her paternal aunt raised her until age 10, when her father remarried and when she went to live with her father and stepmother. Her stepmother was emotionally and physically abusive to Mrs. S. At age 19, Mrs. S. married the father of her two biological children (the son who died in a car accident and a daughter), who eventually became brutally violent. She sustained severe physical injuries such as a broken nose, broken jaw, and broken ribs. She finally was able to escape from her husband with the help of a female friend in her early 30s and filed a restraining order against him. She worked as a janitor at a hospital, went back to school, and became a certified nurse's assistant. In the course of her work, one of her patients was a drug-addicted mother of two very young half-sisters, whom Mrs. S. eventually adopted and raised together with her biological children. Her second marriage, between the ages of 45 and 50, was not overtly abusive, but was also unsuccessful because of her husband's addiction to drugs.

You educate Mrs. S. about prazosin in the context of her hypertension and the possibility of discontinuing her lisinopril. Today her blood pressure is 142/90 mmHg. She agrees to notify her primary care physician and start prazosin 1 mg twice daily, with the plan to increase it as tolerated. You also agree to discontinue the aripiprazole in an effort to minimize polypharmacy. Your clinic does not offer any form of trauma-based psychotherapy, but searching the internet for self-help tools for trauma survivors that have empirical basis you

found a study by Koopman et al. with women survivors of partner violence that piques your interest [46]. The authors randomly assigned women to "expressive writing" and neutral writing groups. "Expressive writing" refers to a form of psychotherapy in which individuals write about a distressing or traumatic event focusing on their most private feelings and thoughts, usually for 20 minutes a day for a minimum of 4 days [47]. Although Koopman et al.'s study did not find significant differences between the study and control groups in PTSD symptoms, there was a significant reduction in depressive symptoms. You thought that it would not harm Mrs. S. and it might actually help her. You used the study's actual prompt for Mrs. S.'s homework assignment: "Today I want you to write about the most traumatic experience of your life; really exploring your very deepest emotions and thoughts."

You and Mrs. S. agree to meet in 6 weeks, as you will be out of the office on vacation in 4 weeks. Time is almost up and you still have not decided whether to ask Mrs. S. about safety concerns with her current husband. While preparing for your third visit with Mrs. S., you read that she is at high risk for revictimization as a survivor of childhood abuse [48] and that PTSD can be a consequence as well as a risk for partner violence [49]. Although at lower rates than younger women, physical and sexual abuse and threats of physical harm are still prevalent in older women and have a significant impact on levels of depressive disorder and chronic pain [50]. You decide that time is too short to conduct an inquiry into partner violence and say goodbye to your patient.

Case 2 Answer 3 (Question 3—What is the role of screening for intimate partner violence in primary care and psychiatric settings?)

Current recommendation from several professional groups is to screen all female patients of childbearing age for intimate partner violence in primary care [51]. Notably, there are no guidelines or recommendations regarding universal screening or case finding in mental health settings issued by major psychiatric organizations. However, recently there have been calls to consider violence against women a public mental health issue [52, 53]. These reviews concluded that mental health professionals continue to under-detect intimate partner violence in their patients [53] despite the well-established reciprocal relationship between psychiatric disorders such as major depressive disorder and PTSD and risk for intimate partner violence exposure and perpetration [52].

There are brief screening tools that have been shown to be acceptable to patients and effective in detecting intimate partner violence. Systematic reviews have shown that there are several effective interventions delivered by non-physicians in primary care settings that are focused on empowerment, empathic listening, discussion of the cycle of violence, safety, and referral to community-based resources [54]. The strength of evidence is highest for universal screening, while it is somewhat lower for screening tools and intervention services [55]. In contrast to recommendations for women of childbearing age, the US Preventive Services Task Force concluded that "the current evidence is insufficient to assess the balance of benefits and harms of screening all older adults or vulnerable adults (physically or mentally dysfunctional) for abuse and neglect" [56]. However, experts recommend a case-finding approach in patients with suggestive signs or symptoms, like in the case of this patient, in female patients not included in groups targeted by universal screening [57].

Case 2 (Continued)

Since your last visit with Mrs. S., you have regretted not being more proactive in addressing her safety in her current relationship. You have been reading more on the subject and thought that the results of a study by Coker et al. gave a tool and the encouragement you needed. Among women seeking services at rural health care clinics, positive answers to any of three questions yielded 95.9% sensitivity and 97.1% specificity for identifying all intimate partner violence cases in their study [58]. Today, Mrs. S. reports feeling worse from her depressive disorder, even though she acknowledges that her nightmares are less frequent and terrifying. She worked on her expressive writing a couple of times right after your last visit with her but explained that she decided to shred what she had written because she did not have a safe place to keep her diary. Her primary care physician agreed to discontinue the lisinopril. She has been adherent to her medications and does not report any changes, positive or negative, in her life that could explain the worsening of her depressive disorder.

On exam, Mrs. S. remains pleasant and even compliments you on your choice of tie. Her blood pressure is 135/88 mmHg. Your intuition tells you that her worsened depressive disorder could be explained by unconscious feelings of rejection triggered by the longer interval between visits. You decide not to explore this possibility and instead ask Mrs. S.'s permission to talk about her current marriage in more depth. After orienting her to the reason for asking questions about intimate partner violence, you read out loud the three prompts of Coker et al.: (1) "Do you feel ashamed of the things your partner does to you?" (2) "Do you feel that your partner can scare you without laying a hand on you?" (3) "Is your partner physically violent toward you? By violent, does he punch, kick, hit, shove, slap, choke, or physically attack you in other ways that could result in an injury? It also means being made to do sexual acts when you do not want to." Besides smiling with embarrassment at the last question while gently shaking her head to indicate "no," she answered in the negative with a firm voice to first two questions. Mrs. S. agrees to your suggestion to increase prazosin to 2 mg twice daily.

Time is up and you need to agree on a time for her next appointment with you, in about a month. With a slight lilt in her voice, she asks you: "Doctor, would you be interested in reading what I write in my journal? I think I can look for a small box with key lock I can afford."

Case 2 Analysis Taking a trauma history from a patient habitually means tapping into conscious, verbal recollections of life events, i.e., relying on what is called episodic-autobiographic memory (for an overview of this memory system, see

[59]). This memory starts to emerge around age 2, concomitantly with the onset of the so-called cognitive self (i.e., mirror self-recognition) [60]. Clinically, however, certain maladaptive behaviors and psychopathology are demonstrably related to earlier events. For example, longitudinal studies have shown that infants who spend more than 60 hours/week in nonmaternal care are at an increased risk of forming a disorganized attachment [61] and observed lack of parental responsiveness in infancy predicts dissociation in young adulthood [62]. We know that prior to the consciously recollected abuse by her stepmother, Mrs. S. experienced the loss of her mother and the transition of caregiver around 2 years of age, of which she does not have autobiographical memories. Although we do not have a great deal of observations up to this point, Mrs. S. has already given indications to her new psychiatrist of an insecure attachment style. We can speculate, therefore, that Mrs. S. will be quite sensitive and responsive to the vicissitudes of a patient-clinician relationship, with predictable clinical improvement and worsening of symptoms in response to micro-lapses or instances of accurate empathic attunement as well as major disruptions in the patient-clinician relationship secondary to unforeseeable (e.g., clinician illness) and predictable (e.g., end of clinical rotation) events.

14.3 Key Points: Trauma- and Stressor-Related Disorders

- Trauma is frequent and its manifestations are heterogeneous.
- PTSD is a common psychiatric disorder and it develops after a traumatic event. Although nobody is immune to the development of PTSD, genetic and epigenetic factors, female sex, a history of childhood maltreatment, prior psychiatric disorders, and increased severity of the trauma all increase the likelihood of developing PTSD.
- Unfortunately, patients with PTSD frequently do not seek help.
- Clinicians may want to conceptualize PTSD as a cardiovascular risk factor and screen for PTSD.
- Older age presents unique life challenges such as role changes, loss, retirement, and increased health problems—any of which may increase stress and deplete resources of the aging individual. In late life, there may be a re-emergence of symptoms related to earlier trauma in the contexts of losses associated with aging [18].
- Traumatic exposure can have substantial and pervasive negative effects for older adults, including deleterious changes in physical and mental health, impairment of functional status, and increased utilization of health care services.
- Biological, psychological, and social factors might lead older adults to experience recent trauma differently than younger victims do [13].
- Patients with psychotic depressive disorder in one study were nearly four times more likely to have PTSD (57.9% vs. 15.7%) [35].
- In a study assessing preexisting PTSD in ICU populations, one in ten survivors experienced ICU-related PTSD (i.e., PTSD anchored to their critical illness) in the year after hospitalization.
- Although at lower rates than younger women, physical and sexual abuse and threats of physical harm are still prevalent in older women and have a significant impact on levels of depressive disorder and chronic pain.
- Mental health professionals continue to under-detect intimate partner violence in their patients [53] despite the well-established reciprocal relationship between psychiatric disorders such as major depressive disorder and PTSD and risk for partner violence exposure and perpetration [52].
- Patients, families, coworkers, outpatient mental health clinicians, and primary care physicians should be vigilant about the possibility of PTSD and the prominent constellation of avoidance and hyperarousal symptoms after critical illness.
- Mental health professionals working with older veterans should assess for exacerbated PTSD symptoms (such as anxious arousal), particularly among those experiencing cognitive difficulties.
- The fear of stigma remains a significant barrier to treatment among older cohorts.
- The context is key when one suspects trauma-related disorders. Using a thorough clinical interview that encourages the patient's full narrative is preferable to a checklist approach (which could be misleading).

14.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Using a checklist rather than a phenomenological and narrative approach can lead to diagnoses that do not fully grasp the underlying or core issue. Which diagnosis should alert us to the possibility of PTSD? Select the best answer.

A. Major depressive disorder, mild, single episode
B. Panic disorder with agoraphobia
C. Major depressive disorder, with psychotic features
D. Borderline personality disorder
E. Multiple substance use disorders

Answer: C

Multiple substance use disorders could certainly mask PTSD (people with unpleasant symptoms or fear of reactivation might use substances to self-medicate, or numb themselves), but they could also co-exist. The same goes for borderline personality disorder, which can be conceptualized as a form of "chronic PTSD." If the trauma that occurred was repeated, severe, it is possible that the sequelae will crystallize in the personality structure more than in an episodic PTSD presentation. Panic disorder and agoraphobia could also co-occur with PTSD or be its main manifestations. For

instance, avoidance of open spaces could stem from a broader syndrome (PTSD), or be a residual manifestation. Depressive disorder can also co-occur or overlap with PTSD. Someone could have had a history of PTSD symptoms and presenting a separate, distinct depressive disorder entity. Depressive disorder with psychotic features though should prompt the clinician to clarify what "psychotic" refers to. For instance, a patient reporting "seeing shadows" or hearing his/her names could be misconstrued as hallucinations (such as the ones from psychotic illness or schizophrenia), while in fact they could fall under the broader, nonspecific category of perceptual disturbances. They could also occur in the context of reexperiencing. Maybe intrusive memories are only "auditory," for instance. Or seeing shadows could be simply misinterpretation of the environment stemming from hyperarousal or paranoia. Therefore, the best answer is C. The overlap is bigger than simple depressive disorder and PTSD; thus, the boundaries are less defined, and when we think we are in front of a major depressive disorder with psychotic features (a DSM construct), we might be in fact in front of a person with PTSD (see Case 2 and [35]). A diagnosis of PTSD might be overlooked if one assumes a person has major depressive disorder with psychotic features. It is therefore important to keep in mind that PTSD should be in the differential and should be ruled out. Again, it is crucial to always put patient's symptoms into context. Most symptoms in psychiatry are nonspecific and not pathognomonic of a single disease.

MCQ 2. Which statement is the most accurate regarding PTSD in late life?

A. Traumatic exposure is less prevalent in older age, so the negative effects on physical and mental health or functional status usually impact combat veterans rather than civilians.
B. The fear of stigma is usually not a significant barrier to seek treatment.
C. Marital status and income were found to mediate the association between early life stressors and depressive disorder in late life.
D. One of the advantages of being old is not having to worry about stress affecting the genome.
E. Cognitive impairment seems to be a protective factor for the re-occurrence of PTSD symptoms in late life.

Answer: C

Even though some studies have shown that some older people are more resilient after a traumatic experience (from stress inoculation), they are still vulnerable, and A is incorrect. The fear of stigma, especially in older cohort whose misconceptions might be more ingrained, is a significant barrier to treatment, so B is false. Epigenetic changes can occur at multiple stages throughout life, including in adulthood, therefore, D is false. Cognitive impairment including memory problems might cause a resurgence of traumatic memories or reexperiencing, therefore E is incorrect. C is correct because marital status and income level might be reflecting the resiliency and self-efficacy factors, therefore they could mediate the impact of early life stressors and depressive disorder in late life.

MCQ 3. Which statements regarding the therapeutic rationale and principles for addressing trauma- and stressor-related disorders in old age is correct?

A. Therapeutic approaches should be designed to increase locus of control, perceived self-efficacy, and positive reappraisal.
B. Exposure therapy is contraindicated for old people because they are too frail and cannot sustain the increase in heart rate or blood pressure.
C. Shared decision-making is a futile and counterproductive step; one has to intervene fast to prevent complications.
D. Victims of elder abuse should not be screened for trauma-based reactions and PTSD because it is a trauma that is not well understood and the guidelines of assessment and treatment are not clear.
E. Interpersonal psychotherapy has been developed for depressive disorder, therefore it has no place in the management of PTSD.

Answer: A

It is implicit to trauma-informed approach as well. Exposure therapy is indicated and some medications (such as clonidine) can be given prior if there is a known cardiovascular disease and higher risk of cardiovascular-related events. It is a matter of precaution, not contraindication. Therefore, statement B is incorrect. Shared decision-making is empowering and healing because it increases the locus of control and not only perceived but actual self-efficacy. It is about acknowledging that the person, no matter how disabled, can use her resources and abilities to make an informed decision and have a say in her/his care. The statement C contradicts A. Even though we are becoming more aware of elder abuse, it is still a legitimate trauma that warrants an evaluation to rule out PTSD. Statement D is incorrect. Statement E is also false: given the relationship between social support and the development and maintenance of PTSD, the potential application for interpersonal therapy to older trauma survivors appears relevant. Plus, depressive features might constitute a residual component of PTSD or co-occur with PTSD. If unaddressed, it can complicate the course. The specific domains of IPT (losses, grief, interpersonal disputes) (see ► Chap. 8) can also apply to the context of trauma (e.g., accident involving death of a relative, domestic violence).

MCQ 4. What is the guideline regarding benzodiazepines and PTSD?

A. They should be initiated early on to prevent memory consolidation of traumatic events and complications.
B. Their risk-benefits ratio is low as long as the older adult is given half the dose compared to younger populations.

C. Clonazepam and alprazolam are usually well tolerated and effective.
D. Benzodiazepines as a class should be avoided.
E. If the benzodiazepine is already initiated, it is better to continue it but monitor for side effects.

Answer: D

The literature does not support the use of any benzodiazepines in PTSD. Temazepam and alprazolam may actually *worsen* PTSD outcomes. In addition to the well-known risk of addiction and perpetuation of depressive disorder, they increase the risk of falls and cognitive problems in older adults, all of which can be problematic, especially if depressive disorder co-occurs or if the depressive symptoms and cognitive symptoms of PTSD are predominant. Although monitoring for side effects is the standard of care, it is never too late to taper and stop a benzodiazepine. It is important to have a discussion about risks and benefits of each treatment with the patients to support our approaches. In this case (statement E), alternatives such as an SSRI or prazosin (depending on the symptoms: anxiety versus insomnia due to nightmares) would be preferred and there could be a cross-switch from the benzodiazepine to the other medication.

MCQ 5. Which statement about triggers is the most accurate?
A. They are a phenomenon specific to combat veterans or refugees from conflict-torn zones.
B. They are best addressed by (i) recognition and (ii) defusion of trauma-based reactions.
C. They indicate poor prognosis.
D. They are specific to PTSD and some anxiety disorders.
E. This concept is not a core component of trauma-informed care.

Answer: B

A trigger is a stimulus, either external (e.g., spouse's angry voice) or internal (e.g., tachycardia) that elicits an intense physiological, emotional, cognitive, or behavioral response (avoidance, panic, drug use), sometimes without the person's awareness of the link between the trigger and the reaction. Although the sharp detonation sounds are a commonly known trigger for people who have experienced war trauma, they are not the only trigger. So statement A is incorrect. There are as many possible triggers as there are permutations of traumatic situation, and it is important to be attentive to each person's patterns of reactions (e.g., whenever a specific aid in a nursing home comes in and the patient has autonomic reactions, it is thus helpful to investigate and find what is the specific stimulus attached to the aid that triggers the trauma-based response: the name, the cologne, the voice?). Even though a person can be unaware of them and constantly experiencing trauma-based reactions because of frequent exposure to stimulus, once identified, it is possible to minimize their impact by developing strategies (such as defusion—see ▶ Chap. 8). The concept of trigger is also an essential element of trauma-informed care (see ▶ Chap. 26). Therefore, statements C and E are false and B is true. They are not specific to PTSD or certain anxiety disorders. Triggers can also be a phenomenon that has repercussions for people who suffer from neurocognitive disorder (see ▶ Chap. 34).

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Late-Life Psychosis

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15.1 Background

15.1.1 Definition

Late-life psychosis is a heterogeneous condition, representing a cluster of clinical features occurring as a result of diverse etiologies. Psychosis is defined by the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), as the presence of hallucinations, delusions, disorganized thinking and speech, grossly disorganized or abnormal motor behavior, or negative symptoms [1]. The term *late life* has come to represent several different groups of older adults with psychosis, differentiated by age of onset and clinical features. A generally accepted broad classification of the condition, which will define the scope of the disorder for this chapter, includes groups of patients with the following:

- Aging with early-onset schizophrenia
- Late-onset (after age 40) and very late-onset (after age 60) schizophrenia and unspecified schizophrenia spectrum disorders
- Delusional disorder
- Psychosis as part of a major neurocognitive disorder (formerly dementia)
- Delirium
- Substance-induced psychosis
- Depressive disorder
- Bipolar disorder
- Systemic medical illnesses
- Neurological conditions

As in younger adults, the disease burden of psychotic disorders has enormous impact on the older patient, the family, caregivers, and society. There are unique characteristics of late-life psychosis that are important in determining etiology and informing appropriate treatment. This chapter will focus on late- and very late-onset schizophrenia, unspecified psychosis, delusional disorder, and psychosis as part of a major neurocognitive disorder. For psychosis related to depressive disorder, bipolar disorder, delirium, and major neurocognitive disorders, please refer to ▶ Chaps. 10, 11, 17, and 22.

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15.1.2 Epidemiology

It has been challenging to accurately determine the epidemiology of late-life psychiatric disorders in general. In particular, identifying cases and distinguishing those individuals who need treatment, as opposed to those experiencing the effects of normal aging, have been difficult. Psychiatric disorders and symptoms may interact with the aging process and other factors occurring in late life. Current classification systems such as DSM present challenges in differentiating psychiatric symptoms from those related to aging, physical illness, frailty, and cognitive impairment. Overall, the prevalence of psychiatric disorders appears to be lower in older adults compared to younger counterparts [2].

The precise prevalence and etiology of psychotic symptoms is further hampered by the occurrence of these symptoms in many systemic medical, neurological, neurodegenerative, and various psychiatric illnesses. Overall, at least 6% of older adults have paranoid symptoms, but most of these will have a neurocognitive disorder to account for their symptoms [3]. A recent review of late-life psychosis summarized the associated epidemiological and clinical features of various conditions, which will be discussed in the following sections [4]. In this review, schizophrenia diagnosed after age 45 and after age 65 has 1% prevalence and 0.3% prevalence, respectively. Delusional disorder has 0.18% lifetime prevalence. In patients with major neurocognitive disorder due to Alzheimer disease, approximately 40% have psychotic symptoms. In Parkinson disease there is a 43% prevalence of psychotic symptoms. In patients with major neurocognitive disorder due to Parkinson disease, the prevalence rate of visual hallucinations is 89%. In those with major neurocognitive disorder with Lewy bodies, the prevalence of hallucinations, misidentifications, and delusions is 78%, 56%, and 25%, respectively.

15.1.3 Etiology and Differential Diagnosis

The approach to the differential diagnosis or etiology of psychotic disorders at any age involves a thorough work-up to rule out reversible contributors, including a detailed history, physical examination, mental status examination, and additional laboratory and radiological investigations. These reversible factors include substances, medications, another primary psychiatric disorder, or an underlying systemic medical or neurological condition and will not be covered in detail in this chapter [5].

This group of disorders has been challenging to study, given the ambiguity of definitions. In evaluating older adults with psychosis, etiology is critically important in informing the correct management. A careful review of history and clinical presentation must be undertaken. Factors to consider include age of onset, acute versus insidious onset, duration of symptoms, family history of psychosis, clinical presentation, and setting. For example, psychotic symptoms appear to be more common in inpatient and institutional settings such as long-term care facilities than in the community or outpatient settings.

15.1.4 Clinical Description

Schizophrenia and Unspecified Schizophrenia Spectrum and Other Psychotic Disorders (Previously Psychosis Not Otherwise Specified)

This category encompasses schizophrenia in all older adults and includes aging individuals with early-onset symptoms, late-onset symptoms, and very late-onset symptoms. Risk factors for late-onset schizophrenia include genetic factors,

female sex, and premorbid paranoid or schizoid personality structure [6]. Very late-onset schizophrenia is likely a heterogeneous condition with multifactorial etiology. Unlike the late-onset schizophrenia, there is no association with a family history of schizophrenia, but a higher association with brain structure abnormalities and cognitive impairment.

The late-onset schizophrenia group is traditionally thought to exhibit distinct clinical features, with higher rates of visual, olfactory, and tactile hallucinations, and persecutory delusions. Auditory hallucinations tend to be less common and milder and, when present, are derogatory in nature, with a third-person running commentary [7–10]. Those with late-onset schizophrenia are generally thought to have lower rates of negative symptoms and thought disorder, although recent findings have challenged this notion and found no significant difference between groups in both negative and positive symptomatology.

Neuroimaging has not been particularly helpful in distinguishing features of late-life schizophrenia, with variable patterns of neurodegeneration and volume loss. Some studies have demonstrated increased periventricular white matter hyperintensities on MRI, and lower frontal and temporal lobe perfusion on PET and fMRI studies, but these conclusions remain variable and have limited correlation with clinical presentations [4].

Delusional Disorder

While its overall prevalence is low, delusional disorder should be considered as a cause of suspiciousness in older adults, in individuals who exhibit non-bizarre delusions (e.g., paranoid, somatic, erotomanic, grandiose) with otherwise intact functioning. Hallucinations are not prominent, but may be present if related to the delusional thought content. Common themes of delusions in older adults are those of persecution and conspiracy. Risk factors for delusional disorder include a family history of paranoid personality traits, personal history of paranoid or schizotypal personality traits, sensory impairment, and social isolation. Risk factors are interrelated, as sensory deficits may limit one's ability to interact with others and may fuel social withdrawal. There are no sex differences in presentation. Immigration and low socioeconomic status may also be risk factors, but the evidence is not compelling. Neuroimaging has not been helpful in distinguishing patients with delusional disorder from other forms of psychosis.

Major Neurocognitive Disorder Due to Alzheimer disease

Psychosis is very common in the context of Alzheimer disease and is a frequent source of agitation, particularly in inpatients. Psychotic symptoms may wax and wane as the major neurocognitive disorder progresses, and patients may also lose the ability to describe their symptoms, making it a challenging area to study. Psychosis in Alzheimer disease is often associated with more rapid cognitive decline, age, and duration of major neurocognitive disorder, but not with sex, education, and family history of psychosis or major neurocognitive disorder [3]. Psychosis in the setting of major neurocognitive disorder is distinct compared to psychosis in other non-dementing illnesses. Hallucinations in Alzheimer disease tend to be visual rather than auditory. Delusions are not as complex or well-formed, with common themes of misidentification, persecution, and theft. (See ► Chap. 22.) Other characteristics include greater executive dysfunction, increased risk of extrapyramidal symptoms and tardive dyskinesia, and increased neurodegeneration.

Major Neurocognitive Disorder with Lewy Bodies

Major neurocognitive disorder with Lewy bodies is recognized as one of the most common type of major neurocognitive disorders after Alzheimer disease-related and mixed (vascular and Alzheimer disease) major neurocognitive disorder. This disorder is often under-recognized yet important given the potential side effects to treatment, notably exquisite sensitivity to antipsychotics. (See ► Chap. 22.) The challenge to refine diagnostic criteria to enhance diagnostic specificity and sensitivity continues. Visual hallucinations, considered rare in Alzheimer disease, are a core clinical feature of major neurocognitive disorder with Lewy bodies, occurring in about two thirds of patients [11]. Visual hallucinations often occur early in Lewy body disease, may be simple or complex, and are considered to be one of the most helpful symptoms in differentiating major neurocognitive disorder with Lewy bodies from Alzheimer disease. The presence of visual hallucinations may give rise to delusions rooted in the visual misperceptions in up to 75% of cases [12]. While less common, patients may also experience auditory, olfactory, or tactile hallucinations, necessitating a work-up to exclude toxidromes or seizure disorders.

As in Alzheimer disease, severity of psychosis is positively correlated with severity of major neurocognitive disorder [13]. Similar to the psychosis of Parkinson disease, visual hallucinations in Lewy body disease are well-formed and often non-distressing. The two disorders are distinguished by the timing and sequence of motor and cognitive symptoms, anecdotally referred to as the "1-year rule." (See ► Chap. 20.) Lewy body neurocognitive disorder typically starts with cognitive impairment, with the motor symptoms of Parkinson disease developing within the first year. In neurocognitive disorder due to Parkinson disease, motor symptoms must be present for a minimum of 1 year prior to the onset of cognitive impairment.

Major Neurocognitive Disorder Due to Parkinson Disease

Patients with Parkinson disease, with or without neurocognitive disorder, are at high risk for developing visual hallucinations. Cognitive dysfunction is strongly associated with the presence of hallucinations, and in those with normal cognition, hallucinations may be a harbinger for later major neurocognitive disorder. Many antiparkinsonian drugs, including the commonly prescribed dopaminergic agents (e.g., levodopa/carbidopa, amantadine), can cause and exacerbate visual hallucinations [14].

Visual hallucinations are the most common psychotic symptom seen in Parkinson disease, which tend to be stereotyped and non-frightening, but hallucinations of any sensory modality may be seen. When present, delusions are generally non-bizarre and persecutory in nature [15]. Unlike in Alzheimer disease, the prevalence of psychosis in Parkinson disease-related neurocognitive disorder is not positively correlated with severity of major neurocognitive disorder [13].

Neuroimaging, while helpful to document gross changes in neuroanatomy representing advanced major neurocognitive disorder, has limited usefulness in diagnosis. It is most often used to rule out significant pathology in the context of sudden alterations in clinical presentations (e.g., subdural hematoma, stroke, tumor). Neuroimaging can help to document suspected neurodegeneration in one area of the brain.

Delirium

While not discussed in depth in this chapter, delirium can present with psychotic symptoms and must always be ruled out first. In brief, delirium is defined by DSM-5 as a disturbance in attention and awareness that develops over a short period of time, is a change from baseline, and fluctuates throughout the day [1]. (For more details, see ► Chap. 17.) Criteria stipulate that there must be an additional disturbance of cognition (i.e., memory, orientation, language, visuospatial ability, perception) [1]. Symptoms must not be solely attributable to preexisting major neurocognitive disorder or severely reduced level of consciousness. There must be evidence that symptoms are clearly linked to another systemic medical condition, substance intoxication/withdrawal, toxin exposure, or multiple etiologies [1]. Additional clinical features of delirium include disturbed sleep-wake cycle, emotional lability, and psychosis [16]. Delirium is frequent in individuals over age 70, more common in inpatient settings such as intensive care, postoperative care, and palliative care, and is usually multifactorial in causation. Common risk factors for delirium include premorbid cognitive and/or functional impairment, sensory deficits, substance abuse, and polypharmacy [16]. The importance of identifying and treating the underlying cause of delirium cannot be overstated, as psychotic symptoms may resolve without the need for long-term antipsychotic treatment.

15.1.5 Diagnostic Evaluation

Clinical History

It can be challenging to determine the cause of psychosis in older adults due to the heterogeneity of clinical presentations. Yet accurate diagnosis is crucial, as treatment is guided by the context within which the psychotic symptoms present. As with all medical problems, the first step involves taking a thorough clinical history. Ideally, both patients and their caregivers or knowledgeable informants should be interviewed to obtain collateral history. This is especially important when psychosis presents in the context of major neurocognitive disorder, where one's cognitive ability to provide an accurate history may be limited. As well, collateral sources can be helpful in describing one's premorbid personality structure and level of functioning. History taking should begin by targeting the patient's area of distress and addressing current symptoms, including symptom onset and age of first onset. This helps to determine whether this is an aging individual with an early-onset psychotic disorder versus a late-onset psychosis. Past psychiatric history should be elicited to identify comorbid psychiatric illnesses, prior need for hospitalization, and past trials of pharmacotherapy or electroconvulsive therapy.

Old medical records may be obtained to corroborate patient's history. Past medical history is essential, including recent infections, other medical illnesses, and recent hospitalizations, as this increases the clinical suspicion for delirium (discussed previously in ► section Delirium). In this vein, a complete medication review is essential, including current medications, those recently discontinued, over-the-counter substances, overall compliance, and medication misuse. It is helpful to have patients bring in their most updated pharmacy record for this purpose.

Substance use history must also be addressed, including both ongoing and discontinued substances, to rule out presentations due to intoxication or withdrawal. As with all history taking, it is important to elicit a family psychiatric history and to discuss social history, including recent or ongoing stressors that may impact one's presentation. A risk assessment should be performed to assess suicidality (discussed in ► Chap. 28, Psychiatric Emergencies in Older Adults) while maintaining vigilance for suspected elder mistreatment or abuse.

Physical Examination

A complete physical examination, including neurological examination, is part of the clinical evaluation of psychosis. Comorbid physical illnesses identified during the exam should be addressed and treated, with referral to the appropriate medical specialty or subspecialty if needed. When antipsychotic medications are initiated or continued, it is important to monitor for extrapyramidal symptoms, including tardive dyskinesia, and to document this in the patient's chart. A commonly used screening tool for extrapyramidal symptoms is the Abnormal Involuntary Movement Scale (AIMS) [17].

Investigations

Laboratory Examination Routine laboratory investigations are obtained to identify potential causes of delirium and to evaluate for systemic medical comorbidities. Screening laboratory studies for late-life psychosis generally include complete blood count, electrolytes (including calcium, magnesium, phosphorus), glucose, creatinine clearance, hepatic function, thyroid function, B_{12}, and folate. When initiating or continuing antipsychotic medications, metabolic monitoring includes fasting blood glucose, hemoglobin A1c, and fasting lipids. If

infection is suspected, urinalysis and chest x-ray should be ordered, given that the most common sources of infection tend to be respiratory and urinary tract. Electrocardiogram should be ordered in individuals with a cardiac history or on medications known to be associated with prolonged QTc, such as certain antipsychotics and antidepressants.

Neuroimaging The role of neuroimaging in late-life psychosis is somewhat controversial. Cases of new-onset psychosis merit imaging with CT of the brain to rule out a structural cause for the presentation. Particularly when psychosis arises in the context of neurocognitive disorder, neuroimaging can be helpful in establishing a clinical baseline for monitoring. Common abnormalities seen on neuroimaging with CT/MRI in late-life psychosis include increased white matter lesions and structural changes with ventricular enlargement, cortical atrophy, and smaller superior temporal gyrus. Abnormalities may also be seen on functional neuroimaging, showing increased dopamine uptake.

Cognitive Examination

Brief cognitive testing such as Montreal Cognitive Assessment (MoCA) and standardized Mini Mental State Examination (sMMSE) should be performed to obtain a cognitive baseline and to monitor cognition serially. Full neuropsychological testing may also be considered. Neuropsychological findings in late-life psychosis show overall decline in frontal lobe function and verbal memory. Late-life psychosis is thought to be related to degenerating cortical structures in the aging brain, resulting in disrupted neurotransmission, and deficits in maintaining attention and filtering information. Cognitive deficits noted are often progressive, but not all cases progress to frank major neurocognitive disorders. It can be challenging to detect deterioration when one's premorbid functional and cognitive baseline is low. As well, these individuals often perform poorly on standardized tests and may appear clinically better than their formal testing suggests.

15.1.6 Treatment

General Principles

Antipsychotics in geriatric patients are associated with various and often serious side effects and must be used judiciously. In general, non-pharmacological management strategies should be tried first, if possible. Safety is paramount, and antipsychotics are indicated when non-pharmacologic strategies have failed and/or psychotic symptoms place the individual or others in their living environment at risk. Is it important to establish therapeutic alliance with the patient and caregivers to promote adherence and to consider the ideal treatment setting for the individual (e.g., inpatient versus community). Decisional capacity to consent to treatment should be assessed prior to initiating treatment, and informed consent should be obtained from the patient or the substitute decision maker and documented in the medical record.

Age-related changes in the pharmacodynamics and pharmacokinetics of psychotropic medications (e.g., longer time to reach steady state, longer half-life, longer elimination time) should be taken into consideration. Lower doses, cautious dose adjustments, and regular reassessment of the need for continuing treatment in the geriatric patient should be considered. Older patients are more vulnerable to adverse effects, including sedation, anticholinergic effects, cognitive decline, extrapyramidal symptoms, and drug-drug interactions. Because of the tendency toward side effects, adherence to treatment may be a challenge. As well, clinicians should be aware of the relevant legislation and regulations in the jurisdiction where they practice, regarding the usage of antipsychotics in long-term care facilities.

Non-pharmacological Management

Non-pharmacologic therapies are used to reduce symptom burden and also to enhance the effectiveness of and adherence to pharmacological treatment [4, 18, 19]. By providing patients with the opportunity to express their fears and expectations regarding treatment, therapeutic rapport is bolstered. Simple distraction techniques may help alleviate the distress associated with psychotic symptoms and enhance self-efficacy and coping. In situations of acute behavioral crises, it is essential for safety purposes to remain calm, nonthreatening, and at a safe distance and to summon help when needed.

There are four general types of psychosocial therapy for schizophrenia: (i) cognitive behavioral therapy (CBT), (ii) social skills training, (iii) family therapy, and (iv) cognitive remediation [4, 18]. Of these, CBT is the most widely used, with evidence for the reduction of positive and negative symptoms, as well as some benefit for treatment adherence [4, 20]. There is limited data on the application of these interventions to geriatric patients with schizophrenia. Other psychosocial treatments have not been studied in late-onset schizophrenia, including supported employment, healthy lifestyle measures, illness self-management training, assertive community training, and family psychoeducation [4, 21, 22]. Exercise can be helpful in reducing cognitive decline and improving functional status, but there is no evidence specifically on the reduction of psychotic symptoms [4, 23].

Pharmacological Management

Schizophrenia

Antipsychotics are the mainstay of treatment in schizophrenia, yet there is limited data on their use in late-onset schizophrenia. There is some evidence supporting the use of atypical antipsychotics such as risperidone and olanzapine [24].

Delusional Disorder

Similarly there are no treatment studies specifically on late-life delusional disorder, and risperidone and olanzapine are most commonly used, with some evidence supporting their use [25].

Major Neurocognitive Disorders

Importantly, there are increased mortality and morbidity risks associated with the use of antipsychotics in the geriatric patients with major neurocognitive disorder, with an increased risk of sudden cardiac death and a small increased risk of cerebrovascular accident [26, 27]. There is no definitive pathophysiologic mechanism for the increased mortality risk, but it is thought to be due to oversedation and the increased risk of aspiration. A significant body of literature including 17 double-blind placebo-controlled trials led to the placement of the US Food and Drug Administration (FDA) black box warning on both typical and atypical antipsychotics in older individuals with major neurocognitive disorders [28]. Nonetheless, Health Canada does support the use of risperidone for "the short-term symptomatic management of aggression or psychotic symptoms in patients with *severe* dementia of the Alzheimer type unresponsive to non-pharmacological approaches and when there is a risk of harm to self or others" [29].

Antipsychotics have modest benefit for the treatment of behavioral disturbances in major neurocognitive disorder. The most efficacious and best-tolerated agents are risperidone, olanzapine, and aripiprazole [8, 30]. Haloperidol should be limited to brief use for the treatment of delirium-associated psychosis and agitation. Antipsychotics are generally not effective for wandering, social withdrawal, vocalizing, pacing, touching, or incontinence.

Antidepressants may also be considered to treat agitation and psychosis in major neurocognitive disorder due to Alzheimer disease, with evidence supporting the use of citalopram and sertraline [31]. In one study, citalopram has been shown to have equal efficacy to risperidone [32]. Individuals more likely to benefit from antidepressants are those with mild cognitive impairment and moderate agitation at baseline [33]. Due to the association of citalopram with QTc prolongation, it should be avoided in those at increased risk for cardiac arrhythmia or with QTc above 500 milliseconds.

Major Neurocognitive Disorder with Lewy Bodies and Major Neurocognitive Disorder Due to Parkinson Disease

Antipsychotics must be used with great caution in Lewy body disease due to the risk of extreme antipsychotic sensitivity in this population. Prior to initiating antipsychotics in Parkinson disease, dopaminergic parkinsonian agents should be reviewed and streamlined, as these can worsen psychosis. As in Lewy body neurocognitive disorder, antipsychotics must be used cautiously due to the risk of exacerbating parkinsonian motor symptoms. In both Lewy body disease and Parkinson disease, low-dose quetiapine is most commonly used. The largest body of evidence exists for the use of low-dose clozapine, although its use is limited by the need for hematologic monitoring and the risk of agranulocytosis [4]. Pimavanserin (a non-dopaminergic atypical antipsychotic) is the first recently approved drug by the FDA to treat hallucinations and delusions associated with Parkinson disease [34]. Cholinesterase inhibitors are recommended as first-line treatment for psychosis in major neurocognitive disorder with Lewy bodies and major neurocognitive disorder due to Parkinson disease, due to the lower comparative risk of toxicity and possible benefit for cognition [35]. A summary of common medications used to treat psychosis in major neurocognitive disorders is presented in ◘ Table 15.1 [36].

Neurostimulation

Neurostimulation refers to the use of electroconvulsive therapy (ECT), transcranial magnetic stimulation (TMS), and deep brain stimulation (DBS). Very limited data is available on the use of neurostimulation in exclusively older psychotic patients, with several ECT trials, no TMS trials, and no DBS trials to date in older adults with schizophrenia [4]. Of these, ECT is the most widely used, with evidence for benefit in treatment-resistant cases, catatonic schizophrenia and schizophrenia with a significant depressive component. As well, maintenance treatment with ECT plus antipsychotics is associated with lower rates of relapse than treatment with antipsychotics alone [4, 37, 38]. There is limited evidence for the use of ECT in psychosis in Parkinson disease [4, 39]. Otherwise, evidence does not generally support the use of ECT for psychosis in major neurocognitive disorder. While DBS can be used to treat motor symptoms in Parkinson disease, it does not improve psychosis and may actually worsen psychotic symptoms [4, 40].

15.2 Case Studies

This section emphasizes clinical case studies used to illustrate common diagnostic challenges and treatment concerns that are associated with managing a geriatric patient with psychosis. Case studies may be used as teaching tools for clinicians and trainees at various levels and may be particularly helpful as "quick-reference" tools in on-call or emergency settings.

15.2.1 Case 1

Case 1 History

You are working in an outpatient geriatric psychiatry clinic, and the following is your first consultation of the day, referred by the patient's primary care physician.

Ms. D. is an 81-year-old widowed female living alone in an apartment, with no past psychiatric history. At her recent checkup, she expressed concerns that her upstairs neighbors are

Table 15.1 Pharmacological management of psychosis in major neurocognitive disorders [36]

Medication category	Daily dosing	Side effect monitoring	Comments
Atypical antipsychotics (AAP)			
Risperidone	Initial: 0.25 mg od-bid Titration: 0.25–0.5 mg q3–7 days Max: 2 mg	Sedation Postural hypotension Falls Anticholinergic side effects (dry mouth, constipation, confusion) EPS, particularly parkinsonian side effects (rigidity, bradykinesia, shuffling gait, masked facies, tremor) Olanzapine and quetiapine are more sedating than risperidone or aripiprazole	Best supported AAP for NPS Most likely AAP to cause EPS
Olanzapine	Initial: 2.5–5 mg qhs Titration: 2.5–5 mg q3–7 days Max: 10 mg		Most likely AAP to cause metabolic side effects
Quetiapine	Initial: 12.5 mg bid Titration: 12.5–25 mg q3–7 days Max: 150 mg		Used for Parkinson disease-related and Lewy body-related NCD at lower doses
Aripiprazole	Initial: 2–5 mg daily Titration: 2–5 mg q3–7 days Max: 10 mg		Most likely AAP to cause akathisia (restlessness)
Typical antipsychotics			
Haloperidol	Initial: 0.25 mg bid Titration: 0.5 mg bid q3–7 days Max: 1.5 mg bid	Haloperidol more likely to cause EPS than AAP	Gold standard for delirium Given IM in ED when other formulations are unavailable
SSRI antidepressants			
Citalopram	Initial: 5–10 mg daily Titration: 10 mg q7 days Max: 20 mg	Headache Nausea (given with food to decrease GI upset) Diarrhea Sweating Insomnia Hyponatremia Risk of GI bleed QTc prolongation at higher dose of citalopram Risk of falls, fractures, and osteoporosis	Citalopram is best supported SSRI for NPS, with evidence for both citalopram and sertraline
Sertraline	Initial: 25 mg daily Titration: 25 mg q7 days Max: 100 mg		
Cholinesterase inhibitors (ChEIs)			
Donepezil	Initial: 2.5–5 mg daily Titration: 2.5–5 mg q4–6 weeks Max: 10 mg	GI upset (nausea/vomiting/diarrhea) Loss of appetite Decreased GI side effects with patch Insomnia, hyper-vivid dreams Bradycardia Urinary incontinence Muscle cramps	ChEIs are first-line agents for psychosis in Parkinson disease-related and Lewy body-related NCD Taken with food to minimize GI upset Rotate patch site
Rivastigmine (oral and transdermal)	Initial: 1.5 mg bid Titration: 1.5 mg q2 weeks Max: 12 mg		
	Initial: 5 cm^2 patch Titration: 5 cm^2 q4 weeks Max: 15 cm^2		
Galantamine (extended release)	Initial: 8 mg qam Titration: 8 mg q4 weeks Max: 24 mg		

Note: bid two times a day, *BZP* benzodiazepine, *ED* emergency department, *EPS* extrapyramidal symptoms, *GI* gastrointestinal, *IM* intramuscular, *NCD* neurocognitive disorder, *NPS* neuropsychiatric symptom, *SSRI* selective serotonin reuptake inhibitor, *tid* three times a day

stealing from her and spying on her. Please advise regarding assessment and treatment recommendations.

Ms. D. presents to the clinic along with her niece. She appears well-dressed and neatly groomed, well hydrated, and well nourished. She is pleasant and cooperative throughout the interview, but appears visibly worried as she tells you about the young couple upstairs who is spying on her. She says that they know when she is a way and break in to hunt for valuables to sell for drugs. She has no proof, but is certain this is happening. She has complained to the landlord, who has "done nothing." She denies any other delusions or hallucinations, and no mood symptoms are elicited. Her past medical history is significant for bilateral hearing loss, yet she refuses to wear hearing aids. She is an ex-smoker and a nondrinker. She is on no medications, other than the occasional acetaminophen for headache. There are no known drug allergies. There is no past psychiatric history.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What additional information is needed to make an accurate diagnosis?

Question 2. What investigations should be ordered?

Question 3. What is the differential diagnosis in late-life psychosis? What is the working diagnosis in this case?

Question 4. What are the risk factors for the development of psychosis in the geriatric population?

Case 1 Answers

Case 1 Answer 1 (Question 1—What additional information is needed to make an accurate diagnosis?)

In general, the key elements to address as part of a thorough evaluation are presented in Table 15.2. In Ms. D.'s case, it would be important to obtain collateral history from her niece, including any safety concerns, cognitive and/or functional decline, and information regarding her premorbid personality structure and functional status. Although she is not on any regularly prescribed medications, the most updated medication list should generally be reviewed, including over-the-counter and herbal preparations, recent changes to medication, and overall treatment compliance. Delirium should always be ruled out with inquiry into acute medical illnesses and recent infectious symptoms (most common source as upper respiratory tract and urinary tract). Cognitive screening should be performed to rule out cognitive impairment and to establish a baseline.

Table 15.2 The work-up in late-life psychosis

History	Sources of information
Current symptoms within overall symptomatic context Age of symptom onset Past psychiatric history Comorbidity Past medical history (including acute systemic medical illness) Family history of psychiatric illness Medications (new, discontinued, over the counter) Substance use (past and present) Premorbid personality and function Stressors, losses	Collateral information from family members/caregivers Old medical records Medication record from pharmacy Laboratory investigations Neuroimaging (e.g., CT, MRI, SPECT) EEG (if justified) Cognitive screening (MMSE, MoCA) Neuropsychological evaluation

Collateral history obtained from her niece reports that Ms. D. has been "obsessed with her neighbors" for the past year. She telephones her niece weekly with these concerns, but has never called the police. There have been no difficulties with memory observed, and she is fully independent with basic and instrumental activities of daily living. She wonders whether her aunt is fearful of living alone, as her husband died several years ago. While she was close to her husband, throughout her life Ms. D. was otherwise "somewhat of a loner, mistrustful, and odd." She has never gotten along well with neighbors. She retired at age 65 from her secretarial job. There is no known family psychiatric history.

Case 1 Answer 2 (Question 2—What investigations should be ordered?)

A standard work-up includes investigations to rule out causes of delirium, including infection, metabolic and electrolyte disturbances, uremia, toxic ingestions, hypoxia, stroke, and myocardial infarction. Particularly in first episode psychosis, neuroimaging should be obtained to rule out structural causes, such as intracranial tumor or hemorrhage. Cognitive screening helps to establish whether the symptoms are occurring in the context of cognitive impairment and provides a baseline for future comparison. Recall that cognitive screening may yield variably valid results during conditions of fluctuating cognitive status such as an acute episode of delirium or other neuropsychiatric illnesses and should always be repeated when symptoms stabilize. The common investigations in the work-up of late-life psychosis are shown in Table 15.3.

Recent laboratory investigations forwarded by Ms. D.'s primary care physician are all within normal limits, and CT of the brain shows mild age-related atrophy, with no vascular changes noted.

Case 1 Answer 3 (Question 3—What is the differential diagnosis in late-life psychosis? What is the working diagnosis in this case?)

The most common cause of late-life psychosis is major neurocognitive disorder due to Alzheimer disease. However, psychosis can present in a variety of clinical conditions, including other types of major neurocognitive disorders, depressive and bipolar disorders, early- and late-onset schizophrenia and schizoaffective disorder, delusional disorder,

Table 15.3 Common investigations in the work-up of late-life psychosis

Laboratory	Neuroimaging	Cognitive
Complete blood count, basic and extended electrolytes, urea/creatinine, glucose Lipids, liver-associated enzymes, thyroid-stimulating hormone, B_{12}, folate Urinalysis Chest x-ray Electrocardiogram Creatine kinase and troponins if indicated	Computed tomography/ magnetic resonance imaging Electroencephalogram if indicated	Montreal Cognitive Assessment, Mini Mental State Examination, Frontal Assessment Battery Consider neuropsychological evaluation

Table 15.4 Differential diagnosis in late-life psychosis

Primary conditions	Secondary conditions
Schizophrenia (early vs. late onset) Schizoaffective disorder Delusional disorder	Major neurocognitive disorder due to Alzheimer disease Major neurocognitive disorder due to other causes (vascular, Lewy body, mixed, frontotemporal type) Major depressive disorder Bipolar disorder (manic or major depressive episode) Secondary causes (systemic medical illness, medication, substance)

Table 15.5 General risk factors for late-life psychosis [42]

Risk factors for psychosis in late life	Female sex Genetic predisposition History of previous psychosis Cognitive impairment Comorbid medical illness/ deteriorating physical health Medications (e.g., dopaminergic, anticholinergic) Substance misuse Sensory deficits Life stressors Social isolation Premorbid personality structure

and in the context of certain systemic medical and neurological illnesses and medication/substance-related conditions. Table 15.4 lists the differential diagnosis to consider in late-life psychosis.

In Ms. D.'s case, she presently does not exhibit any cognitive or functional impairment (MoCA score of 28 out of 30) and thus cannot be called major or mild neurocognitive disorder. However, she should be monitored closely, as late-onset psychosis is often a harbinger of major neurocognitive disorder. Delirium is unlikely in this case as there is no obvious medical cause. As well, her delusion is complex, and the delusions of delirium tend to be transient and poorly systematized, commonly with misinterpretations, illusions, and visual hallucinations. While she did not exhibit any depressive symptoms in today's consultation, psychosis commonly accompanies depression in the older adults, with mood congruent delusions of guilt, nihilism, and persecution.

Ms. D.'s current presentation is most consistent with a delusional disorder, a common cause of suspiciousness in geriatric patients. DSM-5 defines delusional disorder as the presence of at least one delusion of at least 1 month's duration, with no bizarre behavior, no functional impairment, and symptoms that cannot be attributed to the effects of substance use, medical illnesses, or other psychiatric disorders. Any hallucinations present must be related to the delusional theme. The individual cannot ever have met criteria for schizophrenia, and any past depressive or manic episodes must have been brief relative to the duration of the delusions [1]. The lifetime prevalence of delusional disorder is approximately 0.18%, with average age of onset in the late 40s [41]. Ms. D.'s delusions are of a persecutory nature, as is a classic theme in late-onset delusional disorder.

Case 1 Answer 4 (Question 4—What are the risk factors for the development of psychosis in the geriatric population?)

Table 15.5 presents the general risk factors for late-life psychosis [42]. Ms. D.'s case highlights multiple risk factors for late-life psychosis, including female sex, social isolation, and possibly the stressor of losing her husband several years ago. Her bilateral hearing impairment likely causes her to misperceive environmental stimuli, further fueling her delusional beliefs. Her premorbid personality is a particular risk factor, as she is described as somewhat paranoid and mistrustful of others.

Case 1 (Continued)

After completing your assessment, you begin to discuss the treatment plan with Ms. D. and her niece, including optimization of her hearing, trial of an antipsychotic, and involvement in a local day program for cognitive and social stimulation. At the mention of antipsychotics, Ms. D. decides she is not interested and does not wish to return to the clinic. You instruct Ms. D. and her niece to contact you as needed and attempt to book a home visit to follow up in 3 months, but she is not reachable and is ultimately lost to follow-up.

Six months later, you are asked to see Ms. D. again, this time as an inpatient on the acute psychiatric unit. She now believes that the neighbors are taking her to the basement of the building and "doing experiments" on her. She shows you a bruise on her arm as proof. She reports that they release a gas (which claims that she can smell) through the ceiling vents to "knock her out" and have planted a "chip" in her brain to monitor her. She believes they plan to harvest her organs, and she can hear them talking about her. She is no longer eating or attending to her hygiene. There have been no intercurrent infections or medical illnesses, and she continues to be on no medications.

Routine physical examination including screening neurological exam was unremarkable, laboratory studies were normal, and CT of her brain was unchanged from the previous study. Brief cognitive testing at admission showed a MoCA score of 24 out of 30, a decline compared to her previous score 6 months previously. After careful discussion with Ms. D. and her niece, informed consent is provided to start a trial of risperidone, which is gradually titrated to 2 mg at night with good response. After 2 weeks of treatment, you note a mild resting tremor in the hands and slowed gait with decreased arm swing. Risperidone is lowered to 1.5 mg at night with improvement in extrapyramidal symptoms, and Ms. D. is eventually discharged home to follow up with the outpatient team.

Case 1 Analysis Ms. D. initially presents with moderate non-bizarre persecutory delusions in the absence of cognitive and/or functional impairment and lacking prominent mood features. Her clinical picture is in keeping with delusional disorder, a common cause of paranoia in geriatric patients who otherwise lack family psychiatric history. She exhibits a classic constellation of risk factors for the development of delusional disorder, such as sensory impairment, social isolation, and premorbid personality structure. As is evident with her precipitous deterioration in the continuation of the case, late-onset psychosis is often a harbinger of major neurocognitive disorder, and individuals should be monitored closely for cognitive and/or functional decline suggestive of an evolving neurocognitive disorder.

Ms. D.'s case illustrates several general principles of treatment in late-life psychosis. Prior to initiating treatment, it is essential to conduct and to document an informed discussion of the risks and benefits of treatment with patients and their families. Treatment setting should be considered, and in this case, inpatient hospitalization allows for a closely monitored setting to initiate and titrate medication. The extrapyramidal side effects experienced by Ms. D. highlight the older adult's sensitivity to pharmacotherapy. In addition to the increased mortality risks due to sudden death and cerebrovascular events, individuals started on antipsychotics should be monitored closely for anticholinergic side effects, metabolic syndrome, oversedation, drug-drug interactions, and changes in cognitive and functional status [26]. Treatment should be time-limited, and target symptoms should be assessed using validated scales with frequent clinical reassessment [27].

Delusional disorder is typically considered resistant to treatment. There are currently no treatment studies focused on older adults with delusional disorder, and thus it is difficult to draw conclusions about the efficacy of antipsychotics in this population. However, a recent review of late-life schizophrenia reports that, although findings are mixed, there is some evidence supporting the efficacy of both risperidone and olanzapine in treating delusional disorder [25]. This same review found similar efficacy for pimozide, the typical antipsychotic previously considered first-line treatment for delusional disorder in the general population [25]. The one study looking at newer antipsychotics in delusional disorder found that, compared to oral antipsychotics, patients treated with long-acting injectable antipsychotics (e.g., paliperidone, risperidone) had significant improvement in both negative and positive symptoms [43].

15.2.2 Case 2

Case 2 History

You are a psychiatrist working on an inpatient geriatric psychiatry unit. Your new admission today is Mr. E., a 72-year-old single male resident from an assisted living facility. He was brought to the emergency department with "physical aggression and bizarre behaviors." Mr. E. has no known premorbid psychiatric history. Two years ago, he was diagnosed with mild neurocognitive disorder, major depressive disorder, and generalized anxiety disorder. He is unmarried with no children and had been living independently in an apartment until 6 months ago. His recent symptoms of depression and anxiety were attributed to his transition to retirement from teaching at age 65. He had worked as a high school mathematics teacher for 3 decades and was highly active in his local church. Following his retirement, his cognitive decline progressed, and, subsequently, he began to experience progressive parkinsonian symptoms, including mild intention tremor, cogwheeling rigidity, and bradykinesia. Recurrent falls and functional decline led to his eventual admission to the assisted living facility, as he required assistance with bathing, dressing, cooking, and medication management. He was seen by the facility's physician and referred to neurology service for evaluation of his parkinsonian symptoms.

Assisted living staff members report that he appears intermittently confused and disoriented and endorses visual hallucinations of insects and children in his room. He was initially insightful regarding these perceptual disturbances and easily reassured by staff. He was often seen in his room contentedly interacting with hallucinatory figures. Over the past month, he has expressed concerns that someone in the facility wants to harm him and that "nothing is real." He has become increasingly volatile and has been physically aggressive toward coresidents on several occasions, with no apparent trigger. At other times he appears entirely lucid and engages appropriately with staff and coresidents. His sleep is erratic and he has been observed to be thrashing his legs in his bed on nightly rounds. He is eating well, bowel and

bladder function are normal, and he denies any pain. There are no intercurrent medical illnesses and no infectious symptoms noted. There is no known family psychiatric history.

Past medical history is significant for dyslipidemia treated with a statin. He otherwise does not have any vascular risk factors. There is no history of traumatic brain injury. He is a non-smoker and nondrinker, and there is no illicit drug use. His current medications include atorvastatin 40 mg po daily and risperidone 0.5 mg po qhs, recently started by the facility's physician for psychosis. There are no known drug allergies.

On physical examination in emergency department, Mr. E. presented as afebrile with normal vital signs, and worsening parkinsonian symptoms were noted. The emergency physician noted that he appeared "perplexed" and endorsed visual hallucinations of small animals running around the ward. Mental status examination revealed a casually dressed and mildly disheveled older male, who appeared his stated age. He presented as confused, but was able to tolerate short interview. Speech was of normal rate, rhythm, and volume. Mood was described as "not bad" and affect was slightly blunted. Thoughts were disorganized, and perceptions revealed prominent visual hallucinations. He denied suicidality and homicidality. Insight and judgment were impaired due to level of confusion. Brief cognitive testing showed MoCA of 21 out of 30, with deficits in visuospatial and executive function. Laboratory investigations showed dehydration and mild leukocytosis, with urine culture positive for *E. coli* bacteriuria. He was started on intravenous fluids and an antibiotic.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What is your working diagnosis?

Question 2. What are your options for pharmacological management in this case?

Question 3. The medical student on your team asks whether Mr. E. should be referred to the neurology service and started on medication for Parkinson disease. How do you respond?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is your working diagnosis?)

Mr. E.'s clinical history demonstrates many of the core and supporting features of major neurocognitive disorder with Lewy bodies [1]. (See Table 15.6, which highlights the key DSM-5 diagnostic criteria.)

The main feature of major neurocognitive disorder with Lewy bodies is progressive cognitive impairment that tends to manifest as visuospatial and executive dysfunction rather than memory decline per se. Vivid and well-formed visual hallucinations are a hallmark of the disorder, as seen in Mr. E.'s hallucinations of insects and children, and may be accompanied by hallucinations in other modalities, as well as depressive symptoms. Clinical presentations of major neurocognitive disorder with Lewy bodies can fluctuate, and patients often require longitudinal follow-up to capture the diagnosis. As is a common occurrence in older adults, Mr. E.'s presentation was likely also complicated by delirium due to urinary tract infection, and his preexisting cognitive fluctuations worsened to the point of acute confusion and aggression.

Table 15.6 Highlights of the DSM-5 diagnostic criteria for major neurocognitive disorder with Lewy bodies [1]

Core features	Suggestive features
Cognitive fluctuation (attention and alertness) Recurrent visual hallucinations that tend to be well-formed Spontaneous parkinsonism developing subsequent to cognitive decline	Rapid eye movement (REM) sleep behavior disorder Severe antipsychotic sensitivity

Probable diagnosis: 2 core features *or* 1 suggestive feature and ≥ 1 core feature
Possible diagnosis: 1 core feature *or* ≥ 1 suggestive feature

Spontaneous parkinsonism is another core feature, which must begin after the development of cognitive impairment. Parkinsonism must be distinguished from antipsychotic-induced extrapyramidal symptoms, as 50% of individuals do have extreme antipsychotic sensitivity, a supporting feature of the disorder [44]. Mr. E. also demonstrated other supporting features of the disorder, including rapid eye movement (REM) sleep behaviors, as seen in his thrashing behaviors during sleep, as well as frequent falls. Although not present in this case, other supporting features include syncope, transient loss of consciousness, and autonomic dysfunction with orthostatic hypotension and urinary incontinence [45].

Case 2 Answer 2 (Question 2—What are your options for pharmacological management in this case?)

There is limited evidence guiding pharmacotherapy in major neurocognitive disorder with Lewy bodies. Compared to major neurocognitive disorder due to Alzheimer disease, Lewy body neurocognitive disorder is characterized by more severe dopaminergic and cholinergic deficits. As such, cholinesterase inhibitors are recommended as first-line treatment, with modest benefits for cognition and neuropsychiatric symptoms seen with standard doses of rivastigmine and donepezil [46]. Atypical antipsychotics are recommended when cholinesterase inhibitors are ineffective, but must be used very cautiously and with slow dose titration due to the risk of extreme antipsychotic sensitivity. Low doses of quetiapine and/or clozapine (12.5–50 mg) produce transient and lower levels of dopamine blockade and are therefore less likely to cause extrapyramidal symptoms. By extrapolation, a possible future treatment for psychosis is the novel agent pimavanserin, a selective serotonin $5HT_{2A}$ inverse agonist that has been shown to reduce psychosis in Parkinson disease and is well tolerated [46]. For further discussion related to other aspects of treatment for major neurocognitive disorder

Table 15.7 Evidence for pharmacotherapy of psychosis in major neurocognitive disorder with Lewy bodies [46]

Medication class	Drug	Level of evidence
Cognitive enhancers	Rivastigmine Donepezil Memantine	Level I evidence for cognitive symptoms, with both rivastigmine and donepezil. Overall moderate positive benefit. Mixed evidence for use in hallucinations. Memantine shows small significant cognitive improvement, but insufficient evidence
Atypical antipsychotics	Quetiapine Clozapine	Mixed evidence for quetiapine but clinically better tolerated than clozapine. Good evidence for clozapine in Parkinson disease-related neurocognitive disorder, but limited use due to risk of agranulocytosis and hematologic monitoring

with Lewy bodies, such as REM sleep behavior disorder and accompanying depression, please refer to ▶ Chaps. 20 and 24. All medications must be carefully monitored for increased risk of orthostatic hypotension, unsteady gait, and falls. Table 15.7 discusses the evidence regarding pharmacotherapy of psychosis in major neurocognitive disorder with Lewy bodies [46].

Case 2 Answer 3 (Question 3—The medical student on your team asks whether Mr. E. should be referred to the neurology service and started on medication for Parkinson disease. How do you respond?)

The complexity of managing major neurocognitive disorder with Lewy bodies lies in the high sensitivity to drug side effects and the likelihood that treatment with medication may improve one target symptom, yet worsen others. Recall that parkinsonian motor symptoms are due to a lack of dopamine function and are treated with dopaminergic agents. Psychosis is related to excess dopamine function and is treated with dopamine-blocking antipsychotics. Pharmacotherapeutic management of major neurocognitive disorder with Lewy bodies requires the delicate balancing of medications with opposing dopaminergic actions. Dopamine replacement therapy with carbidopa-levodopa, the established treatment for Parkinson disease, is generally less effective in Lewy body disease and increases the risk of worsening psychotic symptoms. The first step in treating this disease is rationalization of all dopaminergic agents to the lowest possible doses. In individuals with significant parkinsonism that is highly functionally impairing, low-dose dopamine replacement with carbidopa-levodopa may be considered with close monitoring for side effects [46]. Such cases require collaboration and regular communication between psychiatry and neurology services for optimal patient care.

Case 2 Analysis This case highlights the emergence of psychotic symptoms as one of the core features of major neurocognitive disorder with Lewy bodies, with well-formed visual hallucinations in the context of parkinsonism. Mr. E. also demonstrates supporting features of the illness, such as antipsychotic sensitivity, recurrent falls, and REM sleep behavior disorder. While it is often misdiagnosed, Lewy body neurocognitive disorder is the second most common form of major neurocognitive disorders after Alzheimer disease type [1]. Recognizing this as a distinct disease entity can be challenging due to the variable and fluctuating clinical presentation and common overlap with other clinical diagnoses that present with psychotic features. It is often not possible to make the diagnosis at a single consultation, and patients must be followed over time for the evolution of symptoms and diagnostic clarity.

Notably lacking from this case is the availability of collateral history, which can often be helpful in making the diagnosis. Mr. E. was initially given diagnoses of mild neurocognitive disorder, depressive disorder, and generalized anxiety disorder. Medical records from his previous consultations should be sought, to clarify the details surrounding his initial presentation and the natural history of his illness. As well, the case describes that Mr. E. is unmarried with no children. Efforts should be made to locate any knowledgeable informants, who may be able to provide information about the temporal sequence of his cognitive and motor symptoms and any known family history of neurocognitive disorders or movement disorders. Mr. E. was admitted from a long-term care facility. Staff members who know him well should be questioned regarding his response to his recent trial of risperidone, as to whether there was any improvement in his psychosis versus worsening with extreme antipsychotic sensitivity.

This case demonstrates the challenges in treating the psychotic symptoms in major neurocognitive disorder with Lewy bodies. The management requires cautious dosing of medication, close follow-up by the treating team, and vigilant monitoring for side effects. In Mr. E.'s case, the risperidone trialed by the primary care physician is not adequately treating his psychosis and, in fact, has worsened his symptoms. Initial steps in his management include stopping the risperidone and monitoring for clearing from potential delirium due to urinary tract infection. It would be reasonable to try a cholinesterase inhibitor as first-line treatment for Lewy body neurocognitive disorder. If the cholinesterase inhibitor is ineffective, or his psychosis continues to be distressing and/or a safety risk, he should be tried on a low dose of an atypical antipsychotic, such as quetiapine or clozapine.

15.3 Key Points: Late-Life Psychosis

- Psychosis can present in a variety of psychiatric and neurological conditions in late life. Symptoms may be part of a premorbid psychiatric illness in an aging individual or may reflect a new-onset disorder in late life, with or without an underlying medical etiology.

- Accurate diagnosis is essential as treatment depends on the context in which the psychosis presents.
- Delirium should always be ruled out first!
- Recall that new-onset psychosis in the geriatric patients is often a harbinger of major neurocognitive disorder, and patients should be followed over time for evolving neurocognitive disorders.
- Non-pharmacological treatment strategies should be tried before medications. If the psychosis is distressing and poses a safety risk, low-dose atypical antipsychotics may be used short term with close monitoring for side effects. Keep in mind the increased risks of morbidity and mortality associated with the use of antipsychotics in the geriatric patients with major neurocognitive disorders, and document informed consent prior to initiating pharmacotherapy.

15.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following statements is true about psychosis in Alzheimer disease?

A. The prevalence of psychosis in Alzheimer disease is about 10%.
B. Psychosis in Alzheimer disease is strongly associated with the patient's sex.
C. Bizarre or complex delusions are common.
D. Misidentification of caregivers is a common feature.

Answer: D

The prevalence of psychosis in Alzheimer disease is approximately 40% (12–75%). Psychosis in Alzheimer disease is associated with age, age at onset of Alzheimer disease, and illness duration, but not with sex, education, or family history of major neurocognitive disorder or other psychiatric illnesses [47]. Paranoid delusions or misidentifications are common in Alzheimer disease, but bizarre or complex delusions (common in late-onset schizophrenia) are uncommon [3]. Therefore, the correct statement is D.

MCQ 2. Which of the following features is *not* preserved in late-life delusional disorder?

A. Basic personality features
B. Intellectual performance
C. Social functioning
D. Occupational functioning

Answer: C

Late-life delusional disorder is associated with significant social functional impairment in which individuals become more reclusive and avoidant, but intellectual performance, occupational functioning, and basic underlying personality features remain relatively well preserved [3]. Thus, the correct answer is C.

MCQ 3. Which of the following medications has been found to be superior in treating symptoms of psychosis in major neurocognitive disorder with Lewy bodies, without worsening motor symptoms, in a double-blind, placebo-controlled trial?

A. Galantamine
B. Rivastigmine
C. Donepezil
D. Memantine

Answer: B

The study by McKeith et al. demonstrated that rivastigmine is twice as likely to show at least 30% improvement in delusions and hallucinations in major neurocognitive disorder with Lewy bodies compared to placebo [48], and the correct answer is B.

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Substance Use Disorders in Late Life

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16.1 Background

16.1.1 Definition

The diagnostic criteria for substance-related and addictive disorders changed significantly from the fourth to fifth editions of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM) (see Table 16.1) [1, 2]. In the fourth edition, disorders of substance use fell into three general categories: substance-induced, substance abuse, and substance dependence disorders [1]. Substance-induced disorders encompassed those (usually) transient disordered states that resulted from the use of a substance, e.g., acute alcohol intoxication, or brief psychotic disorder secondary to hallucinogen ingestion. Substance abuse and dependence disorders, however, identified those disorders related to sustained and continued use of substances over time, characterized by behavioral features (loss of control over one's use, social and functional impairments on account of use, use despite risk of negative consequences) as well as physiological features (tolerance, withdrawal). In practice, substance *abuse* was considered a less severe form of substance *dependence*, given that the presence of tolerance and withdrawal were hallmarks of a diagnosis of substance dependence. However, these diagnostic classifications proved to be ineffective in characterizing and conveying important information about substance-related and addictive disorders. The reliance on the presence of significant physiological features to warrant a dependence diagnosis, in particular, underplayed the importance of the behavioral features in these illnesses.

The DSM-5 maintained the substance-induced disorders as a diagnostic classification but removed the substance abuse and dependence distinction [2]. In their place, a single category was established—substance use disorders (used synonymously with the term addiction)—in which 11 distinct criteria were enumerated (see Table 16.1). The presence of 2–3 criteria marked a "mild" substance use disorder, 4–5 indicated a "moderate" disorder, and 6 or more reflected a "severe" substance use disorder. No longer were tolerance and/or withdrawal necessary or sufficient for one to have a significant disorder relating to substance use. This diagnostic reconfiguration allowed for greater focus on the behavioral features of addiction which form the core of the illness and the significant target of treatment. Other significant changes from DSM-IV to DSM-5 include the removal of legal repercussions as a diagnostic criterion, as well as the addition of craving as a new criterion. From a clinician's perspective, in total, these diagnostic alterations fit better with the illness phenomenology seen in practice and therefore represent helpful steps forward in the diagnostic conceptualization of these illnesses.

Understanding this backdrop is important for several reasons. First, the terms substance abuse and dependence still circulate widely even among medical professionals, and many of the studies on addictive disorders were conducted using these diagnostic constructs. It is therefore important to be familiar with what these older terms referred to and that the newer diagnostic construct emphasizes the importance

Table 16.1 Diagnostic highlights comparing the DSM-IV-TR versus DSM-5 criteria for substance-related and addictive disorders [1, 2]

DSM-IV-TR criteria		DSM-5 criteria
Substance dependence (3 or more in a 12-month period)	*Substance abuse* (1 or more in a 12-month period, without ever having met criteria for dependence for that substance)	*Substance use disorder* Mild: 2–3 criteria Moderate: 4–5 criteria Severe: 6 or more criteria (within a 12-month period)
Tolerance Withdrawal Substance taken in larger amounts and for longer periods than intended Persistent desire or repeated unsuccessful attempts to quit Significant time spent in obtaining, using, or recovering from substance Continued use despite knowledge of adverse consequences	Recurrent use resulting in failure to fulfill major role obligations at work, home, or school Recurrent use in physically hazardous situations Recurrent substance-related legal problems Use continues despite persistent or recurrent social or interpersonal problems caused by substance use	Using the substance in larger amounts or over a longer period than was originally intended Persistent desire to cut down or regulate substance use and reports of multiple unsuccessful attempts to decrease or discontinue use Great deal of time obtaining, using, or recovering from the substance or its effects Craving for substance or behavior (e.g., gambling) Recurrent use of substance resulting in failure to fulfill major role obligations at work, school, or home Continued use despite social or interpersonal problems caused or exacerbated by the effects of the substance or behavior Important social, occupational, or recreational activities may be given up or reduced because of use Recurrent use in situations in which it is physically hazardous Continued use despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused by or exacerbated by the substance Tolerance Withdrawal

of behavioral features of the disorders over and against the previous emphasis on physiological parameters. Secondly, the persistence of these older terms in the common lexicon can erroneously perpetuate the notion that, in the absence of tolerance and/or withdrawal, an addictive disorder is somehow less "severe." In this chapter, we will use the terms substance use disorder and addiction interchangeably.

16.1.2 Epidemiology

According to the 2014 annual National Survey of Drug Use and Health (NSDUH), about 1 in 10 (10.2%) persons in the USA 12 years old and older reported use of an illicit drug in the last 30 days prior to the survey; this represented an increasing trend beginning in 2002 [3]. These results were driven primarily by the use of marijuana (22.2 million) and those using prescription pain relievers for nonmedical reasons (4.3 million). Alcohol use trends, however, have remained relatively stable since 2009 with 52.7% of the US population 12 or older reporting last month use of alcohol and 6.2% reporting heavy alcohol use within the last month (defined in the general population as five or more standard drinks on the same occasion on 5 or more days in the past 30 days) [3].

Survey data paint a mixed picture on the prevalence of substance use disorders in older adults, with illicit substance use appearing lower than in younger cohorts, but with comparable alcohol use patterns. When the NSDUH survey data from 2013 (2014 data breakdowns are not yet available as of 2017) are broken down by age, 6% of respondents aged 50–64 years reported last month use of illicit substances with nonmedical use of prescription medications, with marijuana making up the bulk of the used substances. Of note, though, this represents an increase from rates reported relative to 2002 (2.7%) [4]. This same survey highlighted that 53.6% of those aged 60–64 years reported last month use of alcohol and 4.7% reported heavy alcohol use. In those over 65 years old, 41.7% reported past month use and 2.1% endorsed heavy alcohol use. These data are similar to those obtained in the 2012 NSDUH (41.2% and 2%, respectively). A 2008 Substance Abuse and Mental Health Services Administration (SAMHSA) study revealed that of nearly one million emergency department visits for illicit drug use, less than 1% involved adults over the age of 65 [5].

Data from other studies have demonstrated that illicit substance use is more common in cohorts of older adults born after World War II, relative to those born before, indicating that the "baby boomers" may require more clinical attention and treatment access than previous generations of older adults [6, 7]. Patterns of illicit drug use in older adults have been described to fall into two categories: early onset, where the use of illicit drugs begins earlier in life and persists into later life, and late onset, in which the use of illicit substances begins later in life. Late-onset patterns of illicit drug use in older adults are relatively uncommon, with estimates at less than 10% of the total late-life illicit substance users following this pattern [8].

While the rates of illicit substance and alcohol use in older adults are lower than in younger populations, this should not be a comfort to healthcare providers. Older adults are more vulnerable to serious complications related to substance use, on account of higher co-occurrence of serious systemic medical conditions and consequent increased likelihood of polypharmacy [9, 10], increased risk of suicide (especially among men) [11, 12], decreased cognitive function, increased physical frailty with risk for injury, and decreased psychosocial structure and support (e.g., retirement, loss of spouse, isolation) [10].

Furthermore, studies have demonstrated that substance use disorders in older adults are harder to detect and are associated with worse outcomes than in younger populations [8, 13, 14]. Studies tracking utilization of substance use services have estimated that between 22.5% and 29% of entrants into substance use programs were aged 45 or older, indicating that a relatively low number of those seeking formal treatment are older adults [15]. Together, these data indicate that older adult patients suffer from alcohol and other substance use disorders, enter treatment at a frequency less than their younger counterparts, and are uniquely vulnerable to medical and social consequences of substance use.

Teaching Point

Older adults require routine evaluation for alcohol and other substance use disorders and careful, intense management, including consistent referral to treatment services.

Globally, there has been growing interest in prescription drug misuse (especially opioid analgesics) as a legitimate threat to public health. It is estimated that in the USA, there are over 2.2 million people that have abused opioids [16] with the prevalence of opioid use disorder in individuals 29 years of age or younger estimated at 0.82% and in individuals 65 years of age or older approximately 0.09% [17]. Other studies report that nearly 2% of North American adults aged 50 and older at the turn of the twenty-first century used illicit drugs [18], including opioids like heroin, fentanyl, and contraband hydrocodone and oxycodone. Globally, opioids have become the number one cause for drug-related deaths, and according to the Centers for Disease Control and Prevention, there has been a 200% increase in the number of opioid-related deaths since 2000 [19]. While much of the news media and political attention deservedly has focused on the trends in adolescents and young adults, data highlight that older populations also show concerning trends in use of and consequences from misuse of prescription opioids; studies estimate that prescription drug misuse may affect between 18% and 41% of older adults [20].

Several concerning trends emerge when examining the relationship between older adults and opioid medications, specifically. A first concern is that older adults have been increasingly exposed to opioid medications—a nearly

ninefold increase in opioid prescriptions in older adults between 1995 and 2010 has been documented [21]. Older individuals are more likely to suffer from and be diagnosed with various systemic medical conditions (many of which are associated with chronic pain), and prescription opioids are often prescribed to treat these conditions, which may account for a large part of the increase in opioid prescriptions to older adults.

Teaching Point
Studies found that older adults, when queried, tend to misuse prescription medications to manage pain, anxiety, and insomnia rather than to get "high," unlike their younger counterparts [10].

Secondly, relative to younger cohorts, in adults over 60 years old who misuse prescription opioids, the rate of serious systemic medical outcomes has been documented to be more than double the rate in younger adults [22]. Furthermore, data highlight an increase in the rate of hospital admissions for adults over the age of 55 for prescription opioid-related morbidity from 0.7% in 1992 to 2.8% in 2005 [23].

A third concerning trend is the expectation of increasing strain on the healthcare system due to the growing numbers of geriatric patients with opioid use disorders in conjunction with the overall increase in geriatric population, on account of the estimated 70–80 million aging "baby boomers" in the USA [23]. One study suggests that there will be a 250% increase in the number of older adults in the USA (4.4 million) who will need treatment for substance use disorders in the near future [24].

Fourthly, perhaps on account of many older individuals being exposed to opioids via prescription as opposed to illicit "street" sources, opioid use disorders in older adults often may go relatively undiagnosed or underreported [25], and older adults are more likely to deny the possibility of problems with opioids and are less likely to seek help for opioid use disorder [25, 26].

Finally, evidence suggests that opioid medication-associated mortality in older adults has been increasing. For example, local mortality data from New York/New Jersey/Pennsylvania describe an increase in drug-related deaths in those over 55 years old from 49.5/1,000,000 in 2003 to 66/1,000,000 in 2007 [27–29]. It is often older patients' physicians who introduce them to opioid medications, underscoring that physicians are a key mediator in this illness process, which is a topic we will further explore in this chapter.

Teaching Point
Being aware of the risk for misuse and the unique vulnerabilities in the older population, as well as being mindful of the myriad reasons why opioid medications may become attractive to the geriatric patients (e.g., insomnia, anxiety, pain), can create opportunities for physicians to think judiciously about the use of opioids and to explore alternatives to opioids whenever possible.

The Complex Interaction of Chronic Pain and Potential for Opioid Misuse

Common conditions in old age, such as osteoarthritis, other musculoskeletal conditions, and peripheral neuropathy, contribute to a high burden of chronic pain in older adults. The prevalence varies widely in the literature, from 25% to 76% for community-dwelling older adults, up to 83% to 93% for institutionalized older adults [26], in part due to methodological issues involving the definition of chronic pain, the population studied, and the survey instrument used. Women consistently report chronic pain more frequently than men. In the Canadian National Population Health Survey, the prevalence of chronic pain increased with age in women, but not in men. Compared to women aged 25–29, women aged 70 and older were twice as likely to report chronic pain, with a point prevalence of 28.4%. In men, the prevalence of chronic pain remained relatively stable across the age spectrum, fluctuating between 10.5% and 12.3%, depending on the age stratum [30]. In an age-stratified Swedish sample of 826 adults, the prevalence of chronic pain peaked at 55% in adults in the 60–74 age group, dropping to approximately 50% after age 74 [31]. In the European Multi-Care Cohort Study of primary care patients (mean age, 74 years), intense pain or pain that moderately or severely limited function affected nearly 50% of women and 30% of men who reported chronic pain and was associated with a high burden of comorbidity, averaging 7 chronic conditions [32]. Notably, the study found depressive disorders in 23% of the female participants, versus 11% of the men. Fatigue, higher body mass index, and mobility problems also have been independently associated with chronic pain in older adults [31].

Teaching Point
Misuse of prescription medications, especially opioids, is prevalent in older adult populations. The prevalence of chronic and disabling pain among older adults provides the context in which the prescription and potential misuse of opioids must be understood.

Age-related changes in pharmacodynamics and pharmacokinetics, the risk of adverse drug interactions arising from polypharmacy, and age-associated increases in susceptibility to adverse effects of opioids create an enormous challenge for clinicians, who must decide whether to select and how to dose opioids for pain control in their older patients. This selection represents a delicate balance among tolerable side

effects, optimizing physical function, and quality of life. Concern about side effects, including falls, cognitive impairment, constipation, and iatrogenic opioid dependence, commonly leads to underprescribing of opioid analgesics, which ironically stands in opposition to the epidemiological data presented previously. In a cross-sectional survey of older patients in 8 Italian hospitals, approximately half reported no or inadequate pain relief, and up to 36% reported having had moderate to severe pain lasting 3 months to over a year [33]. Communication barriers between physician and patient may further impede adequate analgesic prescribing, especially if the patient has cognitive impairment or a language barrier, and (as also mentioned previously) many older persons underreport their pain as a result of fear of opioid addiction or culturally influenced beliefs and stoicism [26].

"Pseudoaddiction"

As described previously, use of illicit drugs and misuse of prescription medications, especially opioids, are prevalent in older adult populations. For prescription medications in particular, most misuse derives from opioids legitimately prescribed (and which are commonly renewed) by physicians for acute or chronic pain. In some cases, physicians are responsible for increasing the potential for misuse or diversion of opioids by prescribing more than is needed for acute pain management. In a university urological practice, 67% of patients who received oral opioids following surgery had surplus medication from the initial prescription [34]. Among all age groups, any misuse of opioids has been associated with underlying comorbid psychiatric disorders, principally depressive disorders [35]. In a small case series of older adults (mean age, 63 years) with acknowledged opioid abuse (addiction, seeking illicit opioids and other street drugs from dealers), over half had a regular physician (or other clinician) who prescribed the medication, 86% reported severe physical pain over the past year, and 81% used their opioids, both illicit and prescribed, to treat the pain. The study also identified a high prevalence of comorbid psychiatric symptoms, with 44% of the participants reporting recent severe depression and 28% endorsing severe anxiety [36].

In many patients with pain syndromes[1] who exhibit addictive behaviors toward opioids, the misuse resolves when the pain is adequately treated by the physician. For instance, a person without any history of addiction who suffers from bone cancer is treated by a physician who prescribes opioid analgesics for pain. The physician prescribes the lowest amount of opioid pain medications that he or she feels comfortable prescribing, but the patient continues to report ongoing pain. The patient eventually resorts to taking additional supplementary opioid medications from her husband and tells this to her physician. The provider then increases the opioid prescription dose and/or frequency slightly, and all opioid-seeking behaviors cease. This phenomenon was previously referred to as *pseudoaddiction*, and, as one can see from this example, it can be exceedingly difficult to parse out this kind of addiction-appearing behavior from a true DSM-5 substance use disorder. This is particularly relevant and important as additional restrictions on opioid prescribing are implemented throughout the USA in response to the opioid use epidemic, such as the Centers for Disease Control and Prevention's 2016 guidelines for prescribing opioids for chronic pain [37].

The Psychiatrist's Role in Pain Assessment and Management

Many psychiatrists are reluctant to prescribe antidepressants and/or anxiolytics for patients with active substance abuse, on the grounds that recurrent intoxication can confound the diagnosis of an underlying psychiatric illness and/or compromise clinical response to psychotropic medications. Chronic intoxication with alcohol, itself a depressant, or withdrawal from opioids and/or psychostimulants can mimic syndromal depressive disorder. Moreover, psychotropic medication can adversely interact with drugs of abuse, and some psychopharmacologic treatments (e.g., benzodiazepines) have their own inherent abuse potential. This creates a "catch-22" that often leads to continued abuse of the drug(s) that the individual uses in part to treat their symptoms of depression, anxiety, and/or chronic pain, which are often interrelated.

Although antidepressants have long been used as adjunctive therapy for pain disorders to minimize opioid requirements, data are largely limited to their efficacy for neuropathic pain [26, 38]. As a rule, tricyclic antidepressants, though effective, should be avoided in older patients because of their anticholinergic properties that can predispose one to delirium and other disorders of cognitive impairment, as well as cardiotoxicity and urinary retention. The serotonin-norepinephrine reuptake inhibitors (SNRIs) duloxetine and venlafaxine have demonstrated efficacy in neuropathic pain [38], and duloxetine has been shown to reduce pain from osteoarthritis, chronic low back pain, and fibromyalgia, in addition to diabetic neuropathy [26, 39]. In these conditions, as few as 15 patients ("number needed to treat") are required for one patient to achieve a 50% reduction or more in pain after 4 weeks when duloxetine is used alone, but the effects tend to plateau by 10–12 weeks [39]. Evidence is emerging that plasma serotonin and 5-hydroxyindoleacetic acid levels are inversely correlated with depression and chronic pain, providing a physiological basis for the observed analgesic properties of SNRIs [40]. The proven efficacy of SNRIs for chronic pain as well as depressive and anxiety disorders, plus the strong epidemiologic association of depressive and anxiety disorders with chronic pain, together should lessen

1 The concept of a pain syndrome can be broadly defined and may encompass chronic pain (pain lasting over 6 months) whose genesis was rooted in an acute pain episode (e.g., hip fracture) to a somatic symptom disorder, with predominant pain. This latter diagnostic concept (previous to DSM-5 known as "pain disorder") is defined as a somatic symptom disorder (see DSM-5) whose somatic symptoms predominantly involve pain. Oftentimes, the boundaries between these entities can be blurry and may require significant attention and effort to parse out.

reluctance to recommend an SNRI in substance misusers reporting chronic pain, even when a diagnosis of depressive and/or anxiety disorder(s) is muddled by the ongoing substance misuse.

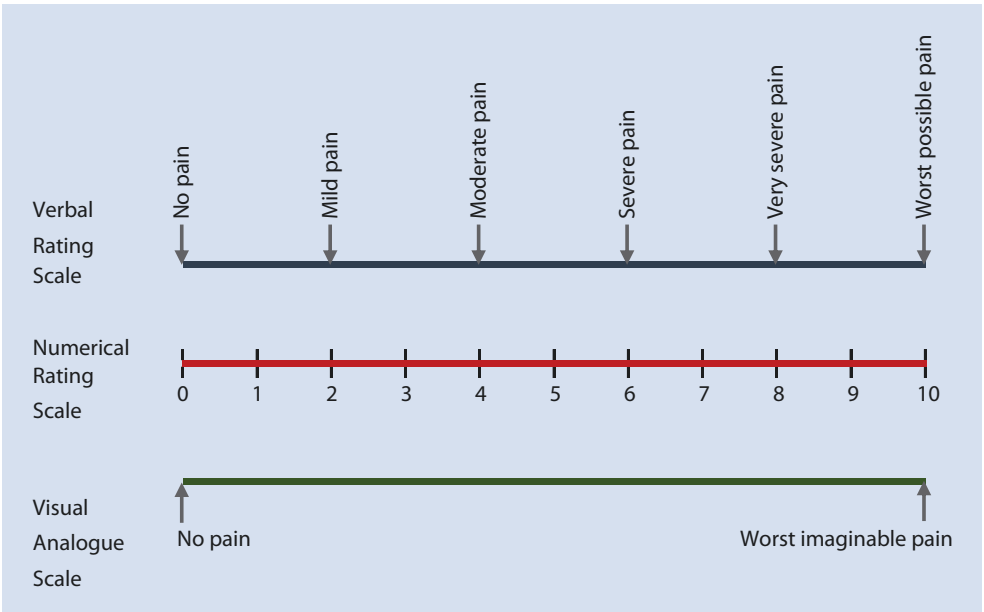
An important exception to a more liberal recommendation for an SNRI antidepressant for a patient with chronic pain and suspected depressive disorder is the additional suspicion of bipolar disorder, rather than depressive disorder being responsible for the depressive episode, leading to concern that the SNRI could precipitate a manic episode. If underlying bipolar disorder is suspected by history, the psychiatrist can recommend a gabapentinoid, such as gabapentin or pregabalin. Although often less favored for mood stabilization compared to lamotrigine because of the relatively greater risk of neurocognitive dysfunction [41], the gabapentinoids represent first-line treatment for neuropathic pain based on their ability to reduce the release of excitatory neurotransmitters like substance P and glutamate in the dorsal horn of the spinal cord and because of robust supportive clinical trial data. Lamotrigine, by contrast, is considered a fourth-line choice [42].

The gabapentinoids can play a role in types of pain other than neuropathy. Some patients with arthritis can experience moderate to severe pain that is disproportionate to radiologically observed structural changes. Similarly, chronic use of moderate to high doses of opioids can lead to apparent tolerance and opioid-seeking behavior ("pseudoaddiction"—as described previously). Both can be linked to central nociceptive sensitization (i.e., a lowering of the threshold for pain), and techniques such as quantitative sensory testing can help identify patients with this condition [43]. The heightened pain from nociceptive sensitization resembles neuropathic pain. The gabapentinoids appear useful in controlling nociceptive sensitization, while the opioid is decreased in an effort to reset this disturbance in central pain processing and restore its efficacy [44].

The Importance of Assessing Pain and the Principles of Management in Geriatric Psychiatry

Because pain's interference with daily functioning and pain severity impede recovery from depressive disorders in older patients [45], psychiatrists should include questions about pain, documenting its location, severity, aggravating factors, and chronicity in their routine evaluation of older patients. In geriatric patients, pain is commonly rated by the Visual Analogue Scale, Numerical Rating Scale, and the Verbal Rating Scale (see ◘ Fig. 16.1). To use the Visual Analogue Scale, patients are asked to mark their pain experience along the 10-cm line anchored by verbal descriptors describing pain intensity. With Numerical Rating Scale, patients are asked to rate their pain on a numeric scale (typically 11, 21, or 101 point spread) anchored by no pain at all at one end and worst pain imaginable at the other end. In Verbal Rating Scale, pain intensity is described by the patient by asking them to choose from a list of adjectives that describe pain intensity [46].

Given the potential adverse side effects of opioids and adjunctive drugs such as antidepressants and anticonvulsants, as well as their impact on the management of comorbid psychiatric disorders, psychiatrists should be familiar with the basic principles of stepped analgesic regimens for chronic pain based on consensus guidelines [26, 38]. In older adults, mild pain should be treated with a non-opioid medication like acetaminophen (also called paracetamol) or nonsteroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen or naproxen, but both classes of medications carry certain precautions worth considering. NSAIDs should be used cautiously, because of potential adverse effects on renal function, gastrointestinal bleeding, and sodium retention; due to the risk of hepatic damage, doses greater than 4 g of acetaminophen in a 24-hour period should be avoided (see ▶ Chap. 5). Even when pain requires the addition of opioids, acetaminophen should be continued whenever possible to



◘ **Fig. 16.1** Visual Analogue Scale versus Numerical Rating Scale versus Verbal Rating Scale for pain [96]

provide a synergistic effect, with the aim of reducing opioid requirements. When opioid use becomes chronic, consideration should be given to adding an adjuvant drug. Given the strong relationship between chronic pain, depression, and anxiety [47], it is appropriate for the psychiatrist to recommend an SSRI or another antidepressant when depressive or anxiety disorders are comorbid and there is no contraindication to their use. A variety of non-pharmacologic approaches may reduce pain and improve function, including mindfulness, meditation, cognitive behavioral therapy for pain, biofeedback, and exercise [26].

For patients with chronic severe pain that is refractory to non-opioid and adjuvant analgesic regimens, escalating doses of opioids may be required that lead to physiological dependence (i.e., with the potential for withdrawal if stopped and gradual development of tolerance). These individuals may benefit from referral to a pain specialist or clinic. Physiological dependence (i.e., emergence of tolerance and/or withdrawal) on a medication resulting from an appropriate, evidence-based analgesic regimen *does not*, in itself, constitute opioid misuse or addiction.

Teaching Point

Drug-seeking behavior to achieve pain control sometimes can be difficult to distinguish from drug seeking stemming from addiction. In the clinical setting, clues for addiction include evidence of doctor-shopping for additional opioids and reported pain severity disproportionate to the patient's appearance and behavior. An example is a patient who smiles and jokes with the physician and looks physically comfortable, but when asked about his or her pain states it is a "10 out of 10."

A prior history of substance misuse is, unsurprisingly, a risk factor for opioid misuse [48], although in one study, over 88% of primary care physicians were somewhat highly likely to prescribe opioid analgesics to patients with prior histories of substance use despite having low confidence and satisfaction levels in treating chronic pain [49]. Patients at risk of opioid misuse theoretically could benefit from pre-emptive counseling, but evidence of efficacy is lacking.

Efforts to Minimize Overprescribing

Acute and chronic pain management overlaps multiple medical specialties, and subspecialists often directly prescribe, rather than recommend, treatment to primary care physicians. Unless meticulous medication reconciliation is performed, multiple physicians can prescribe opioids and/or benzodiazepines, unaware that the patient may have received prescriptions from other sources, leading to overprescribing and enhanced potential for misuse. Accessible prescribing monitoring programs exist in many US states such as California [50] as well as in Canada [51], enabling clinicians to view the chronology of prescriptions for controlled substances and identify patients who "doctor-shop" for additional medication. Institutional requirements for pain contracts, usually with the primary care physician, can help control prescription drug-seeking behavior, especially when linked to an electronic medical record. One important exception to note here is that maintenance methadone for an opioid use disorder administered through a certified narcotic treatment program will not appear in prescription monitoring program databases, owing to privacy protections afforded these clinical services, courtesy of 42 Code of Federal Regulations (CFR), Part 2.

Myriad additional local and national efforts to reduce overprescribing are also underway. As mentioned previously, in 2016 the Centers for Disease Control and Prevention issued the first-ever guidelines for opioid prescribing in chronic pain, and the 21st Century Cures Act (passed in the waning days of 2016) allocated $500 million federal dollars to combat the national opioid epidemic, with significant focus on expanding access to treatment. Also, checking with your local department of Public Health or Health and Human Services will likely provide valuable information about local activities aimed at decreasing general availability of prescription medications, such as the US Drug Enforcement Administration (DEA) or local law enforcement-sponsored drug take-back events.

16.1.3 Etiology

Nora Volkow and George Koob have described addiction as "a complex disease of a complex brain" [52]. In this seemingly simplistic statement, what Volkow and Koob are highlighting is that addiction is fundamentally a disease of the brain with complex neurobiological underpinnings that manifest in the full array of human behavioral complexity. It bears remembering that during many of our readers' lifetimes (and certainly in many of our older patients' lifetimes), addiction has been viewed not as a medical illness, but rather as a moral or spiritual failing in which the sufferer was fundamentally flawed and in need of correction. With this conception, not surprisingly, addiction came to be associated with significant negative stigma, and its treatment was relegated to well outside the medical mainstream. Over the last several decades, however, research has highlighted how addiction represents a well-defined disorder of brain reward circuitry with genetic susceptibilities that resemble many other "medical" chronic relapsing illnesses. This research-driven reconceptualization of addiction has served to spearhead a renewed interest in incorporating addiction evaluation and treatment into the medical establishment.

In a landmark article published in 2000, A. Thomas McLellan and his colleagues made the case for conceptualizing addiction as a chronic relapsing illness by comparing addiction to hypertension, asthma, and diabetes mellitus [53]. This paper highlighted how addiction and these other medical illnesses shared similar patterns of inheritability, responses to treatment, patterns of approach to treatment (i.e., maintaining physician appointments/monitoring, no

permanent cure, medication management with behavioral life changes), and patterns of adherence to recommended treatment. Despite these similarities, addiction has been handled differently than hypertension, diabetes mellitus, and asthma. Significantly, addiction treatment has been relegated outside of the medical establishment, and remaining symptomatic with addiction, it has been seen as patient failure rather than treatment failure. By comparison, if one remains hypertensive despite treatment, we would likely escalate treatment, not attribute their ongoing high blood pressure as a failure of the patient.

Over the past several decades, the neurobiological etiology of addiction has become increasingly clear. Ultimately, brain reward systems (and both acute and chronic alterations stemming from substances' effects on these systems) are heavily implicated in the genesis of addiction pathology. Brain reward systems exist for good reason—through this an organism learns which behaviors are to be repeated, be it eating, sex, or some other pro-existence behaviors. Fundamentally, dopaminergic neurons located in the ventral tegmental area feed into the nucleus accumbens (the so-called reward center of the brain), which then projects out to both subcortical and cortical areas of the brain to help regulate experience and behavior [54]. Crucially, the prefrontal cortex provides "top-down" regulation on the nucleus accumbens, serving to modulate the nucleus accumbens' activity based on higher-order calculations, such as risk/benefit.

Substances of abuse co-opt this reward system and alter not only the system itself but the neural networks that are associated with it. Either directly or indirectly, substances of abuse increase dopamine release in the nucleus accumbens or enhance the effect of dopamine that is endogenously released in the nucleus accumbens. With this in mind, Volkow and Koob have elegantly described the development of addiction through a three-stage model [55]. During the initial binge-intoxication stage, the pleasurable experience of the substance serves to increase the chances of its repetition. Contemporaneous with this, however, endocrinologic stress pathways are activated and the brain's own endogenous ability to mount a reward response (i.e., release dopamine into the nucleus accumbens) begins to diminish.

The second stage of addiction—withdrawal and negative affect—develops out of the neurobiological changes that happen progressively through the binge-intoxication stage. Specifically, as a result of the decreased activity of endogenous dopaminergic systems and increased activity of endocrinologic stress systems, the motivational landscape is modified in favor of continued use. Environmental cues favoring use of substances gain in salience, and the emergence of strongly negative affect and increased stress results in significant dysphoria.

Finally, the preoccupation and anticipation stage represents the further cortical encoding of the neurobiological modifications in limbic and reward circuits occurring throughout the initial two stages. Specifically, impairments in self-regulation, decision making, flexibility, and assignment of salience documented in persons with addictive disorders can be traced back to prefrontal cortical deficits resulting from the evolution of the addiction process.

The underlying neurobiological mechanism for addiction applies to all populations, regardless of age. However, certain aspects of the aging brain and physiology raise unique concerns for older adults. For example, several neurobiological systems involved in the reward circuit change during aging (including decreased dopamine transporter binding and dopaminergic and serotonergic receptor loss), but the clinical significance of these changes has yet to be determined [29]. Polypharmacy and metabolic changes may also alter an older person's relative exposure to a substance [56]. The efficiency of metabolism of alcohol decreases with age, meaning that consumption of the same volume of alcohol may led to greater intoxication when the patient ages [57]. Certain medications may likewise decrease the metabolism of substances producing a similar pattern of greater than expected intoxication. For example, as mentioned above, older adults frequently report to medical care seeking help with issues such as insomnia, anxiety, and pain. Not surprisingly, many of these older adults are prescribed a combination of opioids and sedative-hypnotic medications, such as benzodiazepines. This co-prescription of benzodiazepines and opioids can be problematic, as both classes of medications can directly suppress central respiratory drive as mediated through the medulla oblongata in a dose-dependent fashion [58]. Certain benzodiazepines such as clonazepam and diazepam may not be as efficiently cleared by the liver in later life, adding to the risk of co-use of these medications with opioids. Furthermore, benzodiazepines are known to negatively impact memory, visuospatial learning, and cognitive processing speed [29]. Benzodiazepine dependence in geriatric populations is likely underrecognized, with one study showing an 11.4% prevalence of benzodiazepine misuse in older adults presenting to a geriatric psychiatry clinic [59].

16.1.4 Clinical Description

Substance-Induced Disorder

The presentation of a patient with a substance-induced disorder can vary based on the substance used. Generally speaking, a patient presenting with psychostimulant (e.g., methamphetamine, cocaine) intoxication may demonstrate psychomotor agitation, bruxism, choreoathetoid movements, psychosis (paranoia and auditory hallucinations being prominent), diaphoresis, disorganized thinking, and vital sign elevations. Typically, these symptoms are transient and last only as long as the intoxication from the substance. For example, a patient could be said to have stimulant-induced psychotic disorder because during the 48 hours of intoxication on methamphetamine, they are acutely paranoid and experiencing auditory hallucinations. However, after discontinuation of the stimulant, the patient may undergo withdrawal, during which their mood may be depressed. (See second stage of addiction described previously.)

Conversely, patients presenting with sedative-hypnotic, alcohol, or opioid intoxication may appear psychomotorically depressed, uncoordinated in their movements, and may report suicidal ideation or depressed mood that occurs only in the context of acute intoxication. In these instances, a diagnosis of a substance-induced depressive disorder could be considered.

Substance Use Disorder

Substance use disorders can be difficult to spot, as many patients will go to great lengths to conceal their maladaptive use on account of shame, guilt, or denial. However, certain signs can indicate the presence of a substance use disorder, such as driving under the influence (DUI) charges or other psychosocial declines (e.g., loss of employment, disrupted relationships), weight loss or gain, characteristic laboratory value changes (as described later in the chapter), mood fluctuations, or reports from family and friends. Ultimately, the diagnosis is made by application of the DSM-5 criteria (see ◘ Table 16.1), but sensitivity to the reality that many patients may conceal their use and being attentive to the sometimes subtle changes and warning signs suggestive of a substance use disorder's presence can help propel further exploration.

16.1.5 Diagnostic Evaluation

A comprehensive analysis of patient's clinical history, cognition and function, physical examination including neurological examination, mental status examination, and laboratory evaluation are all essential and can lead to a high degree of confidence in clinical diagnosis.

Application of the DSM-5 diagnostic criteria for substance use disorders may be challenging in the geriatric population. For example, an older person's cognitive decline may impair their ability to accurately recount their recent usage and to discern and fully understand the physical and psychological problems their substance use is creating or exacerbating. Additionally, an older adult may give up certain enjoyable activities for a myriad of medical and functional reasons, making it difficult to discern whether this decreased activity may be related to a substance use disorder or other medical or functional decline reasons.

As mentioned before, comorbid psychiatric illness, especially anxiety and depressive disorders, are particularly common in older adults with substance use disorders. The co-occurrence of alcohol use and depressive disorders is especially common, with estimates as high as 50% of those with alcohol use disorder being also diagnosed with depressive disorders [60]. At-risk and problematic alcohol use (defined as drinking that has a high likelihood of causing some degree of negative physical, emotional, or social consequence, or already has) has been shown to exacerbate depressive and anxiety disorders in older adults, in some cases leading to conversion of subsyndromal depressive disorder into a major depressive disorder [61] and in other cases leading to worse overall prognosis when co-occurring (e.g., increased suicide rates, more social impairment) [62, 63]. Additionally complicating the clinical picture, major neurocognitive disorder has been described in over 20% of older adults in residential substance use treatment [64]. Therefore, screening for alcohol and drug use among older adults, in conjunction with comprehensive systemic medical and psychiatric (including cognitive) evaluations, is critical.

Clinical History

Obtaining a thorough personal and family history is necessary, as is screening specifically for alcohol and other drug use in every older adult patient. SAMHSA Center for Substance Abuse Treatment recommends yearly screening of all patients over the age of 60 and as needed in the event of major life events (e.g., deaths of significant figures, retirement) [65]. For alcohol use disorders, several standardized screening tools are available that have been validated for use in older adults, such as the Alcohol Use Disorders Identification Test (AUDIT) [66] and the Michigan Alcoholism Screening Test-Geriatric Version (MAST-G) [67], both of which are also available in shortened version for easier administration (the 3-item AUDIT-C (68) and SMAST-G [69], respectively) (see ◘ Table 16.2).

Teaching Point

The physiological changes affecting the way the aging body handles alcohol include a decrease in lean body mass and total body water volume content in relation to fat volume, with the resultant decrease in total body volume which increases the serum concentration of alcohol, along with an increase in central nervous system sensitivity to alcohol, and age-associated morbidity, polypharmacy, and alcohol interactions with medications (e.g., alcohol can exacerbate or reduce the therapeutic effect of warfarin and can interfere with the effectiveness of some medications to treat hypertension, gastroesophageal reflux, insomnia, and major depression).

Any use of illicit substances and nicotine has greater risk than benefit. However, alcohol can lead to health benefits at low to moderate consumption as well as increased morbidity when at risk and heavy consumption. Therefore, clinicians should be aware of the drinking limits. The limits are lower for older adults compared with younger adults because of age-related physiological changes, increased morbidity, polypharmacy, and medication interactions with alcohol. It is important to define recommended low drinking limits, at-risk drinking, and heavy drinking. At-risk drinking is defined as alcohol use that is excessive or potentially harmful in combination with select comorbidities or medications. The National Institute on Alcohol Abuse and Alcoholism and the Center for Substance Abuse Treatment, Treatment Improvement Protocol on older adults recommend for low drinking limits that older men (65 years and older) consume no more than one standard drink per day, or seven drinks on

Table 16.2 Comparison of AUDIT-C and SMAST-G hazardous alcohol use screening tools [68, 69]

AUDIT-C	SMAST-G
a = 0 points, b = 1 point, c = 2 points, d = 3 points, e = 4 points In men, a score of 4 or more is positive In women, a score of 3 or more is positive 1. How often do you have a drink containing alcohol? (a) Never (b) Monthly or less (c) 2–4 times a month (d) 2–3 times a week (e) 4 or more times a week 2. How many standard drinks containing alcohol do you have on a typical day? (a) 1 or 2 (b) 3 or 4 (c) 5 or 6 (d) 7–9 (e) 10 or more 3. How often do you have 6 or more drinks on one occasion? (a) Never (b) Less than monthly (c) Monthly (d) Weekly (e) Daily or almost daily	10 Yes/no questions Score 1 point for each yes answer A score of 2 or more is positive 1. When talking with others, do you ever underestimate how much you drink? 2. After a few drinks, have you sometimes not eaten or been able to skip a meal because you didn't feel hungry? 3. Does having a few drinks help decrease your shakiness or tremors? 4. Does alcohol sometimes make it hard for you to remember parts of the day or night? 5. Do you usually take a drink to calm your nerves? 6. Do you drink to take your mind off your problems? 7. Have you ever increased your drinking after experiencing a loss in your life? 8. Has a doctor or nurse ever said they were worried or concerned about your drinking? 9. Have you ever made rules to manage your drinking? 10. When you feel lonely, does having a drink help?

average per week, and no more than four standard drinks on any drinking day. The standards for older women are stricter: no more than one drink per day or four drinks per week. Another consideration is the number of drinks consumed in a single session, with five or more drinks for men and four or more for women constituting risky drinking.

Teaching Point

It is important to note that, while low to moderate alcohol consumption (e.g., 1–2 standard drinks on most days) generally confers health benefits, older adults may experience negative health consequences from even moderate amounts of consumption. One standard drink is usually about 5 ounces of wine (12% alcohol), 12 ounces of regular beer (5% alcohol), and 1.5 ounces of distilled spirits (40% alcohol).

Comparably less research has been done on validating illicit drug or prescription medication misuse screening tools specifically in geriatric populations. However, the Alcohol, Smoking and Substance Involvement Screening Test (ASSIST) has nonetheless been employed in geriatric population studies to assess for substance use in addition to alcohol [70]. The ASSIST is somewhat more involved to employ than the AUDIT-C or SMAST-G but is nonetheless nonproprietary and widely available online. (See ► https://www.drugabuse.gov/sites/default/files/pdf/nmassist.pdf.)

As with all patients, ensuring that the patient interview is conducted in a suitably private and secure location is essential for establishing rapport and maintaining appropriate confidentiality. Patients with substance use disorders may be defensive about their use and/or may feel a tremendous amount of shame and guilt related to their use and its effects on their lives. Geriatric patients, in particular, may present with certain preconceived negative impressions of what addiction is, tempered by previous societal conceptions of addiction as a primarily moral or spiritual failing (see described previously). Asking questions during the interview in a manner that is honest, open, curious, and nonjudgmental from an empathic interpersonal stance can lead to more effective interactions.

In addition to taking comprehensive psychiatric, systemic medical, social, developmental, and family histories, a systematic approach for collecting information on the various substances used currently and in the past can ensure that important data is not missed. For more details, please refer to ► Chap. 6, "The Assessment of the Patient," by Greenfield SF and Hennessy G, in *The American Psychiatric Publishing Textbook of Substance Abuse Treatment*, fifth edition, which is further summarized [71]. To start, organizing the interview around the various classes of substance of abuse can be helpful:

- Central nervous system depressants, such as alcohol, benzodiazepines, and barbiturates
- Psychostimulants such as methylphenidate, caffeine, cocaine, methamphetamine, and phencyclidine (PCP)
- Cannabis (including edibles, hashish, hash oil)
- Opioids (prescription and nonprescription)
- Hallucinogens
- Nicotine
- Inhalants
- Designer drugs like ketamine, 3,4-methylenedioxymethamphetamine (MDMA)

For each substance of abuse, it is important to systematically examine the following:

- Age at first use.
- Frequency of use.
- Amount of substance taken during an episode of use.
- Route of administration (e.g., intravenous, oral, inhaled, smoked, transdermal).
- Consequences of use.
- Treatment history (including formal addiction treatment through the various levels of care from outpatient, psychopharmacological, intensive outpatient, partial hospital, inpatient psychiatric, 12-step program engagement, residential).
- Inquiring about medical admissions related or unrelated to addiction may provide further insight into the severity of previous treatment episodes that could shape present management.
- Patients with prior alcohol withdrawal seizures or delirium tremens, for example, may be uniquely vulnerable to recurrence of these sequelae of substance discontinuation owing to the so-called "kindling" effect, wherein seizures or delirium tremens may occur after shorter relapse periods, with relapse involving relatively lower amounts of alcohol [72].
- Periods of abstinence.
- Relapse history.

Habitually asking this series of questions, per substance used, helps the clinician formulate a more consistent approach to assessing severity of illness and triage risk. For example, a 65-year-old alcohol-using patient with myriad relapses, few significant periods of abstinence, and multiple withdrawal seizures from alcohol and who drinks 2 standard drinks daily after starting drinking when he was 12 years old may require a more intensive approach to intervention than a similarly aged and matched man with no withdrawal seizure history.

Psychiatric, Cognitive, and Functional Assessment

Historically, the psychiatric assessment of patients with active substance use has unfortunately favored the adage: "Don't diagnose or treat until sober." Growing consensus among addiction specialists, however, reflects a new approach that favors the integration of evaluation and treatment of co-occurring psychiatric and substance use disorders, even if substance use is active [73, 74]. This may require adjustment in diagnosis or treatment approach as the clinical landscape shifts during treatment, but it also acknowledges and begins to address the complex relationship between comorbid psychiatric disorders and substance use. To that end, a comprehensive psychiatric evaluation that encompasses all major domains of psychiatric illness (neurodevelopmental, anxiety, psychotic, depressive, bipolar, neurocognitive, personality, trauma-related, eating, sleep, and somatic symptom disorders), in addition to substance use, is critical.

Of particular relevance to the older adult population is evaluation of neurocognitive disorders, since the prevalence of neurocognitive disorders increases with age and the use of certain substances (i.e., alcohol, cannabis, sedative-hypnotics, opioids) can negatively impact cognitive function. While they are covered in more detail elsewhere in this book, it is nonetheless worth noting that several easy-to-administer bedside neurocognitive assessment tools are available, including the Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE). Using these tools as an initial screen for cognitive impairment can be highly informative, but bear in mind that deficits noted in these initial screens may warrant further specific formal neuropsychiatric testing. Cognitive testing alone may not provide a full picture of functional impairment, however, since different domains of functionality may be affected disproportionally. Therefore, asking specific questions about certain critical functions (e.g., bill-paying strategies, food obtainment, and preparation approaches) may provide useful information about a patient's actual functional status over and against what the MoCA or MMSE alone may provide. When available and appropriate, questioning family, friends, and other providers about functional capacity can also provide valuable assessment data.

Physical Examination

Along with a thorough history, a comprehensive physical examination with neurological examination is essential for clinical diagnosis. Initial observations about appearance, general hygiene, and even odor can be in some cases diagnostic. For example, a disheveled person smelling strongly of alcohol and tobacco cigarettes would certainly raise suspicions of alcohol and tobacco use disorders. Cachexia and pallor could suggest significant medical illness such as cancer but also could be reflective of failing self-care in the setting of depressive, neurocognitive, and/or substance use disorder(s). Track marks and skin breakdown in patterns consistent with injection drug use would also raise concerns of an active intravenous substance use disorder. Psychomotor retardation and depressed level of consciousness can be associated with sedative-hypnotic, alcohol, and/or opioid use, or even psychostimulant withdrawal, while psychomotor agitation may be associated with psychostimulant intoxication. Cannabis intoxication can be associated with conjunctival injection, while stimulant or cannabis intoxication (as well as severe withdrawal from alcohol and sedative-hypnotics) can be associated with hallucinations. Slurred speech and thought disorganization can be likewise associated with sedative-hypnotic, alcohol, opioid, and even sometimes psychostimulant use. Bruxism and choreoathetoid movements can also be consistent with psychostimulant intoxication. Vital sign changes can be particularly important. Depressed respiratory rate, for example, can herald overdose on sedative-hypnotic medications, alcohol, and/or opioids. Tachycardia and hypertension, conversely, can be associated with withdrawal from sedative-hypnotics and/or alcohol or intoxication on psychostimulants. Geriatric patients may be particularly vulnerable to negative consequences (e.g., cerebrovascular accident, myocardial infarction) from these vital sign changes due to decreased physiological reserves.

Laboratory Investigations

Laboratory investigations are exceedingly important when evaluating older adults with substance use disorders. It is critically important to determine whether changes in mental status, hygiene, cognition, or appearance are the result of correctable metabolic abnormalities (e.g., hypo- or hypernatremia) or substance use. Therefore, first-line laboratory studies should include baseline complete blood cell count with differential, comprehensive metabolic panel including liver-associated enzymes, thyroid-stimulating hormone, and urinalysis. Urine, blood, saliva, and hair testing directly for substances of abuse are widely available, with urine toxicology screens perhaps the most common. These screens are typically immunoassays, with highly specific confirmatory testing typically undertaken through gas chromatography when definitive confirmation is necessary. While toxicology screens can assess for substances or their metabolites directly, several laboratory studies can also indirectly assess for substance use or a particular substance's hallmark effects on the body. For example, elevated mean corpuscular volume (MCV), decreased platelet count, decreased white blood cell count, and elevated serum transaminases may all suggest chronic heavy use of alcohol [75, 76]. Elevations in the hepatic enzyme gamma-glutamyl transpeptidase (GTT) or carbohydrate-deficient transferrin (CDT) also suggest heavy chronic alcohol use and may be more specific than standard transaminase assessment. Ethyl glucuronide (EtG), a metabolite of alcohol, can be detected in serum or urine and can detect use of alcohol in patients where accurate confirmation of alcohol exposure is critical [77].

Neuroimaging can play an important role in the evaluation and treatment of older adults with addictive disorders. In the acute phase of intoxication, when the patient may present with altered mental status of unknown etiology, head computerized tomography (CT) or brain magnetic resonance imaging (MRI) may be indicated to rule out stroke, other mass effect, or demyelinating process occurring sometimes in conjunction with substance intoxication. Neuroimaging studies may also provide valuable structural information about the status of brain physiology—with age and with heavy substance use, global cerebral atrophy can help provide radiologic evidence to support poor cognitive performance on MoCA or MMSE or other measures of functional status. In chronic, heavy alcohol users, MRI evidence of atrophy of the mammillary bodies as well as thalamus and hippocampus can support a diagnosis of Wernicke encephalopathy and can be used to track progression of illness serially in time [78].

16.1.6 Differential Diagnosis

Differential diagnosis generation is driven largely by clinical presentation and history. Acute intoxication may generate a differential that includes (in addition to substance-induced disorder) delirium, cerebrovascular accident, infection, thyroid disorders, vitamin B_{12} and other vitamin deficiencies, traumatic brain injury, neurocognitive disorder, psychotic disorders, depressive disorders, personality disorders, and/or even brain tumor. When a substance use disorder is suspected outside of acute intoxication, this same panel of diagnoses must also be explored or excluded.

16.1.7 Treatment

Pharmacological Treatment

Intoxication and *withdrawal* states are often managed pharmacologically to ensure safe and comfortable detoxification. Benzodiazepines are frequently employed in managing psychostimulant or hallucinogen intoxications along with behavioral and environmental approaches, such as providing a low-stimulus environment. Antipsychotics such as haloperidol, ziprasidone, or olanzapine are sometimes used in the event of severe agitation with safety concerns, but caution is recommended as the combination of psychostimulants and antipsychotics can lead to hyperthermia and/or seizures. For decades, pharmacologic alcohol detoxification has been driven by the principle of replacing central GABA-tone absent when alcohol use has been discontinued through judicious use of symptom-triggered or standing tapers of GABAergic medications such as benzodiazepines or barbiturates. For patients requiring detoxification from sedative-hypnotic medications, slow, controlled taper of the specific sedative-hypnotic being used by the patient may be required. Opioid-dependent patients are often tapered slowly using long-acting opioids such as methadone or buprenorphine or have their withdrawal symptoms treated symptomatically using combinations of antacids, gastrointestinal antispasmodics, NSAIDs, acetaminophen, the off-label use of the central alpha-2 agonist antihypertensive clonidine (decreases sympathetic tone which is often elevated in the context of acute opioid withdrawal), or even low doses of benzodiazepines.

Currently, the FDA- and Health Canada-approved *maintenance* pharmacotherapy for treatment of substance use disorders includes methadone, buprenorphine, and naltrexone (oral and month-long-acting injectable formulations) for opioid use disorders; bupropion, nicotine replacement (transdermal patch, gum, lozenge, inhaler), and varenicline for nicotine use disorders; and acamprosate, naltrexone (oral and long-acting injectable formulations), and disulfiram, for alcohol use disorders (see Table 16.3). However, there are no trials of disulfiram used specifically in older adults. Disulfiram is seldom used in older adults because of concerns related to adverse events in those with preexisting systemic medical conditions. The use of maintenance medications for substance use disorders is often referred to as Medication-Assisted Treatment (MAT). Intranasal naloxone was recently approved by both the FDA and Health Canada as a rescue treatment for opioid overdose. Currently, there are no FDA- or Health Canada-approved maintenance pharmacotherapies for cannabis use or stimulant use disorders.

For all psychopharmacotherapies used in the treatment of substance use disorders in older adults, it is imperative

Table 16.3 Maintenance medications for substance use disorders approved by the US FDA and Health Canada

Maintenance medication	Indicated substance use disorder	Proposed mechanism of action
Naltrexone (oral and available in long-acting injectable (Vivitrol ®) formulation[a])	Opioid use disorder Alcohol use disorder	Competitively antagonizes mu-opioid receptors, decreasing reinforcement from endogenous opioids (alcohol) and blocking binding of exogenous opioids (e.g., heroin)
Disulfiram[b]	Alcohol use disorder	Irreversible inhibition of aldehyde dehydrogenase, resulting in toxic accumulation of acetaldehyde when alcohol is consumed
Acamprosate	Alcohol use disorder	Central glutamate and GABA modulation
Bupropion	Tobacco use disorder (smoking cessation)	Weak reuptake inhibition of norepinephrine and dopamine, but the mechanism of action relating to smoking cessation is unknown
Nicotine (available in transdermal, sublingual/transbuccal, intranasal, inhaled formulations)	Tobacco use disorder (smoking cessation)	Nicotinic cholinergic receptor agonist replacement
Varenicline	Tobacco use disorder (smoking cessation)	High-affinity nicotinic acetylcholine receptor binding, producing agonist effects
Methadone	Opioid use disorder	Mu-opioid receptor full agonist replacement
Buprenorphine (available in diversion-deterrent formulation in combination with naloxone)	Opioid use disorder	Sublingually available, mu-opioid receptor partial agonist replacement

[a]Approved for use in the USA
[b]No longer approved for use in Canada

to consider carefully the patient's underlying medical conditions (renal and hepatic function, in particular) when considering what medication options and doses. Recall that medication metabolism in older patients can be significantly less efficient than that in younger patients, and, as a result, lower doing with tighter observation and management may be necessary.

Non-pharmacological Treatment

As mentioned above, non-pharmacological treatments of substance *intoxications* are a mainstay of management. With all substance intoxications, but especially with psychostimulants and hallucinogens, a low-stimulus environment may be necessary to prevent agitation and minimize the need for pharmacological intervention or physical restraint. For many patients, allowing them a safe place and time for metabolism of the substance alone may be adequate management. However, especially in the case of alcohol- and sedative-hypnotic-dependent geriatric patients, close medical monitoring should be undertaken as symptoms of withdrawal heralding a dangerous escalation in condition that may require medication management can commence insidiously.

Brief interventions, such as motivational interviewing, have been shown to be effective in older populations, although the evidence base is scant. Studies have demonstrated at least short-lived positive effects of motivational interviewing in smoking cessation as well as other substance use disorders, especially when tailored to geriatric populations with education regarding population-specific risks and cognitive behavioral therapy approaches [79].

Other psychosocial interventions for substance use disorders in older adults have also shown promise, such as relapse prevention focused management of those unique antecedents to substance relapse in geriatric populations (e.g., isolation, loneliness, pain, grief) [80, 81]. Manualized group-based treatments such as SAMHSA's Substance Abuse Relapse Prevention for Older Adults: A Group Treatment Approach have also been validated [82]. While data regarding efficacy of 12-step programs is difficult to determine for any age group, 12-step programs may provide unique advantages in geriatric populations for whom social connection is tenuous. Older adult meetings of 12-step programs are ubiquitous, and patients can be encouraged to explore these as demographically appropriate options.

It bears mentioning that in the context of co-occurring major neurocognitive disorders, cognitive- and psychosocial-based treatment interventions may be less effective, and treatment approaches targeting management of the major neurocognitive disorder may be paramount. Encouragingly, there is evidence to suggest that older adults who do engage in treatment for substance use disorders do better relative to younger cohorts [81, 83, 84].

16.2 Case Studies

The following case-based studies are reflective of the symptomatology, evaluation, and treatment of older adults with substance use disorders.

16.2.1 Case 1

Case 1 History

Mrs. Z. a 76-year-old female, is followed by her primary care physician for back pain. Twelve months ago, she slipped and fell while in her home, leading to soft tissue trauma to her lower back. She was examined in the emergency room, given oxycodone for pain control, and was asked to follow up with her primary care physician.

Mrs. Z. found the opioids helpful in managing her back pain and was continued on the same dose by her primary care physician. On further history and evaluation, Mrs. Z. also endorsed anxiety, somatic complaints, and insomnia since her husband passed away 2 years ago. Mental status examination revealed a well-kempt woman who appeared her stated age. She reported her mood as "nervous" and her affect was anxious, but full range and appropriately reactive. She was somewhat preoccupied with somatic complaints such as pain; however, she was redirectable, and her thought process and speech were normal. There was no evidence of somatic, nihilistic, or persecutory delusions, and she denied visual or auditory hallucinations. She was oriented to person, place, and date, though no formal cognitive testing had been done in the past. Mrs. Z. felt her pain and anxiety symptoms both improved greatly in the first 3 months following opioid prescription and consequently asked her primary care physician for repeat prescriptions. Given her continued complaints and symptom improvement on opioids, her primary care physician renewed the prescription for oxycodone controlled-release 10 mg by mouth every 12 hours.

Over the next 2 months, Mrs. Z. started using oxycodone more often than prescribed, e.g., when feeling anxious about paying her bills, worrying about her health, hearing sad news, or after arguments with her daughter. She asked her primary care physician for higher and more frequent doses and often runs out before her prescription was due for refill and has begun to visit walk-in clinics and after-hour services. Mrs. Z.'s daughter noticed that she is more withdrawn, forgetful, and at times seemingly drowsy when her daughter visits.

Mrs. Z. is physically quite healthy for her age, but her past medical history is significant for hypertension, for which she takes ramipril 5 mg by mouth daily, and she has a past surgical history revealing of a hysterectomy 12 years ago for uterine fibroids. She has no formal psychiatric history, with no previous diagnoses or treatment engagements including admissions to day treatment programs or inpatient psychiatric care, and she has never been in psychotherapy. She denies prior substance use disorder or substance misuse history. Family history is noncontributory. On social history, Mrs. Z. was married for 54 years prior to her husband's death 2 years ago from prostate cancer. She has two children: a daughter who lives nearby with three small grandchildren and a son who lives several hours away. Her work was primarily in the home as she raised her children. She was actively involved with her church group until 5 years ago when she became the primary caregiver for her husband when he was diagnosed with cancer. Laboratory studies ordered by her primary care physician in the last 6 months have been normal, including complete blood count, comprehensive metabolic panel, and thyroid function.

After several months, Mrs. Z. sustained another fall at home and was unable to visit her primary care physician or present to the emergency room to ask for medications. By the end of the week at home, she began to experience significantly increased anxiety, nausea and diarrhea, and sweating. Her daughter called and felt Mrs. Z. sounded confused, so arrangements were made for Mrs. Z. to see her primary care physician next week.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What is your working diagnosis and differential diagnosis?

Question 2. What are the features of substance misuse and substance use disorder?

Question 3. What strategies can be implemented to prevent opioid misuse?

Question 4. Which withdrawal symptoms do patients experience in opioid withdrawal, and what treatments can be offered in the short and long term?

Question 5. What must clinicians consider specific to opioid use in the geriatric population?

Case 1 Answers

Case 1 Answer 1 (Question 1—What is your working diagnosis and differential diagnosis?)

The clinical vignette centers on Mrs. Z.'s opioid use, revealing symptoms concerning for opioid use disorder, including escalating doses suggestive of the development of tolerance, as well as withdrawal symptoms when the opioid was discontinued. There is also evidence of anxiety and/or mood or grief symptoms, as well as chronic pain symptoms. Her cognitive status has not yet been formally assessed, but her daughter notes some evidence of forgetfulness, although this started seemingly only after initiation of opioid treatment. For Mrs. Z. therefore, differential and comorbid diagnoses to consider include:

- Somatic symptom disorder
- Generalized anxiety disorder
- Major depressive disorder
- Major or mild neurocognitive disorder
- Delirium
- Grief
- Opioid use disorder

Working through the differential stepwise is an important diagnostic exercise.

Somatic symptom disorder is defined in the DSM-5 as preoccupation with one or more distressing somatic symptoms resulting in disruption of daily activities and associated with excessive thoughts, feelings, or behaviors devoted to these symptoms, but these symptoms have to be not better accounted for by another medical or psychiatric condition [2]. Further evaluation of the extent and severity of Mrs. Z.'s somatic concerns and the impact of them on her daily life is therefore warranted. Generalized anxiety disorder, on the other hand, is defined by excessive anxiety or worry about a number of events or activities occurring more days than not for at least a 6-month period. Three of the following must be associated with the anxiety: (1) restlessness, (2) easy fatigue, (3) difficulty concentrating, (4) irritability, (5) muscle tension, and (6) sleep disturbance [2].

Further, the clinical vignette describes her daughter's concern about Mrs. Z. becoming increasingly more withdrawn and forgetful. These may be manifestations of Mrs. Z.'s opioid use; however in all geriatric patients presenting with forgetfulness, major depression, major or mild neurocognitive disorder, and delirium must be considered and ruled out. Further history from the patient and family, as well as performing a MoCA or MMSE, would be warranted as part of a comprehensive, thoughtful, workup. Opioid medications themselves are a common cause of delirium in older adults. Additionally, opioid withdrawal, her fall (and/or pain), or an underlying infection or medical condition could cause delirium or work synergistically with her opioids to increase the vulnerability to delirium episodes.

More detailed history would be required to screen for symptoms of depressive disorders. Further information that would be helpful would be screening specifically for low mood or irritability, loss of interest in previously enjoyed activities, changes in sleep patterns, appetite or concentration, decreased energy, guilt, psychomotor retardation, and/or suicidal ideation. Differentiating grief from depressive illnesses can be difficult. One helpful strategy to help make this differentiation is asking about and observing whether the patient is able to experience joy or happiness, contextually. For patients with syndromal depression, the ability to experience joy and happiness is impaired, while patients suffering from grief may report that at times they are able to "forget" about their low emotional state and experience (for a time) the range of pleasure. In Mrs. Z.'s case, her ability to emote normally in office-based interview would speak against the presence of a depressive illness, even though the 2 years that have elapsed since the death of her husband is longer than one might expect with normal grief. Nonetheless, it is important to continue screening for depression and suicidal ideation at each clinical interaction. Considering comorbidity and differential diagnoses in geriatric patients using opioids is integral for complete care as treatment may differ significantly in a patient with no comorbidities. Pending further data, the working diagnosis of Mrs. Z. is generalized anxiety disorder, opioid misuse (rule out opioid use disorder), rule out delirium, and normal grief.

Case 1 Answer 2 (Question 2—What are the features of substance misuse and substance use disorder?)

Substance misuse involves any use of a drug that is inconsistent with the precise indication and manner in which it was prescribed by a clinician. As such, substance misuse includes use with the intent to get "high," self-increased doses, or increased dose frequency, changing the route of administration (e.g., intravenous or inhalation use of an oral or transdermal medication), and seeking out multiple prescribers or illicit sources of the drug. Mrs. Z. displayed a number of behaviors consistent with opioid misuse: using her oxycodone more often than prescribed, running out before a prescription refill was due, and seeking multiple providers to prescribe the drug.

Recall from earlier that a diagnosis of opioid use disorder, as per the DSM-5, requires at least 2 of 11 criteria to be met within a 12-month period (see Table 16.1) [2]. Mild opioid use disorder is defined as meeting two to three criteria, moderate opioid use disorder requires four to five criteria, and severe opioid use disorder meets six or more criteria above [2].

From the clinical history, we see that Mrs. Z. meets at least three of the criteria for opioid use disorder in the past 12 months, including taking larger amounts, tolerance, and withdrawal. Obtaining further history from Mrs. Z. regarding the impact of opioid use on her daily activities including social, occupational, and recreational activities and responsibilities would be important in assessing the severity of her opioid use disorder.

Case 1 Answer 3 (Question 3—What strategies can be implemented to prevent opioid misuse?)

Many patients are started on opioid medications for pain management. As in the case of Mrs. Z., many patients' first exposure to an opioid medication is through prescription for a legitimate pain condition. However, sometimes patients may find the benefits (aside from analgesia) favorable and consequently seek to continue these medications. Particularly for primary care physicians who will be following patients and renewing prescriptions, taking steps to minimize the risk of subsequent opioid misuse and disorder from the outset is integral to patient care.

Knowledge of the patient's past history, including comorbidities such as treated or untreated substance abuse and concurrent medications, is important. Clinicians can consider establishing a treatment plan or contract with their patient prior to commencing treatment with opioid medication, including a discussion of the risks of misuse and disordered use. It should be made clear that only one provider should be prescribing the medication and that use of multiple providers is not advisable as it may lead to doubling prescriptions, unclear dosing, and lack of consistency in the management plan. Multiple opioid prescribers may also indicate opioid misuse. Dosing should be limited to the lowest

effective dose and for the shortest duration for the patient. Using drugs with longer half-lives can also potentially reduce the incidence of withdrawal symptoms and minimize risk for misuse. Similarly, routine, rather than "as-needed," dosing may reduce the likelihood of self-administration of more frequent dosing. Regular follow-up appointments can be pre-scheduled by the clinician to ensure close monitoring of opioid use patterns and symptoms. Checking available prescription monitoring programs can be an excellent way of determining if a patient is receiving prescriptions for controlled substances from multiple sources. Finally, involving the patient's family in the care plan and in follow-up appointments can be useful for collecting collateral history about the patient's opioid use and their overall health and daily functioning.

In many cases, frank discussions with patients about the full spectrum of benefits they are receiving from opioids that drive their behaviors around the medications can provide opportunities to discover previously un- or underappreciated co-occurring illnesses (such as anxiety in Mrs. Z. case) which could be managed with other, non-opioid, pharmacological, and behavioral therapies.

Case 1 Answer 4 (Question 4—Which withdrawal symptoms do patients experience in opioid withdrawal, and what treatments can be offered in the short and long term?)

After sustaining a second fall and being unable to refill her opioid prescription, Mrs. Z. began to experience increased anxiety, nausea and diarrhea, sweating, and confusion—all symptoms consistent with opioid withdrawal. Opioid withdrawal is characterized by gastrointestinal, sympathetic, and parasympathetic symptoms. The clinical manifestations of withdrawal reflect the mechanisms by which opioids take action in the body. Mu-, kappa-, and delta-opioid receptors are found predominantly in the brain, spinal cord, and gastrointestinal system, and the cellular adaptation that occurs in chronic opioid use leads to the responses seen when the opioid is withdrawn.

Opioid action in the gastrointestinal system leads to slowed intestinal transit time with constipation, nausea, and bloating. In turn, gastrointestinal opioid withdrawal symptoms include diarrhea, nausea, vomiting, and abdominal cramping. Opioids also act to depress the nervous system, leading to analgesia, sedation, decreased heart rate and blood pressure, decreased respiratory rate, and constricted pupils. Consequently, in withdrawal, people experience increased pain, increased blood pressure and heart rate, dilated pupils, anxiety, agitation, and restlessness. Finally, parasympathetic symptoms of opioid withdrawal include rhinorrhea (runny nose), lacrimation (teary eyes), diaphoresis (sweating), piloerection (goose bumps), and shivering.

Mrs. Z.'s symptoms began about 1 week after she ran out of her opioid prescription. The timing of opioid withdrawal is dependent upon the rapidity of metabolism of the particular opioid in the body. Mrs. Z. was taking controlled-release oxycodone, which has a half-life of approximately 3–4 days, and as such, she did not begin to experience her withdrawal symptoms until the end of the week. For more rapidly metabolized opioids such as diacetylmorphine (heroin) or rapid-release oxycodone, withdrawal symptoms would be expected to appear much more quickly after cessation of the drug.

Treatment of opioid withdrawal includes both short-term symptom management and long-term treatment. In the acute setting where management of acute symptoms is desired, a number of medications may be indicated. Anxiety and agitation can be treated acutely with an oral benzodiazepine, ideally one with a longer half-life, such as diazepam or clonazepam, although caution should be used in the geriatric population due to active metabolites and drug-drug interactions. Diarrhea may be managed with oral loperamide, and nausea and vomiting can be treated with ondansetron; however, caution should be use due to the adverse anticholinergic effects of loperamide and the corrected *QT* (QTc) interval prolongation for heart rate with the use of ondansetron in the geriatric population. If pain is a concern, management with ibuprofen or acetaminophen may be indicated. Generalized sympathetic overload can be managed with clonidine, although monitoring blood pressure to ensure that the patient does not become hypotensive is critical, especially in older adults. Cross-referencing these symptomatic medications with a patient's usual medications is essential to prevent untoward drug-drug interactions, and many electronic pharmacopeias have this functionality (e.g., Micromedex®). However, each of the medications above addresses only the symptomatic consequence of opioid withdrawal and not the primary cause.

Opioid substitution therapy with methadone or buprenorphine may be used in the acute withdrawal setting or as long-term opioid maintenance therapy for patients seeking treatment for opioid use disorder. Methadone is a full agonist synthetic opioid that binds to the mu-opioid receptors and has a long duration of action. Methadone can prevent opioid craving and withdrawal symptoms, and when taken daily as prescribed (e.g., in a narcotic treatment program), it is not as euphorigenic as other shorter-acting opioids. However, methadone can still be abused, and given its unusual pharmacodynamics (long time needed to reach steady state), methadone overdose is particularly concerning. Methadone can also provide pain relief in itself, but the once-daily dosing of methadone in narcotic treatment programs typically is not aimed at analgesia. In methadone maintenance therapy, patients are required to abstain from continued illicit opioid use, evaluated by routine urine drug screens.

Buprenorphine is a semisynthetic opioid that works as a partial agonist at the mu-opioid receptors in the brain. As it has both agonistic and antagonistic effects, buprenorphine has the ability to block the effects of concurrently used illicit opioids. In turn, it can also produce acute withdrawal in an opioid-intoxicated patient. However, buprenorphine is an effective strategy in the long-term treatment of opioid use disorder, and due to its partial antagonist properties, it is associated with less lethal overdose than methadone either alone or when combined with illicit opioids.

Case 1 Answer 5 (Question 5—What must clinicians consider specific to opioid use in the geriatric population?)

Older adults more commonly have co-occurring medical conditions that may complicate both the effects of opioids and opioid withdrawal. Opioid-induced respiratory depression is associated with higher risk in the context of chronic obstructive pulmonary disease. The orthostatic hypotension, bradycardia, and cognitive dulling associated with opioid use may similarly lead to higher risk of falls in older adults who are already at risk for falls at baseline. Opioid metabolism and elimination may also differ, due to medical comorbidities or medication interactions, affecting opioid dosing requirements. Finally, in both opioid use and withdrawal, geriatric patients are at higher risk for delirium.

Teaching Point

Special considerations must exist for the care of geriatric patients using opioids due to their higher burden of medical comorbidities, concurrent medications, changing social supports, and ability to access healthcare services.

Importantly, older adults are also more likely to have chronic pain, which needs to be appropriately appreciated and managed. However, there is also the potential of under-recognition of opioid use disorder in this age group given the assumption that older adults do not use drugs recreationally. Routine urine drug screening is much less common in this age group compared to younger adults. Taken together, many geriatric patients with opioid use disorder may go undiagnosed and fail to receive appropriate treatment. Also, recalling the previous discussion relating to "pseudoaddiction," many older patients may also suffer from undertreatment of their pain, the result of which can be the appearance of an addiction, when in reality the symptoms emblematic of addiction disappear when pain is adequately treated.

Case 1 Analysis As seen in the case of Mrs. Z., suspicion for opioid use disorder was not raised by the primary care physician despite Mrs. Z. displaying behaviors consistent with the disorder. Mrs. Z. experienced adverse effects on her cognition associated with both her opioid use and withdrawal, in the form of forgetfulness, drowsiness, and confusion. Whether Mrs. Z.'s fall was precipitated by opioid use is unclear in this case; however, her subsequent inability to access healthcare services led to her experiencing opioid withdrawal. An appropriate management strategy for Mrs. Z. would include formal cognitive testing; referral for comprehensive pain management evaluation that could include behavioral interventions such as yoga, mindfulness, and exercise; and non-opioid analgesics. Also, further evaluation and management specifically of her grief, anxiety, and possible depressive disorder is imperative, as it is possible that her pain medication requirements would proportionally decrease as these conditions are more effectively dealt with. Lastly, it would be important to counsel her and her family about hallmarks of opioid use disorder and the availability of treatment options for that illness, should they persist in her following the retooling of her overall management (cognitive, pain, psychiatric evaluations, and management).

16.2.2 Case 2

Case 2 History

Mr. R.'s is a 78-year-old man who has just begun seeing a new primary care physician, Dr. B., after previously receiving his primary care at a Veterans Administration clinic. At their initial visit, Dr. B.'s documents that Mr. R. is a retired construction manager and former marine infantryman who, when asked where he served, states he "saw a lot of horrible things during the Vietnam War" but refused to say more. He has four children and eight grandchildren. His wife of 45 years passed away 2 years previously from cancer, and since that time, he says he has been on his own. His children live out of state and seldom visit or call. His known medical problems include hypertension, well-controlled with lisinopril, gastroesophageal reflux disorder for which he takes a proton-pump inhibitor, and chronic pain in his ankles, right hip, and back, which he attributes to arthritis stemming from a "broken back and busted ankles" sustained in the service. He manages his pain with topical (menthol and/or capsaicin-containing) creams and naproxen 500 mg twice daily as needed and his own "grit."

He says he enjoys yard work but admits he does not get out much since his wife died. In record review, Dr. B. notes that at the time that Mr. R.'s wife passed away, he was prescribed alprazolam for anxiety. Mr. R. obtains all his medications from the department of Veterans Affairs system because of his service connection. When asked about his anxiety and whether he has seen a psychiatrist for it, Mr. R. becomes defensive and states that he does not believe in psychiatrists and insists he takes the alprazolam "occasionally" for sleep when his pain keeps him awake. He reports that he drinks one "shot of scotch whiskey" (1.5 ounces of spirits with 40% alcohol) every night for the past 45 years and indicates that he smoked tobacco cigarettes for 30 years (one pack per day) but quit several decades ago. He denies use of other drugs, including cannabis. Mr. R. still sees an orthopedist at the VA, whom he describes as "my mechanic."

On physical exam, Mr. R. is noted to be quite thin, with some scratches, bruises, and excoriations on his forearms and shins, which Mr. R. attributes to "those darned blackberry vines in the garden." His seated blood pressure is 128/82 mm Hg and heart rate is 72 beats per minute. Otherwise, he is robust appearing. His neurologic exam is notable only for limp and decreased visual acuity from a cataract in his right eye. Routine laboratory studies on presentation reveal slightly elevated transaminases (although still within upper limits of normal), normal kidney function markers, and

otherwise normal metabolic panel. His complete blood count is notable for decreased hemoglobin of 12.6 g/dl (126 g/L) and slightly elevated mean corpuscular volume (MCV) at 100 fL. Stool guaiac test (for fecal occult blood) is negative. Thyroid function is normal. Electrocardiogram is performed and notable only for a left anterior hemiblock with a normal QTc interval of 440 milliseconds.

Several months later, Dr. B.'s receives notification from the university hospital that Mr. R.'s has been admitted to their orthopedic service for management of a right femoral neck fracture sustained that morning after a fall down his front steps. His medications and medical history are verified with Dr. B.'s, and the team assures Dr. B.'s they will provide updates for coordination of care. Mr. R.'s oldest son, Jim, is said to be en route from out of state.

Three mornings later, now post-op day 1 and hospital day 3 for Mr. R., Dr. B.'s receives a call from the consulting internist inquiring about any prior psychiatric history or agitation in his patient. The internist states that their team was called to manage worsening hypertension and associated tachycardia (177/105 mm Hg, pulse 115 beats per minute but regular) discovered when vital signs were checked several hours earlier. The nurse caring for him also noted him to be diaphoretic and very restless and anxious at the beginning of her shift. When she accidentally dropped his bedside telephone on the floor, he reportedly sat up in bed and shouted, "Take cover!" Since 9 AM he has become increasingly agitated and keeps pointing at various places in his room and shouting "Get outta here!" He has attempted to strike the physicians when they try to examine him. He also has been trying to remove his hospital gown and rubbing his arms, occasionally yelling, "Get these bugs off me!" He is showing occasional myoclonic jerks but does not appear tremulous when he raises his hands. The internist tells Dr. B. that the patient appears to be having auditory as well as visual hallucinations, looking over his shoulder and saying to no one in particular, "G. . . . . it! That buzzing is driving me crazy!" and then continuing to mumble incoherent words. Dr. B.'s explains that he is unaware of any previous similar episodes and is not immediately aware of any pressing medical conditions that could result in his current condition.

A psychiatry consult is ordered to evaluate altered mental status in the context of chronic anxiety disorder and rule out posttraumatic stress disorder (PTSD). On mental status examination, the patient is hyperalert and mildly restless, with a Richmond Agitation-Sedation Scale (RASS) score or +1, thought process is circumstantial and he is somewhat distractible; he denies suicidal and homicidal ideation. He does endorse auditory and visual hallucinations of mechanical buzzing sounds and vaguely described figures in the hospital room. MoCA was 18 out of 30 points with 0/5 on delayed memory task and 0/3 on attention task and showed poor orientation to place and time. He was diagnosed with delirium, rule out PTSD, and rule out benzodiazepine use disorder/withdrawal.

Case 2 Questions and Answers

Case 2 Questions

Question 1. At this time, what is/are your working diagnosis(es) and differential diagnosis?

Question 2. What additional information would be helpful at this time to narrow down the etiology of Mr. R.'s delirium and overall clinical presentation?

Question 3. What is the management in this case?

Question 4. What additional tests, studies, follow-up, or recommendations might be warranted at this time or in the near future?

Case 2 Answers

Case 2 Answer 1 (Question 1—At this time, what is/are your working diagnosis(es) and differential diagnosis?)

Mr. R. appears delirious (see ▶ Chap. 17). Although he cannot be formally evaluated by neuropsychiatric testing, his confusional state clearly is acute in onset and associated with poor attention (as evidenced by his distractibility) and evident change in his level of consciousness with agitation. The differential diagnosis is broad, including drug-induced delirium from opioids administered for pain, acute infection, possible administration of other centrally acting medication such as antihistamines or other anticholinergic drugs, acute metabolic derangement, and substance withdrawal. He has not complained of chest pain or shown focal neurological signs to suggest either acute myocardial infarction or stroke. While alcohol intake was low to moderate in this case (i.e., one standard drink per day), some older adults with increased morbidity may experience negative health consequences from even low to moderate quantities of alcohol consumption. Withdrawal enters the differential diagnosis because of the history of daily alcohol intake and as-needed use of alprazolam, and the clinical presentation timeline (last possible use approximately 72 hours prior, just before admission) could fit with a withdrawal syndrome.

Mr. R.'s diaphoresis and labile vital signs raise concern about delirium tremens (alcohol withdrawal delirium), but there are additional findings that are atypical for alcohol withdrawal. He does not appear to be tremulous but is rather having myoclonic jerks and appears to be experiencing formication (skin "crawling") and tinnitus, features sometimes associated with benzodiazepine withdrawal (see ◘ Table 16.4) [85].

Among benzodiazepines, alprazolam stands out as carrying a particularly strong risk for dependency and addiction and for more severe withdrawal reactions [86]. The highest prevalence of long-term use of benzodiazepines (i.e., over 6 months) and benzodiazepine dependence occurs among older adults despite their increased vulnerability to adverse reactions [87, 88]. Many older patients began taking alprazolam for anxiety, depression, or PTSD and tend to take a

Table 16.4 Symptoms suggestive of benzodiazepine withdrawal [85]

Benzodiazepine withdrawal symptoms	Perceptual distortions (e.g., false sense of movement, distortions of body image)
	Depersonalization
	Derealization
	Paresthesias (e.g., numbness, tingling)
	Formication (i.e., crawling sensation on the skin, as from ants)
	Sensory hypersensitivity (e.g., to light, sound, taste, smell)
	Abnormal motor activity (e.g., myoclonic jerks, twitches, fasciculations)
	Tinnitus
	Psychotic symptoms (e.g., visual and/or auditory hallucinations)[a]
	Delirium[a]
	Withdrawal seizures[a]

[a]Usually limited to rapid or abrupt withdrawal from a high dose of benzodiazepine

steady, low dose without dose escalation. Patients' fear of withdrawal symptoms, such as rebound anxiety and nightmares, perpetuates dependence, as do prescribers' ongoing renewals of alprazolam (and other benzodiazepines) despite the drug's potential harm [88]. Long-term use is facilitated by having multiple prescribers, the difficulty encountered by prescribers in tapering the benzodiazepines (particularly alprazolam), and some prescribers' belief that a stable, low dose of benzodiazepine that appears to be controlling symptoms without apparent side effects constitutes acceptable treatment, despite the drug class' well-documented potential harm in older patients.

Another unusual feature of Mr. R.'s delirium is the nature of his behavior just prior to the development of agitation and psychosis. He displayed significant anxiety, complete with autonomic signs, but also showed a telling startle response to the loud crash of his telephone falling to the floor, which might make one suspicious of a flashback and the hyperarousal seen in PTSD. During his full-flown agitated psychosis, his shouting, "Get outta here!", and pointing were consistent with the delusion of being attacked and reliving his Vietnam War experiences. Little has been written about PTSD in older patients, but it can be delayed in onset, sometimes for many years [89], coming to the surface when previous coping mechanisms begin to break down through loss of purpose following retirement, loss of support systems (such as the death of a spouse), and cognitive decline. Patients with PTSD often have concomitant major depression, anxiety, phobias, and alcohol abuse and may also abuse illicit drugs [89]. Mr. R.'s anxiety and, in retrospect, insomnia appear to have become worse following the death of his wife. As is true of many men of his generation, admission of psychological distress was perceived as a sign of weakness, and he used his chronic pain as an excuse to request alprazolam, which his orthopedist appeared willing to renew. In the context of active delirium, however, it would be impossible to make the definitive diagnosis of PTSD, but this would be a topic to consider exploring with Mr. R. when the delirium has resolved.

Case 2 Answer 2 (Question 2—What additional information would be helpful at this time to narrow down the etiology of Mr. R.'s delirium and overall clinical presentation?)

A targeted laboratory workup aimed at identifying contributors to his delirium is warranted (see ▶ Chap. 17). Mr. R.'s further clinical presentation revealed that he had an indwelling urinary catheter and was intubated, therefore, a nosocomial infection must be ruled out as a contributor to his delirium. Empiric treatment with a long-acting benzodiazepine will treat both alcohol and benzodiazepine withdrawal, but a benzodiazepine could worsen delirium if alcohol or benzodiazepine withdrawal was not a major underlying factor. Further collateral information, perhaps from Mr. R.'s son regarding his estimated alcohol consumption, and a review of his alprazolam prescription history (a prescription monitoring program query would be helpful in this regard, as would be contacting Mr. R.'s orthopedist's office) would also help elucidate the risk of Mr. R.'s suffering from alcohol and/or sedative-hypnotic withdrawal. Thus, Mr. R.'s clinicians needed additional information. A liquid chromatographic comprehensive toxicology screen of the urine might still detect the alprazolam, which is excreted in the urine with a half-life of over 16 hours in older persons. However, information about chronic use of benzodiazepine is critical.

Case 2 Answer 3 (Question 3—What is the management in this case?)

In the case of Mr. R., initial treatment must consist of prompt control of his psychosis and agitation. (See ▶ Chap. 17). Parenteral haloperidol has long been used as an agent for managing delirious agitation, but in some institutions, it has fallen out of favor owing to the potential that haloperidol can increase the QTc interval and thus precipitate torsades de pointes and ventricular tachycardia. If used in geriatric patients, lower doses of parenteral haloperidol and careful cardiac and behavioral monitoring are required. Mr. R. has had a normal QTc in the recent past. However, it is not uncommon for postoperative patients and those receiving opioids to experience nausea and to receive ondansetron, which prolongs the QTc, or to be receiving other QTc-prolonging medications. Owing to QTc concerns with haloperidol, other antipsychotics such as the newer atypical antipsychotics are often considered first line in many institutions (although they still carry some risk of QTc prolongation). Relative to the other atypical antipsychotics, aripiprazole is known to cause minimal QTc prolongation, but is not known for being particularly sedating. For an agitated, uncooperative delirious

patient, sometimes the highly sedating atypical antipsychotic olanzapine is a preferred option particularly because it comes in a parenteral formulation, although it carries some anticholinergic activity. Mr. R.'s team opts to start him on olanzapine 2.5 mg every 8 hour as needed for behavioral control resulting from agitation in delirium. His team notes that he becomes significantly calmer after the first dose.

Further review of clinical presentation reveals that Dr. B., also concerned about possible alcohol abuse and/or alprazolam dependence, contacts the VA and is able to obtain Mr. R.'s prescribing history for alprazolam. Dr. B. also runs a prescription monitoring program query and discovers no other reported prescribers of alprazolam aside from Mr. R.'s orthopedist. Nonetheless, Mr. R. has continued to obtain alprazolam prescriptions from his outpatient orthopedist, at doses of 1–2 mg three times daily, as needed, with 30-day supplies (180 pills monthly of 1 mg per pill) that have been renewed consistently up until and including the current month [90].

This information, relayed to the treating team, justifies the use of benzodiazepine for Mr. R.'s agitation. For alcohol withdrawal alone, administration of benzodiazepine only as needed for symptoms, based on the scoring protocol of the Clinical Institute Withdrawal Assessment of Alcohol Scale, Revised (CIWA-Ar) [91, 92], would be appropriate, but the presence of alprazolam withdrawal complicates the treatment. For benzodiazepine in general, a very gradual, stepwise taper is recommended over 6–8 weeks, with dose reductions of as little as 0.10–0.125 of the total daily dose every 1–2 weeks. Although a 6–8-week tapered withdrawal is considered optimal by some experts, tapering must be individualized and can take up to a year [85]. In alprazolam-dependent patients, even a gradual taper in dose can cause withdrawal symptoms, which may be severe [93]. Lorazepam, with an elimination half-life of 10–20 hours, may fail to halt withdrawal symptoms from alprazolam [86]. In theory, long-acting benzodiazepines like clonazepam may prevent withdrawal symptoms from shorter-duration benzodiazepine like alprazolam. Published evidence is largely limited to case reports in the general adult population, which support the use of clonazepam, started at a daily dose equivalent to the alprazolam [90, 94, 95], with or without concomitant psychological counseling. For Mr. R. an appropriate treatment option to consider would be the administration of clonazepam starting at 2 mg po twice daily and increasing to 3 mg po twice daily if needed and reducing the dose for excess sedation. If this management strategy is ineffective, continuing to seek other etiologies for his ongoing delirium, as well as considering starting a standard alprazolam taper, would be indicated.

Mr. R.'s agitation, hypertension, tachycardia, hyperarousal, hallucinations, myoclonic jerks, tinnitus, and diaphoresis are largely resolved 24 hours after starting clonazepam 2 mg po twice daily, in conjunction with continued clinical monitoring, as-needed olanzapine administration, and behavioral interventions such as frequent reorientations and minimization of opioids and other potentially deliriogenic medications. However, he remained intermittently disoriented to time and circumstance but was easily reoriented. His MoCA improved to 23 out of 30 during the day on hospital day 5. However, that evening he experienced mild agitation and removed his intravenous catheter during the night, and subsequently he received 5 mg of rapidly dissolving olanzapine, with good resolution of agitation noted. He was discharged to a nursing home for rehabilitation on hospital day 7, with plans for psychiatric follow-up to implement a slow taper of clonazepam.

Case 2 Answer 4 (Question 4—What additional tests, studies, follow-up, or recommendations might be warranted at this time or in the near future?)

Continued cognitive assessments at intervals following his hospitalization would be important to (1) track his improvement clinically, (2) assess for his readiness to care for himself outside of a monitored setting (being mindful of the fact that he lives alone), and (3) guide whether further, more comprehensive, cognitive assessment batteries may be indicated in assessing whether he, at his baseline, has a degree of cognitive impairment. Further laboratory and imaging studies may be necessary, ultimately, to fully characterize the extent of his cognitive status and rule out any contributory reversible causes. MRI of brain, for example, could provide data regarding extent of cortical atrophy, if any. MRI could also provide information regarding whether his mammillary bodies have undergone any volume loss which would be consistent with Wernicke encephalopathy, development of which is increased in the setting of chronic alcohol use.

Additionally, educating both the patient and his family about the risks of alprazolam (and other medications such as opioids) use in older adults, as well as the risks of alcohol use, is imperative. Coordinating care with his other clinicians will also be essential to ensure that all providers are aware of this patient's particular challenges and his now increased risk of delirium in the future.

Finally, a comprehensive psychiatric evaluation to assess for PTSD, depression, and anxiety and help plot a treatment course would be helpful. Knowing that he has been historically resistant to this, perhaps guiding him toward a veterans-based provider or program may serve to lessen some of the stigma and increase his likelihood of participation.

Case 2 Analysis Mr. R. presented with a clinical picture of delirium most likely caused by benzodiazepine and/or alcohol withdrawal, in addition to other potential contributors related to his recent surgical procedure. Other underlying psychiatric disorders, such as anxiety, depressive, trauma-related, and/or major or mild neurocognitive disorder, would be impossible to rule out in the context of his active delirium, and this would need to be explored when his delirium has resolved. A comprehensive psychiatric evaluation to assess for psychiatric disorders and provide adequate management, as well as strategies to minimize stigma and increase his likelihood of participation in treatment, are crucial. Educating both Mr. R. and his family about the risks of benzodiazepine, alcohol, and other medication use (such as opioid use) in older adults is essential. Coordinating care among his clinicians will be critical to ensure that providers are aware of his increased risk of develop-

ing delirium. Serial cognitive evaluations, a more comprehensive neuropsychological assessment battery, if needed, or further laboratory and neuroimaging studies, may be necessary to rule out any modifiable and non-modifiable risk factors for delirium in this case. (See ► Chap. 17)

16.3 Key Points: Substance Use Disorders in Late Life

- Substance use disorders in older adults are difficult to recognize and are associated with worse outcomes than in younger adults.
- Studies show that older adult patients who suffer from alcohol and other substance (e.g., benzodiazepine, opioid; illicit) use disorders enter treatment at a frequency less than their younger counterparts and are uniquely vulnerable to medical and social consequences of substance use.
- Older adults have various systemic medical comorbidities, and prescription opioids are often prescribed to treat these conditions; this may account for a large part of the increase in opioid prescriptions to older adults. Therefore, use of illicit drugs and misuse of prescription medications especially opioids is prevalent in older adult populations.
- Older adults tend to misuse prescription medications to manage pain, anxiety, and insomnia rather than to get "high," unlike their younger counterparts.
- Older adults are more likely to deny problems with opioids and are less likely to seek help for opioid use disorder, and thus opioid use disorders often may go undiagnosed or underreported in older adults.
- Providing education to the patient and family about the risks of substance use in older adults is an essential step.
- Coordinating care with the patient's clinicians will also be essential to ensure that all providers are aware of the patient's particular challenges and care needs in prescribing and clinical monitoring.
- A comprehensive psychiatric evaluation to assess for comorbid psychiatric disorders is needed in these patients, with comprehensive psychiatric management of all psychiatric comorbid illnesses simultaneously with management of substance-associated conditions.

16.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. What is the mechanism of action of acamprosate?

A. Competitively antagonizes mu-opioid receptors
B. Irreversible inhibition of aldehyde dehydrogenase
C. Central glutamate and GABA modulation
D. Reuptake inhibition of norepinephrine and dopamine
E. High-affinity nicotinic acetylcholine receptor agonist

Answer: C

Naltrexone is hypothesized to competitively antagonize mu-opioid receptors, decreasing reinforcement from endogenous opioids (alcohol) and blocking binding of exogenous opioids (e.g., heroin); thus statement A is incorrect. Irreversible inhibition of aldehyde dehydrogenase, resulting in toxic accumulation of acetaldehyde when alcohol is consumed, reflects the mechanism of action of disulfiram, not acamprosate, which makes statement B incorrect. Reuptake inhibition of norepinephrine and dopamine is the proposed mechanism of action of bupropion relating to smoking cessation, and therefore statement D is incorrect. High-affinity nicotinic acetylcholine receptor binding, producing agonist effects, is specific for varenicline used for smoking cessation, and statement E is incorrect. Central glutamate and GABA modulation is the proposed mechanism of action of acamprosate, and thus statement C is correct.

MCQ 2. What is the criterion for "severe" substance use disorder per DSM-5?

A. Tolerance
B. Withdrawal
C. Six or more of DSM-5 criteria, must include both tolerance and withdrawal
D. Eight or more DSM-5 criteria, need not include tolerance and withdrawal
E. Six or more of DSM-5 criteria, need not include tolerance and withdrawal

Answer: E

The presence of 2–3 DSM-5 diagnostic criteria mark a "mild" substance use disorder, while 4–5 criteria indicate a "moderate" substance use disorder, and 6 or more criteria denote a "severe" substance use disorder. Although tolerance and withdrawal both represent one of the 11 distinct DSM-5 criteria for substance use disorder, they are not necessary nor sufficient for one to have a significant disorder relating to substance use. Therefore, the correct answer is E.

MCQ 3. Which is the preferred class of antidepressants for a chronic pain indication in geriatric psychiatry?

A. Monoamine oxidase inhibitors
B. Tricyclic antidepressants
C. Selective-serotonin reuptake inhibitors
D. Bupropion
E. Serotonin-norepinephrine reuptake inhibitors

Answer: E

Monoamine oxidase inhibitors, although infrequently used in the geriatric population, have limited effectiveness for the treatment of chronic pain. Tricyclic antidepressants, though effective for chronic pain, should be avoided in geriatric patients because of their anticholinergic properties that can predispose to delirium, cardiotoxicity, and urinary retention. Although there has been a lack of evidence to prove that selective-serotonin reuptake inhibitors and bupropion are

effective in the treatment of neuropathic pain, the serotonin-norepinephrine reuptake inhibitors (duloxetine and venlafaxine) have demonstrated efficacy in neuropathic pain; moreover, duloxetine has been shown to reduce pain from osteoarthritis, chronic low back pain, and fibromyalgia in addition to diabetic neuropathy. Therefore, the correct answer is E.

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Delirium in Older Adults

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17.1 Background

17.1.1 Definition

Delirium has many descriptive terms and synonyms (see Table 17.1). "Confusion" or "acute confusional" state is a common term for delirium, which encompasses global cognitive dysfunction. The term "delirium" is a consensus term supported by both the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5), and the *International Classification of Diseases, 10th Revision* (ICD-10), systems [1, 2]. According to the DSM-5, the essential "core" or "defining" feature of delirium is a disturbance of *attention and awareness* that is accompanied by a sudden or acute change in baseline cognition, which cannot be better explained by a major or mild neurocognitive disorder [1]. Fig. 17.1 highlights the key DSM-5 and ICD-10 diagnostic criteria for delirium. For a complete review of these criteria, the reader is referred to the DSM-5 and ICD-10 manuals [1, 2].

Table 17.1 Synonyms for delirium

Descriptive terms for delirium	Acute cerebral insufficiency
	Acute confusional state
	Acute global cognitive dysfunction
	Altered mental status
	Confusion
	ICU psychosis
	Terminal restlessness (in palliative care patients)
	Toxic metabolic encephalopathy
	Sundowning

17.1.2 Epidemiology

In the setting of a general hospital admission, the incidence of delirium in older adults ranges from 6% to 56% [3]. Based on hospital setting, the incidence is higher in more specialized populations such as postoperative, intensive care, and palliative care settings. Postoperative delirium occurs in 15–53% of geriatric surgical patients [4]. Under-recognition is a significant problem; it is estimated that one-third to two-thirds of delirium cases go unrecognized by both physicians and nurses [5, 6]. Some authors found that delirium is particularly underrecognized in the intensive care unit, where incidence of geriatric delirium can reach 80% [7, 8]. Approximately 90% of terminally ill patients have delirium before death that is often underrecognized, which can interfere with assessment of other clinical problems [9, 10]. The overall prevalence of delirium in the community setting is 1–2% [11], but its presence in patients who, by definition, are not in an acute medical facility indicates cognitive dysfunction not due to a progressive neurocognitive disorder. It may result from undiagnosed illness or represent toxicity from chronic psychotropic medications, and may be misattributed to "dementia" or "senility" and not receive an appropriate assessment. In the emergency department, delirium is present in 8–17% of geriatric patients, whereas in nursing homes, up to 40% of residents may have delirium at any given time, reflecting the neurocognitive effects of their acute and chronic illnesses and

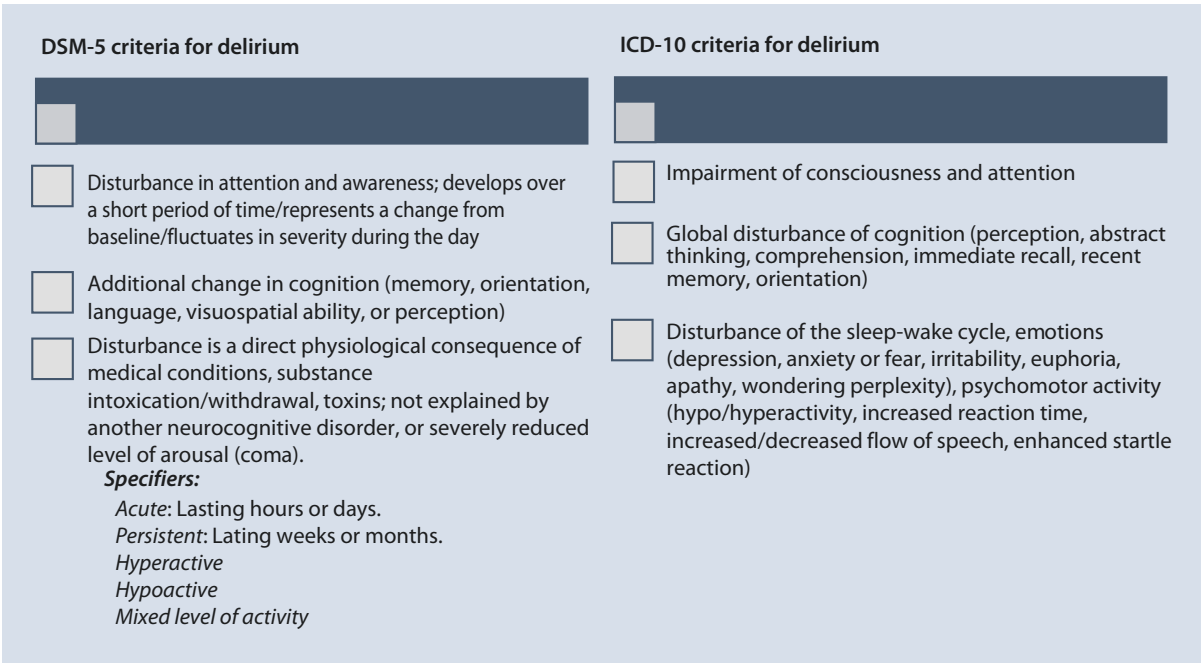


Fig. 17.1 Diagnostic highlights of the DSM-5 and ICD-10 criteria for delirium [1, 2]

treatment, or be additional cognitive dysfunction superimposed on a major neurocognitive disorder [11].

Although the delirium subtypes (hypoactive, hyperactive, mixed) will be detailed later in the chapter, the relative frequency of the subtypes may vary depending upon the setting. One study found that the overall prevalence of delirium in surgical and trauma patients was 70%, with two-thirds experiencing the hypoactive delirium [12]. The prevalence of hyperactive delirium in this population was quite low. In another study, hypoactive delirium was much more frequent in emergency departments but was missed by emergency physicians in 76% of the cases [6]. Over 90% of cases of delirium that were missed by emergency physicians were also missed by hospital physicians at the time of admission in this study [6]. This lack of recognition has serious consequences, which can prolong the severity of delirium and lead to permanent cognitive deficits and premature death [6].

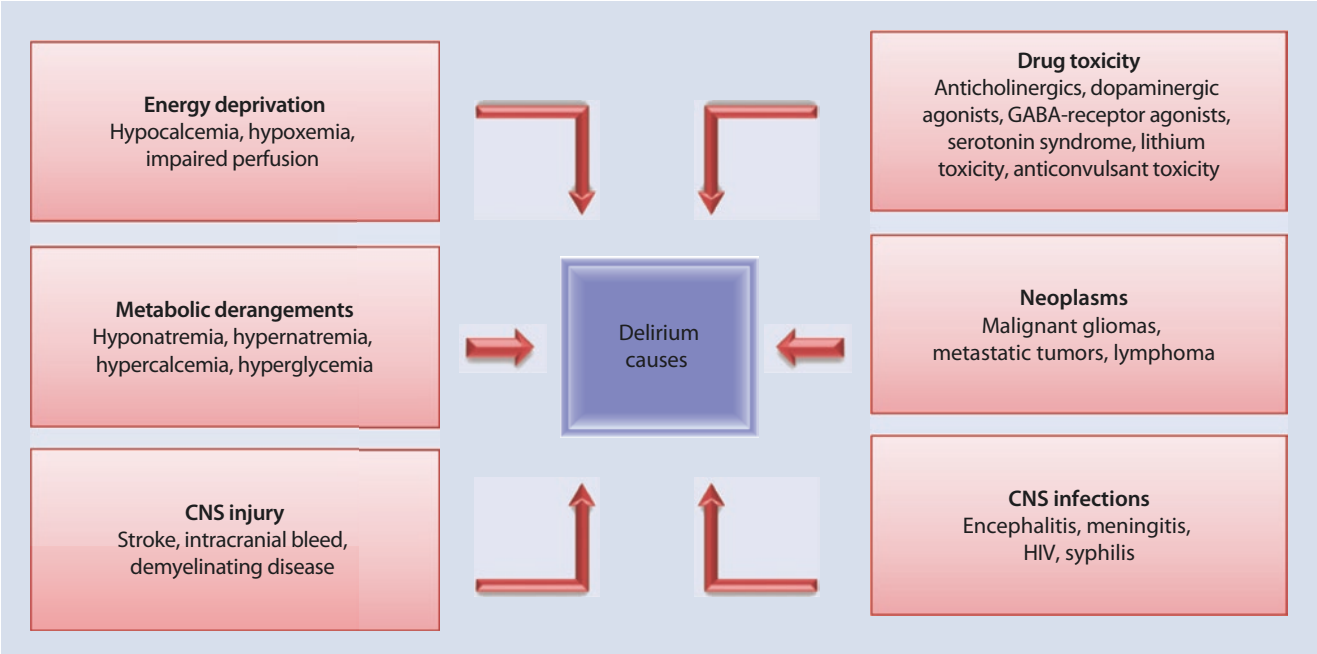
17.1.3 Etiology and Risk Factors

The etiologies of delirium are often multifactorial (with many patients having multiple causes simultaneously), and they reflect the pathophysiological consequences of acute systemic medical and/or surgical conditions and medication and/or substance effects. A complex interaction among multiple risk factors (see ◘ Fig. 17.2) can trigger development of delirium. Predisposing (non-modifiable) and precipitating (modifiable) factors for geriatric delirium include advanced age, male sex, premorbid cognitive impairment (including mild neurocognitive disorder), substance use, central nervous system diseases, cardiovascular events, infections, dehydration and other metabolic abnormalities, medications, poor nutrition, sensory deprivation (e.g., impaired vision and/or hearing), sleep deprivation, and low level of physical activity [3, 13–15]. Among geriatric patients, one of the most prominent risk factors for delirium is premorbid major or mild neurocognitive disorder. A preexisting major neurocognitive disorder (formerly dementia) is present in as many as two-thirds of patients with delirium [3].

Teaching Point

It is important to recognize that the more predisposing factors that the patient has, the fewer precipitating factors are needed to tip the "sensitive balance" in older adults leading to the development of delirium.

Multiple risk factors and their complex interactions contribute to the development of delirium. A systematic review of 27 prospective studies assessing delirium risk factors in patients over 50 years of age revealed major neurocognitive disorder, depressive disorders, visual impairment, and abnormal serum sodium levels to be significantly associated with the onset of delirium [3]. This same review also found multiple studies with much methodological heterogeneity that found alcohol abuse, impairment in activities of daily living, auditory impairment, male sex, and severe systemic medical illness to be significantly associated with delirium. A more recent meta-analysis of nine cohort and two case-control studies in patients 55 years and older revealed that although most results were limited by significant methodological heterogeneity, eight risk factors were significantly related to the development of delirium [13]. These included major neurocognitive disorder (formerly dementia), urinary



◘ **Fig. 17.2** Central nervous system (CNS) insults and delirium

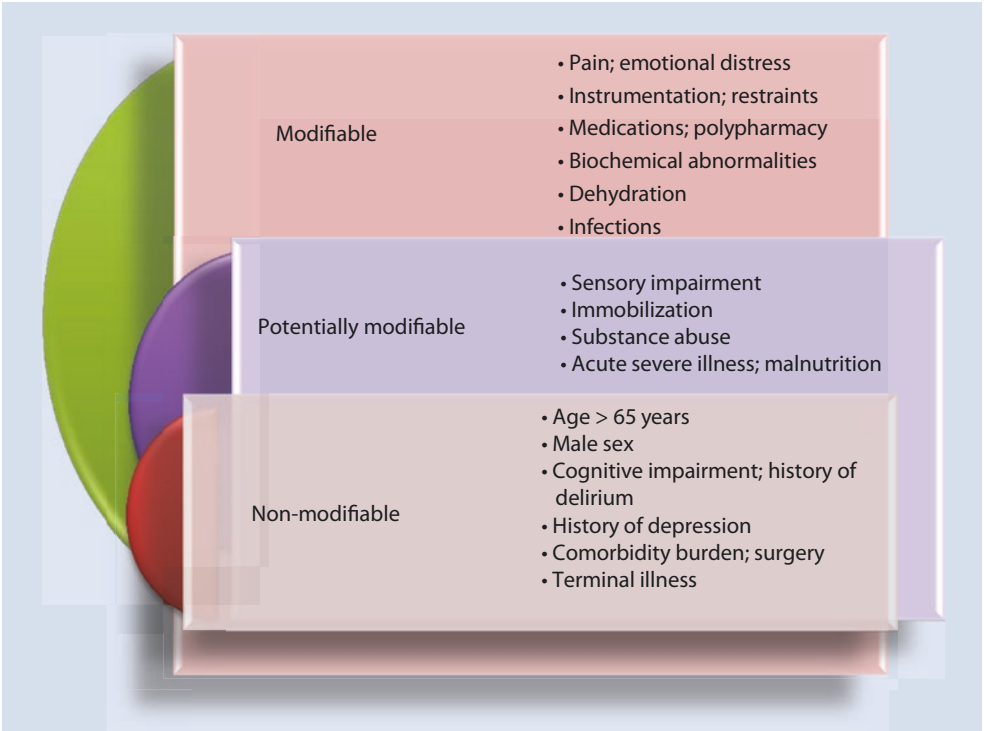


Fig. 17.3 Common modifiable, potentially modifiable, and non-modifiable risk factors for geriatric delirium [3, 13–15]

catheterization, visual deficit, longer hospital stay, increased severity of systemic illness, polypharmacy, lower serum albumin, and older age. Some of these factors are precipitating (modifiable or potentially modifiable), which are targets for preventative interventions [3]. Figure 17.3 shows some common modifiable, potentially modifiable, and non-modifiable risk factors for geriatric delirium. Common medications associated with delirium are presented in ▶ Chap. 28, Table 28.3. Protective factors for delirium include timely recognition of at-risk patients and targeted multicomponent interventions.

17.1.4 Pathophysiology

Historically, delirium has been considered a disorder of the brain which did not correlate with any particular gross anatomic pathology. Delirium is usually multifactorial, and each individual episode is believed to have specific and, sometimes, discrete etiological contributors sufficient to trigger delirium, but the search for a single mechanism for delirium to explain the "final common pathway" remains inconclusive [12]. Evidence suggests that multiple biological factors interact in delirium, resulting in disruption of neuronal networks, leading to acute cognitive dysfunction [12].

Some of the main hypothesized mechanisms contributing to delirium involve neurotransmitters, infections, inflammation, physiologic stressors, metabolic derangements, electrolyte disorders, and medications/substances [12] (see Fig. 17.2). Many neurotransmitters are likely involved in delirium, but a relative acetylcholinergic deficiency and/or dopamine excess (often present simultaneously) are the most commonly implicated [12]. Serotonin has also been implicated in delirium, as evidenced by delirium being common in the presentation of serotonin syndrome. Infections and the associated systemic inflammatory responses may result in a cascade of central nervous system neuroinflammation triggered by inflammatory cytokines, leading to endothelial activation, impaired blood flow, microglial over-activation, and neurotoxic responses, with neuronal apoptosis and injury, which may manifest as a delirium syndrome. The central nervous system can also be activated by peripheral inflammation through several routes, including vagal afferents and circulating pro-inflammatory cytokines, leading to disruption of the blood-brain barrier, endothelial activation, and microglial over-activation [12]. Local and distant pathophysiological factors in delirium together account for overall and regional cerebral perfusion abnormalities, with loss of cerebral autoregulation observed in neuroimaging studies [12]. In most cases of delirium, "anatomical" structural brain scans are normal, whereas "functional" scans (e.g., electroencephalogram) are usually abnormal. Electroencephalography usually reveals diffuse slow-wave activity.

Delirium can occur at any age, but the extremes of the age spectrum (the young and the old) are at the highest risk. Older adults are more susceptible to delirium when biological stressors cause persistent microscopic damage to neuronal cell bodies, dendrites, receptors, and microglia; in a more macroscopic sense, delirium is associated with the impact of cerebrovascular disease and/or traumatic brain injury, particularly in those patients with premorbid cognitive impairment [12]. Some patients may fully recover from an episode of delirium, and some develop persistent neurological (including cognitive) damage [16]. Because neurocognitive disorder due to Alzheimer disease may represent a state of neuroinflammation

induced by pro-inflammatory amyloid plaque, the superimposition of more neuroinflammation plausibly could accelerate neurocognitive decline, explaining why some Alzheimer patients exhibit a more rapid downward trajectory after experiencing delirium. Understanding the pathophysiological mechanisms leading to persistent neurological damage from delirium will advance the concept of risk stratification, cognitive reserve, and future therapeutic approaches.

17.1.5 Motor Subtypes of Delirium and Clinical Presentation

According to the patient's symptoms, delirium can be classified into three motor subtypes [17]:

- Hyperactive-hyperalert (i.e., the patient is confused, restless, and agitated)
- Hypoactive-hypoalert (i.e., the patient is confused, lethargic, and often appears depressed)
- Mixed level of activity (i.e., with alternating periods of both hyperactivity and hypoactivity)

In some studies, mixed delirium is the most common subtype of delirium [17]. The prognostic significance of the motor subtypes remains unclear, with conflicting results. Marcantonio et al. [18] reported that hyperactive delirium is associated with the highest mortality rate, while Rabinowitz [19] reported that the hypoactive subtype had the worst prognosis. The conflicting results may reflect data from different clinical settings and differences in recognition. Hypoactive delirium is more likely to go unrecognized, resulting in delays in diagnosing serious underlying infectious or metabolic disorders precipitating the delirium, whereas nurses, aides, and family are less likely to miss agitated, hyperactive delirium. However, interventions to manage delirium, such as restraints and tranquilizers, are themselves associated with complications that may affect prognosis.

Delirium represents an acute change from the patient's baseline cognitive status, develops over a short period of time (usually hours to a few days), and tends to fluctuate in severity during the course of a day (see ◘ Fig. 17.1). The basis for the fluctuations in severity and level of arousal remains unknown. The severity of delirium follows a continuum that should not be confused with the level of arousal; "hypoactive" delirium can be as severe as "hyperactive" delirium, and researchers have even recognized a state of subsyndromal delirium (pre-delirium).

Subsyndromal delirium falls between the baseline cognitive state and a full-blown, syndromal delirium [11] and occurs in 13–19% of medical inpatients [20, 21]. However, this distinction is clinically challenging, given the fluctuating course of delirium, as clinical manifestations may range from a spectrum of normality to subsyndromal and to full syndromal delirium during a short period of time, all within an overall episode of delirium. Full syndromal delirium has been found to have significantly poorer clinical outcomes, compared with subsyndromal delirium [22]; subsyndromal delirium was found to have poorer outcomes compared with cognitively normal individuals [23]. Engaging the patient in a conversation and asking interviewing questions that require attention and organized thought can provide clues to the possibility of delirium and subsyndromal delirium without performing a formal screen. The hypoactive subtype of delirium is more common than the hyperactive delirium in older orthopedic patients and is associated with worse outcomes such as nursing home placement and mortality [18, 24, 25]. Nevertheless, hypoactive delirium is more likely to be underrecognized, especially when drowsiness may be attributed to psychotropic medications and/or misattributed to an episode of depressive disorder.

Teaching Points

Subsyndromal delirium is a condition of clinical interest which predicts outcomes that are between those with symptoms fully meeting diagnostic criteria for delirium and those without any symptoms of delirium. Although subsyndromal delirium is a useful research construct, it is not included in current clinical diagnostic criteria for delirium because of the frequent fluctuation in symptoms over short period of time leading to difficulties with diagnostic precision. However, the DSM-5 category of "other specified delirium" has a designation of "attenuated delirium syndrome," which applies in cases of delirium in which the full diagnostic criteria are not met [1]. Given that delirium fluctuates dramatically over time, confirming a diagnosis which meets full diagnostic criteria for delirium could depend on when the clinician captures a "window period" of more severe delirium symptoms.

Fluctuations among the three delirium subtypes commonly occur because none of the subtypes of delirium are necessarily stable over time [26]. Regardless of the motor subtype or severity, delirium is typically a medical emergency, as it may represent potentially life-threatening organ system dysfunction (e.g., myocardial infarction, stroke), metabolic derangement (e.g., acute hepatic or renal dysfunction), infection, drug intoxication/withdrawal, drug-drug interaction, and/or adverse drug reaction (see ◘ Fig. 17.2). For example, worsened parkinsonism associated with antipsychotic medication use should alert the clinician about the associated dysphagia and the risk of aspiration, which in turn could precipitate delirium. The anticholinergic activity of olanzapine administered in a patient with prostatic hypertrophy may contribute to urinary retention, which could lead to delirium. The self-neglect associated with major depressive disorder may lead to the patient not taking his or her antiplatelet therapy, resulting in stent occlusion and acute coronary ischemia and thus leading to delirium.

As mentioned previously, delirium can be specified as the hyperactive-hyperalert, hypoactive-hypoalert, or mixed subtype, in which patients may rapidly switch from one type to another. The hyperactive subtype is often associated with medication side effects [27]. Alcohol and other substance use disorders are often associated with the hyperactive subtype

of delirium, especially with withdrawal from sedating substances (alcohol, benzodiazepines). The hypoactive subtype may occur more frequently in patients with severe metabolic abnormalities (e.g., hepatic failure, hypoxia, hypoglycemia, electrolyte abnormalities) and is often underrecognized in geriatric patients. These patients often appear lethargic and confused. Although hallucinations, delusions, language abnormalities, mood lability, and sleep disturbance may occur more frequently in hyperactive patients [28], these symptoms can occur in hypoactive patients as well. A study on delirium patients in a palliative care unit has shown that cognitive profiles were similar across the three subtypes, but mixed cases usually had more severe delirium and differed in the expression of several non-cognitive features (sleep-wake cycle disturbance, hallucinations, delusions, and language abnormalities), although those with no motor alteration experienced less severe delirium [29].

The patients with hyperactive delirium manifest with psychomotor hyperactivity, abnormal alertness and arousal, and inappropriate startle responses to irrelevant stimuli [30]. The patient may stay in bed, not keep clothes on, and become violent when directed or resisted. This may be mistaken for a manic episode with or without psychotic features. The patients with hypoactive delirium manifest with psychomotor hypoactivity and drowsiness [30]. The patients may sleep excessively, become difficult to arouse, and have hallucinations and disturbed vocalization (e.g., muttering quietly). They may be mistaken for patients with major depressive disorder or schizophrenia. Hypoactive delirium also can be mistaken for drowsiness related to the acute illness or surgical intervention and can be masked as well as caused by opioids, sedative-hypnotics, and first-generation antihistamines.

17.1.6 The Neuropsychiatric Symptoms of Delirium

Meagher et al. [31] investigated the neuropsychiatric symptoms associated with delirium and determined that sleep-wake cycle disturbance was the most frequent (73%), while delusions were the least frequent symptom (9%). Within the category of cognitive symptoms associated with delirium, inattention was the most frequent (73%), while disorientation was the least frequent symptom (42%). Other symptoms associated with moderate or severe severity of delirium included visuospatial deficits (64%), long-term (64%) and short-term (53%) memory deficits, psychomotor retardation (37%), psychomotor agitation (27%), perceptual disturbances including hallucinations (26%), language disturbance (25%), thought process abnormalities (22%), and affect lability (18%) [31]. Interestingly, in this study, delirious patients with psychosis had either perceptual disturbances or delusions, but not both, and neither delusions nor hallucinations were significantly correlated with cognitive symptoms [31]. Some investigators believe that delirium may trigger, uncover, or exacerbate psychotic symptoms, which may arise due to underlying brain dysfunction. In this view, Charlton and Kavanau [32] suggest that in less severe forms of delirium where the actual syndrome of delirium may be missed, the overt psychotic symptoms caused by delirium such as hallucinations, bizarre delusions, and thought disorder can be the only predominant clinical manifestation of delirium.

Teaching Point

Although the core features of delirium are adequate to make the diagnosis, clinicians must be aware of the frequency of other symptoms, such as psychotic symptoms and profound sleep disturbance, which may dominate the clinical picture. Focusing on these symptoms out of context may lead to under-recognition of the underlying core symptoms of delirium. This is particularly true with the hypoactive form of delirium.

17.1.7 Recognition of Delirium

Gold Standard: Psychiatric Evaluation

The diagnosis of delirium is made on clinical grounds. Because delirium affects the cortex diffusely, it can have a widely variable clinical presentation with neuropsychiatric symptoms such as cognitive, mood, anxiety, and psychotic symptoms being central in the delirium presentation. Due to the diffuse nature of the cortical pathology, it is axiomatic that *delirium can result in any psychiatric symptom(s).* Therefore, the clinician must differentiate delirium from other conditions with similar and/or overlapping symptoms. Consequently, delirium is often missed, misattributed, and underdiagnosed, and referral to psychiatric consult services may help with case-finding recognition and consideration of psychiatric comorbidity. Disruptive behavior is the main reason for referral to psychiatric consult services in hospitalized patients with delirium [33]. Delayed psychiatric consultation due to nonrecognition of delirium is related to factors such as older age, history of major neurocognitive disorder, and clinical presentation of hypoactive delirium [33]. Clinical practice guidelines have been developed to improve recognition of delirium [34–37].

Because delirium is characterized by an acute (usually over hours to days) change in baseline cognition, behavior, and function in mental status, evaluating a patient with delirium involves obtaining collateral information from family members, other caregivers, or staff members over the previous 24–48 hours.

Patients with delirium demonstrate fluctuating attention, awareness, and level of consciousness. This fluctuation in attention and awareness can result in conflicting reports from various caregivers at different times about the patient's mental status; the fluctuation over time is a *sine qua non* in delirium diagnosis, as other psychiatric syndromes tend to be more persistent in symptom manifestations. Fluctuations in other cognitive abilities, including memory, language, and organization, are also common. This pattern, combined with disorientation to date, place, person, and circumstances and decreased nighttime environmental cues, can create an

especially hazardous situation in patients who are at risk for falling and/or pulling out an intravenous line, Foley catheter, or nasogastric tubing or disturbing surgical wound dressings. Disorientation can go unrecognized if patients are not directly asked for this information. For example, family members and other caregivers may assume that a patient is fully oriented only to be alarmed when the patient insists that he or she is in a another geographic location and that the date is years earlier.

The psychiatric evaluation of delirium typically includes examining levels of arousal, psychomotor activity, affect, perceptual disturbances, cognition (e.g., orientation, attention, memory, language), judgment, and insight. Right from the start, certain clues to suggest delirium include a patient falling asleep during the interview, staring off into space, lethargy, and decreased psychomotor activity, which are abnormal in patients with only major neurocognitive disorder but can be common in hypoactive delirium. However, inappropriately falling asleep in the middle of a conversation with the interviewer can also occur from oversedation with opioids or other psychoactive medications and can result from sleep deprivation, which can occur in all hospital settings but is most severe in intensive care. Because major or mild neurocognitive disorder is the most common predisposing factor for delirium in older adults, it is common to encounter patients with delirium superimposed on complex neurocognitive disorders such as a major neurocognitive disorder. A clinical history of recurrent delirium should raise the suspicion for a preexisting major neurocognitive disorder. Unlike the rapid onset and fluctuating course of delirium, the onset of major neurocognitive disorder is typically insidious and not associated with fluctuations in mental status, except in Lewy body disease, which is one of the core features, and some acute presentations of major neurocognitive disorder following large strokes. (See ▶ Chaps. 20 and 21.) A change from baseline cognition and function is often key to confirming the diagnosis of delirium in patients with preexisting cognitive deficits.

In evaluating delirium, the clinician should also assess for sleep-wake disturbance, anxiety, mood disturbances, and agitation (in the hyperactive subtype) or apathy (in the hypoactive subtype). Clinicians should ask the patient, family (if present), and nurse about the presence of vivid dreams, nightmares, and/or poor sleep quality during the previous 24–48 hours, although many patients have little recollection of the night before. New-onset mild disorientation, hypervigilance, hypersensitivity to environmental stimuli, incontinence, falls, dysphagia, dysarthria, and refusal to mobilize can represent the relatively subtle manifestations of subsyndromal delirium, which then can progress to more dramatic agitation, anxiety, or psychotic symptoms as the patient transitions into syndromal delirium.

Insomnia, anorexia, and psychomotor changes are neuropsychiatric symptoms that can present not only in delirium but also in major neurocognitive disorder and major depressive disorder. During the psychiatric evaluation, presence of poor attention and distractibility, acute new-onset visual hallucinations, and behavioral disturbances, such as "picking at the air" or disrobing, helps differentiate delirium from a major neurocognitive disorder. Dramatic changes in attention and level of consciousness are not expected in patients with a major depressive disorder, unlike delirium, which has characteristically fluctuating mental status disturbances. ◘ Table 17.2 summarizes common findings in the psychiatric examination of a patient with delirium.

Affect The affect of the delirious patient tends to be labile, with rapid fluctuations between elated and depressed states. This can be similar to the affect in major neurocognitive disorder, but the magnitude of the fluctuations is usually greater in delirium. Patients may seem at times to be facetious. The blunted affect of patients with hypoactive delirium may be mistaken for a depressed mood.

Misperceptions, hallucinations, and delusions Altered perceptions can cause disturbing experiences for a patient with delirium. A plausible explanation is that the impaired attention and distractibility may result in improper registration and recollection of the environment. Disturbances of the shape perception (e.g., micropsia or macropsia, where objects appear smaller or larger than normal, respectively) and size (e.g., Lilliputian hallucinations, where miniature people and objects appear) are also characteristic of the perceptual disturbances in delirium.

In delirium, visual hallucinations are more common than auditory hallucinations, whereas in psychotic disorders (e.g., schizophrenia) auditory hallucinations are more common. Hallucinations of animals and insects occur in alcohol withdrawal delirium, drug-induced delirium, and delirium due to other toxic states. They tend to become worse at night and provoke fear and agitation which can lead to application of physical or chemical restraints, both of which can themselves exacerbate the syndrome of delirium.

Delusional misidentification syndromes are delusional beliefs that occur in patients who believe that their milieu or people around them are changed. Common experiences include:

- Reduplicative paramnesia: the patient believes that his or her current environment is relocated to another geographic site (e.g., the patient's hospital room is in the patient's home). The altered perceptions may also play a role in the paramnestic experiences so that, for example, the patient who believes that his or her hospital room is the living room may perceive the intravenous equipment as a Christmas tree.
- Capgras syndrome: the patient believes those around him or her (frequently close relatives) have been replaced by others (e.g., his or her spouse is not actually the spouse).
- Fregoli syndrome: the patient believes that the two or more persons he or she encounters are the same person in different disguises.

Misinterpretations and illusions are common in delirium but do also occur in major neurocognitive disorder. Misinterpretations due to sensory impairment (e.g., seeing a shadow on the wall could be mistaken for an intruder in the house) must be differentiated from delusions (i.e., fixed,

Table 17.2 Key findings in the psychiatric examination of a patient with delirium

Main domain	Symptom	*Comments*
Behavior	Agitation	Patients may become agitated due to their disorientation; e.g., patients may think they are at home instead of in a hospital, and nursing staff may be mistaken for intruders in the home; thus, the patients may appear as not to comply with bed restrictions (may try to climb over the bed rails to get out of bed) or with intravenous and oxygen tubing (may remove tubes as not recognized as necessary)
	Apathy, withdrawal	Patients may appear to be depressed due to blunted affect, decreased motivation, and sleep disruption; patients may periodically fall asleep during the interview
Affect	Emotional lability	Patients may display a wide range of emotions: tearfulness, sadness, anxiety, and euphoria; they can have more than one of these emotions during the course of delirium
Cognition	Attention impairment	Patients may not remember instructions and ask that questions be repeated. These patients often cannot attend to calculations that require sustained concentration. Useful screening method is asking the patient to spell a word backward or perform serial seven subtraction starting at 100 (counting backward from 100 by sevens)
	Disorientation	Disorientation to date, place, and circumstances is common
	Memory impairment	Memory deficits, especially for recent events, are prominent (e.g., unable to recall reason for hospitalization or the care provided by nursing staff thus repeating the request)
	Language impairment	Anomic aphasia, paraphasias, impaired comprehension, agraphia, and word-finding difficulties are common; sometimes naming errors is difficult to distinguish from fluent aphasia. Agraphia may be common in delirium
	Abstract reasoning deficit	Thought processes requiring sustained concentration, problem solving, and abstract reasoning are difficult. Performance on abstraction tasks, such as similarities or proverb interpretation, is poor
Perceptions, thought content, and thought process	Misperceptions, hallucinations, delusions	There may be distortions of shape or size. Visual hallucinations are more common than auditory hallucinations. Patients may have difficulty with visuoconstructional tasks such as clock drawing or copying a figure. Delusions are more fragmented, less organized, and more transient than in psychotic disorder. Thought process requiring sequential or logical analysis with sustained concentration becomes difficult
Judgment and insight	Problem-solving impairment	Patients perseverate with difficulty in changing sets and other frontal lobe executive functions. Impaired judgment and insight into his or her own personal situation is obvious
	Neglect of illness	Neglect of illness (anosognosia) is a feature of right hemisphere dysfunction, although delirium affects the brain globally. Patients are often unconcerned and can deny being ill. The impaired judgment and lack of insight into the illness may render the patient being incapable of making decisions (e.g., to give or withhold informed consent for medical investigations or treatment procedures)

false beliefs). As stated previously, visual hallucinations are common in delirium but do also occur in a number of other medical conditions. Therefore, delirium-related visual hallucinations must be differentiated from:

- Neurodegenerative causes of parkinsonian syndromes (e.g., Parkinson disease, Lewy body disease, progressive supranuclear palsy, multiple system atrophy, corticobasal degeneration).
- Illusions and visual release hallucinations (e.g., Charles Bonnet syndrome), which are typically associated with vision impairment.
- Sleep-related perceptual experiences such as hypnagogia and hypnopompia (a transition to and from sleep occurring at night or during daytime sleep episodes), which can range from barely perceptible sensory experiences to vivid hallucinations.
- Abnormal behavior during rapid eye movement (REM) sleep behavior disorder. REM sleep behavior disorder is commonly associated with advancing age, Parkinson disease, Lewy body disease, and multiple system atrophy [38].

Patients often develop frank paranoid delusions resembling those of schizophrenia, but typically they are more fragmented, less organized, and more transient, which contrast those occurring in late-onset schizophrenia, which are well systematized, persistent, and elaborated. Delusional reports of theft by a geriatric patient may seem plausible at first and can delay recognition as a psychotic symptom; however, the pattern of new onset and fluctuating course of the clinical picture suggests an episode of delirium. Delusions in major depressive disorder and bipolar disorder are usually mood congruent, with common themes of persecution,

guilt, nihilism, or grandiosity (reflective of the mood state). However, a pattern of a fluctuating course, inattention, and decreased level of awareness in these delusional patients is suggestive of delirium.

Language, attention, and memory Complex language tasks that require attention, memory, and abstract reasoning can be impaired. Anomic aphasia, paraphasias, impaired comprehension, agraphia, and word-finding difficulties are common in delirium. In delirium, naming errors can arise from global cognitive dysfunction, rather than from a focal aphasic disturbance that is common in certain types of major or mild neurocognitive disorders. Naming errors are sometimes difficult to distinguish from fluent aphasia. Agraphia (i.e., the loss of the ability to write and spell when writing) is believed to be particularly common to delirium but is not often examined. Chédru and Geschwind [39] reported that patients with delirium typically make spelling errors, word substitutions, alterations and perseverations of the last letters of the words, and spatial aberrations when writing [39]. It is possible that writing is readily disturbed because it may depend on multiple components (motor, praxis, visuospatial, kinetic, and linguistic) [39].

A prospective study on the neuropsychological course of adult hematopoietic stem cell transplantation patients has shown that those with delirium performed more poorly than the comparison group without delirium and the healthy control group on cross-sectional and trend analyses [40]. Deficits were in areas of attention, memory, psychomotor speed, and learning. In this study, most patients with delirium showed a mild decline in the clinic visit before the onset of delirium, a sharp decline with delirium onset, and variable performance in the following days, while they did not return to normative "average" performance on any test during the observation period [40]. Memory impairment, especially for recent events, is prominent (e.g., the patient cannot give reason for hospitalization or cannot recall care being given by nursing staff just shortly prior and repeats the care request).

Abstract reasoning, insight, and judgment Thought processes requiring sustained concentration, problem solving, or abstract reasoning become difficult in patients with delirium. Performance on abstraction tasks such as similarities or proverb interpretation is poor, with concrete or bizarre interpretation. On Trail Making Test and other frontal lobe executive functions, patients perseverate with difficulty in "changing set." In their less agitated states, delirium patients attempt to rationalize their hallucinations and delusions so as to give the clinician a plausible explanation for their paranoid beliefs. Neglect of illness (anosognosia) is also a feature of delirium, as it relates to right hemisphere dysfunction. Patients are often unconcerned and deny being ill. The impaired judgment may render the patient with delirium to lack decision-making capacity for medical investigations or treatment procedures. Brief lucid cognitive intervals can occur because of the fluctuating course of delirium which can pose legal challenges when there is a variable manifestation of decisional capacity. Patients may not later remember the informed consent discussion that was accomplished during the brief lucid intervals during subsequent more symptomatic periods. In many cases, patients may not be able to provide informed consent until the entire episode of delirium is resolved. Decision-making capacity for financial matters may also be impaired in a similar way. The evaluation of financial decision-making capacity should be deferred during an episode of delirium, unless there is an urgent necessity to accomplish this. There may be medicolegal ramifications in cases of delirium with fluctuating decisional capacity, especially with regard to the validity of informed consent (or refusal) for a procedure or treatment that may have been given when the patient was delirious. It is helpful to document decisional capacity and to perform a cognitive examination on every patient encounter in a delirium case to assist these determinations. When there is doubt about the patient's decisional capacity as it pertains to informed consent, the psychiatric consultant should immediately contact the primary medical team, as the surgery may need to be deferred until the patient regains decisional capacity or a legal surrogate decision-maker can provide consent on behalf of the patient.

Alterations of the sleep-wake cycle Circadian rhythm disturbance is not uncommon in geriatric patients, especially when they are admitted to the hospital. Early identification of preexisting sleep disorders and sleep aid medication use, along with proactive nursing interventions to promote uninterrupted sleep, are needed. The clinician may see a quiet, sleepy patient during the day. Sleep disturbance may represent a sleep-wake cycle disorder versus a disorder of control of arousal, and it is a useful marker of identifying a subsyndromal or full syndromal delirium. Sleep deprivation is both caused by and contributes to delirium. Delirium usually becomes worse in the evening. Nocturnal worsening of agitation is common in delirium, sometimes referred to as "sundowning," which is a term also frequently used for a specific pattern of agitation in major neurocognitive disorders (including those without delirium). Onset of sundowning has been associated with decreased light exposure and dysfunctional sleep-wake cycle.

Table 17.3 illustrates the main clinical differences among delirium, major neurocognitive disorder due to Alzheimer disease, and major depressive disorder.

Assessment Scales for Delirium

Although commonly used, the Montreal Cognitive Assessment (MoCA) and the Mini Mental State Examination (MMSE) are not by themselves screening tools for delirium or for differentiating it from major neurocognitive disorder. Brief bedside methods include testing for inattention by asking the patient to recite days of the week or months of the year backward or by serial subtractions of the same number from a starting point. Observing the patient for problems focusing, staring off into space, or losing track of questions can help in identifying delirium. Common assessment instruments used to identify (screening tools) and monitor (rating tools) delirium are presented in Table 17.4 [3, 41, 42]. Some

Table 17.3 Characteristic features of medical conditions that mimic delirium

Features	Delirium	Major neurocognitive disorder (e.g., Alzheimer disease)	Major depressive disorder	Psychotic disorder
Key clinical feature	Inattention, confusion	Memory impairment	Sadness, anhedonia	Lost contact with reality
Onset	Acute	Insidious	Subacute	Acute or subacute
Course	Fluctuating, often worse in the evening/at night	Chronic, progressive (no daily fluctuations)	Single/recurrent/ chronic episode	Chronic, with exacerbations
Duration	Hours to weeks	Years	Weeks to months	Months to years
Level of awareness/ alertness/wakefulness	Altered	Normal	Normal	Normal
Attention	Impaired; performance characterized by short attention span	Normal, except in late stages; guesses and wrong answers during testing	May be impaired; "I don't know, I can't" responses	May be impaired
Orientation	Fluctuates	Disturbed	Normal	Normal
Speech	Incoherent	Mild errors	Normal or slow	Normal, slow, or pressured
Thought	Disorganized	Impoverished	Normal	Disorganized
Hallucinations	Common (often visual)	Rare, except in late stages	Not usually	Common (often auditory)
Psychomotor changes	Present	Apathy, agitation	Present	Present
Insight	Minimize deficit	Minimize deficit despite impaired memory and executive function	Subjective cognitive deficit that exceeds objective deficit	
Reversibility	Usually, can be prolonged	Irreversible	Usually	Rarely
EEG	Moderate to severe background slowing	Normal or mild diffuse slowing	Normal	Normal
Resemblance with NPS of NCDs	Usually easily mistaken	NPS common with disease progression	Not usually	Not usually
Treatment	Directed at underlying cause and management of agitation	Few effective treatments	Antidepressants Psychotherapeutic treatments	Antipsychotics

Note: EEG electroencephalogram, *NCD* neurocognitive disorder, *NPS* neuropsychiatric symptoms

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instruments (e.g., Memorial Delirium Assessment Scale) are stand-alone tools, while others (e.g., Confusion Assessment Method) require administration of separate cognitive screens, including the MMSE and Digit Span [3].

Although a large number of delirium screening tools exist, only a small number of scales may be considered to be useful particularly in the geriatric population, such as the Confusion Assessment Method (CAM), Delirium Rating Scale-Revised-98 (DRS-R-98), Memorial Delirium Assessment Scale (MDAS), and the NEECHAM Confusion Scale (NEECHAM) (see Table 17.4) [3, 41, 42]. Delirium assessment scales differ according to the diagnostic classification system they were based on, length of time to administer, and whether they are screening scales or designed to measure symptom severity. The CAM and CAM-ICU, the gold standard for use in critically ill patient, are validated tools for frontline clinicians that can be used to identify the presence of delirium, even in a patient with a preexisting major neurocognitive disorder. The CAM includes four features: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. The CAM algorithm includes features 1 and 2 plus either 3 or 4 as indicating the presence of delirium [42]. The CAM and NEECHAM appear to be most suitable as a screening instrument, while the Delirium Rating Scale-Revised-98 (DRS-R-98) seems to be particularly useful for measuring delirium severity or monitoring change (see Table 17.4).

Table 17.4 Common assessment scales for delirium [3, 41, 42]

Abbreviation	Scale name	Type of scale	Comments
CAM	Confusion Assessment Method	Screening Diagnostic	Recommended; some training required; most widely used screening test for delirium; a four-item scale; requires the presence of acute onset and fluctuating course, inattention, and either disorganized thinking or loss of consciousness; time to administer < 5 minutes
CAM-ICU	Confusion Assessment Method for Intensive Care Unit	Screening Diagnostic	Recommended; can only be administered if the patient is arousable in response to a voice without the need for physical stimulation
DRS-R-98	Delirium Rating Scale (Revised)-98	Diagnostic Severity	Recommended; easy to use; a 16-item scale (3 diagnostic and 13 severity items); score ≥ 15 indicates delirium; severity scores range from 0 to 39 (higher scores indicate more severe delirium)
MDAS	Memorial Delirium Assessment Scale	Severity	A 10-item, 4-point observer-rated scale with scores that range from 0 to 30
CTD	Cognitive Test for Delirium	Screening	Measures cognition (orientation, attention, memory, comprehension and vigilance); can be used with patients unable to speak or write; scores range from 0 to 30 (higher scores indicate better cognitive function)
DSI	Delirium Symptom Interview	Diagnostic	A structured interview; delirium is present if disorientation, perceptual disturbance, or disturbance of consciousness is presented within the past 24 hours; time to administer very lengthy
NEECHAM	NEECHAM Confusion Scale	Screening Diagnostic Severity	A nine-item scale divided into three subscales—I, information processing; II, behavior; and III, performance—assesses vital function; total scores can range from 0 (minimal function) to 30 (normal function); score ≤ 24 indicates delirium; time to administer < 10 minutes
ICDSC	Intensive Care Delirium Screening Checklist	Screening	An eight-item scale; bedside screening tool for delirium in the intensive care unit setting; score ≥ 4 indicates delirium

Differentiation of Delirium and Unrecognized Major Neurocognitive Disorder

Delirium is not always reversible, even with aggressive medical management, and can result in prolonged delirium and/or long-term cognitive changes, especially in the geriatric population [3, 12]. Delirium superimposed on major neurocognitive disorder is common in many institutional settings. The clinician must determine whether the patient has delirium, major neurocognitive disorder separate from delirium, or delirium superimposed on a preexisting major neurocognitive disorder. One study found that the prevalence of delirium superimposed on a major neurocognitive disorder ranged from 22% to 89% of hospitalized and community populations [43]. A study on rehabilitation inpatients found that the prevalence of delirium superimposed on a major neurocognitive disorder was 8% [44]. In this study, delirium superimposed on a major neurocognitive disorder was significantly associated with a fivefold increase in the risk of institutionalization and an almost twofold increase in the risk of mortality [44]. In a Dutch study, the risk for delirium was three times greater in nursing home patients who had a diagnosis of a major neurocognitive disorder [45]. However, this correlation seems bidirectional, as older hip surgery patients with a history of postoperative delirium were found to have a nearly doubled risk of incident major or mild neurocognitive disorder, suggesting that delirium may indicate underlying major or mild neurocognitive disorder [46]. Delirium was also found to increase the rate of cognitive decline three times in patients with Alzheimer disease compared with those without delirium [47]. This suggests that pathological processes associated with delirium may cause direct neuronal injury which in turn precipitates or accelerates persistent cognitive impairment, suggesting a reciprocal relationship between major neurocognitive disorder and delirium [3]. The overall prognosis of patients with major neurocognitive disorder and superimposed delirium is worse than in those without delirium [3].

Distinguishing delirium from major neurocognitive disorder is particularly difficult in geriatric patients who develop a persistent cognitive impairment after a delirium episode [48]. This is especially difficult in patients who develop delirium in the presence of a preexisting major neurocognitive disorder, where the delirium symptoms can persist over prolonged period of time and the full resolution of delirium may not be easily identified. Memory, thinking, and language impairment are common to both syndromes, but patients with major neurocognitive disorders alone are typically alert, have a clear sensorium, and do not experience the disturbance in attention and awareness that is characteristic of delirium (see Table 17.3).

In a study exploring patients with delirium, major neurocognitive disorder, comorbid delirium-major neurocognitive disorder, and cognitively normal controls, using the scales Revised Delirium Rating Scale (DRS-R-98) and Cognitive Test for Delirium (CTD) (see Table 17.4 for common scales for delirium), delirium only and comorbid delirium-major neurocognitive disorder had comparable scores on both scales [49]. In this study, symptoms such as inattention and disorientation were more severe in the delirium-alone group compared with the major neurocognitive disorder-alone group. Spatial span backward was significantly lower in all patients with cognitive impairment (delirium alone, comorbid delirium-major neurocognitive disorder, or the major neurocognitive disorder alone) compared with controls, whereas spatial span forward was significantly diminished in delirium compared with major neurocognitive disorder, suggesting usefulness as a differentiating screening test [49].

Formal neuropsychological testing may help detect and distinguish delirium from a chronic major neurocognitive disorder. Clinically, the chronological onset and course of cognitive impairment are helpful in distinguishing between delirium and major neurocognitive disorder. The typical onset of delirium symptoms is much more rapid (i.e., usually hours to days), which contrasts with the more gradual or insidious onset in a major neurocognitive disorder. Symptom severity typically fluctuates during a 24-hour period in delirium, in contrast with major neurocognitive disorder which does not typically exhibit this temporal fluctuation. Collateral information from medical records, family members, or other caregivers may be helpful in determining whether the symptoms of a major neurocognitive disorder preexisted those of delirium.

Teaching Point

Delirium (an acute state) and major neurocognitive disorder (a chronic state) often occur together, possibly because these conditions may be pathophysiologically related (see ► Sect. 17.1.4 on pathophysiology of delirium). Considering these two conditions as mutually exclusive diagnoses does not do justice to the actual clinical picture of delirium, which is often mixed.

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17.1.8 Medical Evaluation

There is no "standard" medical workup for acute delirium, and prioritization of individual tests should be tailored to the patient's individual risk factors, taking into consideration that delirium often is multifactorial. A default diagnosis of idiopathic delirium should not be made until treatable causes have been ruled out. Dubin et al. found that four screening determinants reliably distinguished patients with acute "organic brain syndrome" (a synonym for delirium) from other neuropsychiatric disorders in an emergency department setting [50]. These were (1) disorientation, (2) abnormal vital signs, (3) clouded consciousness (decreased level of alertness), and (4) age older than 40 years with no previous psychiatric history.

In clinically ambiguous cases, the electroencephalogram (EEG) can be useful in the diagnostic workup. EEG findings may indicate generalized slowing or dropout of the posterior dominant rhythm and generalized slow theta and delta waves, findings that are more common in delirium than in advanced stages of major neurocognitive disorders. Delirium cases in which the patient's previous cognitive status is unknown may benefit from EEG evaluation, including suspicion of subclinical seizures, status epilepticus, or when delirium improvement has reached a plateau at a lower level of cognitive function than before the onset of the delirium episode. Table 17.5 provides a systematic approach to delirium assessment [51–53], whereas Fig. 17.4 (Part a and b) provides a summary flowchart by cause for the diagnostic workup of delirium.

17.1.9 Essential Role of Nurses, Other Health Professionals, and Family Caregivers

The prevention and management of delirium continue to pose a significant challenge for healthcare organizations, especially in older patients. Not only is delirium often poorly recognized and understood, but usual hospital care continues to use physical and chemical restraints that have the potential to cause more harm than benefit in older patients.

Collaborating with the entire healthcare team and including family members/significant others who can be particularly helpful to identify predisposing risk factors and to promptly eliminate or reduce precipitating factors may not only prevent delirium but decrease the severity if it occurs [54]. Best practice multicomponent, multidisciplinary interventions need to be implemented in all at-risk patients within 24 hours of admission to maximize opportunities to prevent delirium. This needs to include implementation of targeted risk-based interventions that include environmental, patient, and medical interventions, nursing education, geriatric consultation and a tailored plan for patient mobilization, reorientation, cognitive stimulation, maintenance of nutrition and hydration, sleep enhancement, and vision and hearing adaptation/correction [55]. Of importance, essentially, all of these patient interventions are considered basic nursing care that should be implemented for all patients. Educating family members and encouraging their involvement as much as possible at the bedside foster familiarity and reality orientation and offer education by the volunteers and nursing staff in important interventions they can perform. Delirium screening by nursing staff in at-risk seniors at least daily (ideally, on every nursing shift) and collaborating with the entire medical care team are critical. The medical care team needs to closely monitor and prevent/treat infection, pain, dehydration, and electrolyte disturbances, optimize oxygen delivery, nutrition

Table 17.5 A targeted stepwise approach to the medical workup of delirium in geriatric patients [51–53]

Step	Assessment	Comments
Assessment that should be performed in nearly all cases		
1	Obtain vital signs. Include oxygen saturation and core temperature. Pulse rate and type (regular v irregular) and respiratory rate should be accurately obtained by counting for at least 20 seconds	A fever of ≥ 38°C should be taken as a sign of infection until proven otherwise. True tachypnea (respiratory rate > 18) suggests an acute pulmonary process. A room-air SaO_2 < 92% implies pulmonary compromise unless the patient has known underlying chronic lung disease. A heart rate ≥ 100 beats per minute suggests possible cardiopulmonary distress. Patients with prolonged bedrest are at risk for pulmonary embolism, for which an unexplained tachycardia is the most sensitive indicator
2	Medical history	Are there underlying medical conditions that increase the risk of metabolic compromise? Examples: Diabetes, especially if on glucose-lowering medication Significant chronic lung disease that predisposes to hypoglycemia History of admissions for heart failure Chronic liver disease, with potential for hyperammonemia Any history or suspicion of drug or alcohol withdrawal? If yes, the patient should empirically receive 100 mg of thiamine before receiving intravenous glucose to prevent Wernicke syndrome *Any person suspected of diabetes mellitus should have a stat finger-stick glucose obtained*
3	Review medications	Any new medications (or dose changes in medications) with action on the CNS? Medications are the most common cause of delirium in the elderly. Patients recently started on valproic acid or on an increased dose should have a stat ammonia level obtained
4	*Targeted* stat/urgent laboratory testing, based on underlying conditions and the resulting probability of clinically significant abnormalities	A complete blood count (CBC) should be obtained in all patients. A urinalysis usually should be obtained, especially in a patient with a current or recently discontinued bladder catheter, history of prostatic hypertrophy, or urinary retention. Available evidence supports an association between urinary tract infection and delirium. Both men and women at prolonged bed rest have an increased risk for urinary retention. An electrolyte panel (Na, K, BUN, creatinine) should be obtained in patients who could have a high serum sodium (from dehydration) or hyponatremia from diuretics or the inappropriate secretion of antidiuretic hormone. Additional electrolyte studies like calcium (looking for hypercalcemia) should be targeted toward patients whose past medical history suggests increased risk (e.g., hyperparathyroidism, excessive vitamin D or calcium ingestion). A cardiac troponin level should be obtained if coronary ischemia is suspected. *Nonurgent*: folate, B_{12} levels can be obtained if erythrocyte macrocytosis is seen or nutritional deficiencies suspected. A magnesium level should be obtained in patients on chronic diuretics but is not a recognized cause of delirium.
5	*Targeted* electrocardiogram (ECG)	An ECG is indicated when coronary ischemia or an arrhythmia is suspected based on known risk factors. Because coronary heart disease is prevalent in the elderly and an atypical presentation of coronary ischemia is relatively common, an ECG is indicated in *most* cases (along with a troponin level), provided another explanation is not readily apparent
6	Poorly controlled pain	Inadequately controlled pain in patients unable to articulate their symptoms can present as delirium
Testing that should be performed only in specific circumstances		
7	*Targeted* imaging studies	Chest X-ray (CXR): if the patient has no respiratory symptoms, normal vital signs, and clear lungs on auscultation and probable etiologic factors have been identified, a CXR is not required. However, one should be obtained if readily available, since delirium is associated with an increased risk of aspiration pneumonitis and pneumonia may present atypically. Cranial imaging (computed tomography or magnetic resonance imaging): these have a low yield and should be limited to patients in whom a head injury is suspected, those taking anticoagulation in whom an intracranial hemorrhage is being considered, and those in whom new abnormal neurological findings raise suspicion of an acute stroke-like event
8	*Targeted* electroencephalogram (EEG)	In delirium, the EEG generally displays nonspecific slowing with generalized theta or delta slow-wave activity and has utility only in the rare circumstance when akinetic seizures are suspected—usually when delirium is sustained and no other causes can be identified
9	*Targeted* lumbar puncture (LP)	Rarely should a LP be performed in the evaluation of delirium. The exception is in patients with an acute or subacute neurocognitive decline unexplained by other causes and for which an encephalitis is suspected

(continued)

Table 17.5 (continued)

Step	Assessment	Comments
Miscellaneous conditions associated with delirium that should be considered		
10	Fecal impaction	If the patient has not had a bowel movement recorded for days, a rectal examination and/or an abdominal X-ray should be obtained if no other causes of delirium have been identified
	Urinary retention	Similarly, urinary retention has been associated with delirium. A post-void residual by bladder ultrasound or in-and-out catheterization should be obtained if no other causes of delirium have been identified. Note that a fecal impaction can cause urinary retention

From: *On-Call Geriatric Psychiatry book*, 2016 Springer, Chapter 11, Physical Complaints, Table 11.1. A targeted stepwise approach to the differential diagnosis of acute delirium in geriatric patients; used with permission of Springer Nature

and sensory input, and regulate bowel and bladder function. It is critical to recognize the unique vulnerability of the older patient and proactively collaborate with ancillary disciplines as needed. Nursing is in a unique role as the "24/7" bedside caregivers to provide the basic nursing interventions needed to prevent and manage delirium and to reassure and educate the family/significant others. Consulting pharmacists to minimize adverse drug interactions/reactions, rehabilitation therapists to promote function and cognition, nutritional services to ensure adequate nutrition, palliative and chaplain services to guide spiritual and end-of-life care, and social services can help address social issues.

17.1.10 Prevention

Because the etiology of delirium usually is multifactorial, strategies for prevention should be multifaceted. The primary prevention of delirium targets factors that are linked to an increased vulnerability to delirium and the associated underlying pathophysiological mechanisms. Secondary prevention to prevent recurrence and reduce severity and duration of delirium once it has occurred overlaps with treatment as well as tertiary prevention. Tertiary prevention involves minimizing complications that arise from delirium and/or its management (e.g., poor oral and nutritional intake, falls, aspiration pneumonia).

The medical team discharging the patient may promote prevention of delirium by coding "delirium, improved or recovered" as a separate illness in the medical record, including specific medical recommendations to the primary care physician in the discharge summary and detailed nursing recommendations and family education. It is common for patients to be discharged with residual cognitive deficits related to their resolving delirium; the discharging team should arrange timely follow-up with the primary care physician or psychiatrist for ongoing delirium surveillance and serial cognitive assessments over time. Patients who have recovered from an episode of delirium should be especially well monitored for outpatient medication use, with high risk/deliriogenic medications (e.g., anticholinergics, benzodiazepines, opioids) routinely avoided thereafter.

Primary Prevention

Primary prevention aims to reduce the incidence of delirium. A multitude of factors have been associated with an increased risk of developing delirium, while others represent direct insults to the central nervous system (e.g., stroke, hypoglycemia, neurotoxic medications) (see Fig. 17.2). Primary prevention must address general measures that reduce overall vulnerability, identify and correct stressors to organ system homeostasis, and promote the functional integrity of the central nervous system. The role of the psychiatrist, neurologist, or geriatrician is to help the team identify systemic medical diseases, neurocognitive disorders, and functional risk factors in the patient that can be corrected or mitigated before delirium develops. Various non-pharmacological approaches have been tried in the prevention of delirium in hospitalized patients, which will be further described.

Non-pharmacological Interventions

Although there is no strong evidence from randomized controlled trials of delirium prevention to clearly dictate clinical care [56], there is sufficient evidence that delirium can be prevented at least 30% of the time with dedicated multicomponent multidisciplinary interventions [56] and significantly reduced by geriatric consultation after hip fracture [57]. Medications, on the other hand, must be reserved for emergent situations and supportive therapy when behavioral interventions are ineffective. The American Geriatric Society (AGS), which considers delirium to be the most critical topic in the care of older adults, strongly recommends a non-pharmacological, multicomponent approach [58]. The AGS clinical practice guideline for delirium prevention in older adults shows that proactive early risk assessment decreased incident delirium during hospitalization in an analysis of seven trials with 1691 patients [59]. Risk assessment, delirium screening at least daily, and multicomponent behavioral interventions are considered best practice for delirium prevention.

Multicomponent interventions associated with delirium prevention include environmental interventions to promote reality orientation and sleep; medical interventions; medication review; assessment and management of infection, dehydration, pain, constipation, and hypoxia; and patient-centered behavioral interventions to optimize communication and

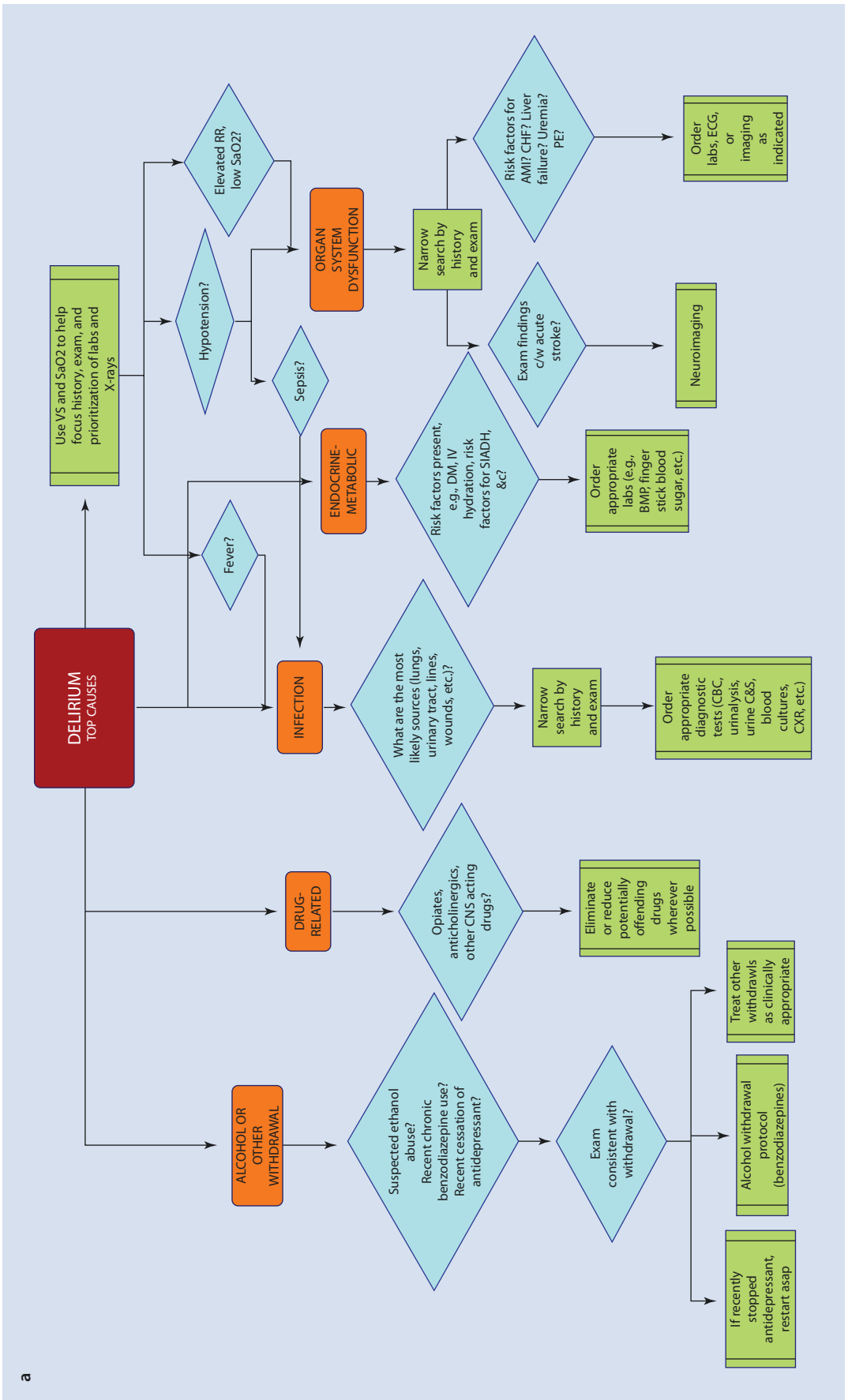

Fig. 17.4 Summary flowchart for the diagnostic workup of delirium. **a** Common causes of delirium

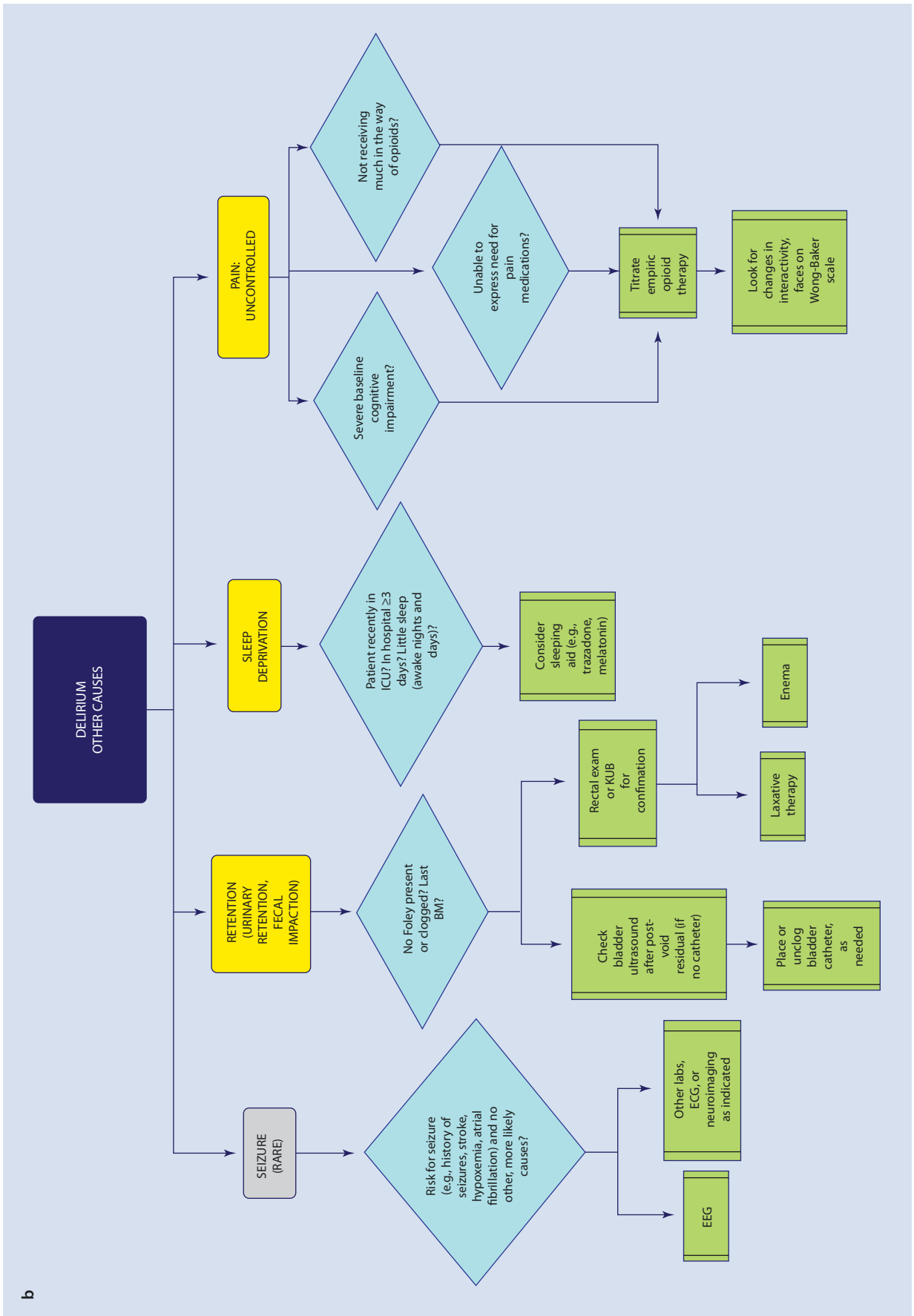

Fig. 17.4 (continued) **b** other causes of delirium

maximize physical and cognitive function. The Hospital Elder Life Program (HELP), considered the gold standard in hospital delirium prevention and management, is a multicomponent program adopted widely as best practice in the USA, Canada, and elsewhere. These programs utilize not only geriatric training and rounding with a geriatrician and/or advanced practice nurse but utilizes volunteers at the bedside daily as much as possible during waking hours to implement targeted nursing interventions. These specially trained volunteers ensure use of assistive devices as needed to optimize communication and are trained in therapeutic cognitively based communication strategies. They also provide out-of-bed mobilization and range of motion exercise, hydration, reality orientation, cognitively appropriate therapeutic activities to keep patients mentally and physically engaged, and sleep promotion. Patients on the sleep protocol are offered warm milk or herbal tea, a hand or foot massage, earplugs, eyeshields, and soothing music, while nursing staff cluster care interventions and ensure an ongoing plan for adequate rest and sleep. The National Institute for Health and Care Excellence (NICE) in the UK [55] developed HELP-inspired delirium clinical practice guidelines and included three more protocols to address the risk factors of hypoxia, infection, and pain. HELP programs have adopted these interventions and expanded the dehydration intervention to address constipation and urinary retention.

Randomized controlled trials of 1691 patients found multicomponent interventions to be associated with a decreased risk of incident delirium and accidental falls [59]. A systematic review found that the findings were replicated in 14 randomized controlled trials and matched interventional studies with over 4200 patients. Tailoring non-pharmacological interventions for the individual patient entails effective application of HELP programs. A summary of the identification and non-pharmacological approaches for delirium is presented in ◘ Table 17.6 [60]. Management strategies for delirium, once delirium has developed, are focused on secondary and tertiary prevention and symptom management, which will be further discussed.

Secondary and Tertiary Prevention

Secondary prevention strategies require optimal clinical management at the time of delirium, whereas tertiary prevention addresses the morbidity and increased risk of mortality arising as a consequence of delirium. Once delirium has developed, attention should be redirected toward preventing recurrence and reducing severity, duration, and complications. The primary prevention nursing interventions, outlined previously in ▶ Sect. 17.1.10, Primary Prevention should be applied in secondary and tertiary prevention, with emphasis on reorientation, reassurance, and redirection for agitated behavior. Providing a familiar and reassuring presence during periods of fear, anxiety, and confusion can play a critical role. Sitters can provide helpful redirection and distraction to mitigate the patient's agitation. Patients treated with antipsychotics may become calm, possibly masking hyperactive delirium that has been converted to the hypoactive form. Differentiating hypoactive delirium from fatigue or napping is essential and involves engaging the patient during the daytime and early evening in order to qualitatively assess mental status. Optimal sleep hygiene becomes especially important due to disrupted sleep-wake cycle in delirium, and a balance between close monitoring and allowing undisturbed rest must be found.

Because delirium usually is multifactorial, identification and treatment of a *single* precipitating factor may not be sufficient to remove *additional factors* that may have contributed to the onset and persistence of delirium. Medications should be reviewed in order to discontinue or minimize potentially "deliriogenic" medications. The patient's medications require careful scrutiny for potential drug-drug interactions and adverse drug reactions. The Beers Criteria (focused on medications used in North America) and the STOPP/START criteria (focused on European pharmacopeia) are commonly used tools to identify medications whose potential adverse effects exceed potential benefits in older patients, especially when safer alternatives exist. These are termed "potentially inappropriate medications" (PIM) [61] (also see ▶ Chap. 5). Anticholinergics are among the most "deliriogenic" medications and should be avoided or minimized. Anticholinergic medications have a cumulative effect and can cause a significant anticholinergic burden when taken concomitantly [60]. Antihistamines (e.g., diphenhydramine) and sedative-hypnotics (e.g., benzodiazepines) should be avoided, with the exception of benzodiazepines to manage alcohol or sedative/hypnotic withdrawal delirium. While pain is a risk factor for delirium, analgesics like acetaminophen should be employed before using opioids [62]. Nonsteroidal anti-inflammatory drugs (NSAIDS) should be used cautiously in older patients because they may injure the kidney and cause gastrointestinal bleeding. For patients with insomnia, sleep hygiene techniques and warm milk (containing tryptophan) represent a first-line approach (see ◘ Table 17.6). Melatonin 3–9 mg at bedtime can be tried [63]. Trazadone 25–50 mg or mirtazapine 3.75–7.5 mg at bedtime can be used for insomnia, but caution should be employed if the patient takes another serotonergic medication due to a theoretical risk of serotonin syndrome; these medications should not be used if the delirium episode is directly attributed to serotonin syndrome (for further management strategies in delirium, also see ▶ section Case 2 Answers, described later in this chapter, as well as ▶ Chap. 26).

Pharmacological Interventions

Antipsychotics Based on the hypothesized theory of delirium symptoms being attributed to an excess of dopamine activity, antipsychotics theoretically may help to prevent delirium. To date, published data on the use of antipsychotics for delirium prevention have been limited to surgical patients. A systematic review and meta-analysis of studies of delirium prophylaxis found considerable heterogeneity among the six eligible studies for analysis (differing settings and types of surgery; different antipsychotics, doses, and routes of administration; and different timing and duration of prophylaxis) [64]. One study used risperidone, one used olanzapine, and four used haloperidol. In a mixed-effects model, antipsychotics reduced the incidence of postoperative delirium

Table 17.6 Identification and non-pharmacological management of delirium [60]

Identification of risk for delirium	
Implement delirium prevention measures for patients: Admitted with altered level of consciousness (LOC)/delirium *or* with known risk factors for delirium Age: ≥ 70 History of cognitive impairment/delirium Functional impairment Vision impairment History of alcohol abuse Comorbidity burden (e.g., stroke, depression)	
Identification of delirium Use formal instrument, such as the Confusion Assessment Method (CAM), CAM-ICU, months of the year backward to identify delirium *Acute* onset (abrupt, within minutes, hours, shifts, days—up to 2 weeks) of *any change* in cognition (inattention, memory loss, disorientation, hallucinations, delusions): Altered and fluctuating LOC: hyperactive or hypoactive; remember lethargy, falling asleep, staring off into space, and decreased motor activity are *not normal* in older adults with major neurocognitive disorder Disorganized thinking, disorientation Inattention: assess by asking to say days of the week backward or spell WORLD backward and by observing for problems focusing, staring off into space, or losing track of questions	
Component	**Nursing intervention: identify etiology and provide supportive care**
Maintain safety	**Maintain airway; prevent aspiration, skin breakdown, and falls**
Physiologic stability Infection Hypoxia Dehydration Electrolyte imbalance Medications Pain Urinary retention Impaction Immobility Sleep deprivation Sensory impairment	Reduce psychoactive medications and polypharmacy: avoid benzodiazepines, anticholinergics, and other deliriogenic medications; monitor for side effects; consult pharmacy as needed Monitor labs to prevent electrolyte abnormalities and infection Maintain hydration/nutrition: offer fluids with each encounter, if not on IV fluids Optimize oxygenation with early mobilization, incentive spirometer and O_2 as indicated Optimize sleep and sensory input and progressively mobilize per below Proactively assess/treat pain with non-opiates and opiates for breakthrough pain Monitor for impaction or retention: ensure scheduled/prompted voiding and bowel regimen Notify physician of any acute change in behavior or mental status
Sleep promotion	Normalize sleep-wake cycle: goal is to ensure 4–6 hours of uninterrupted sleep at night Identify and maintain patient's sleep pattern/routine as much as possible (e.g., identify history of sleep disturbance/aides and notify physician) Optimize sleep-wake cycle with out-of-bed daytime activity/limited napping and quiet at night Open blinds during the day and close at night; adjust lighting to low level at night Promote bedtime ritual with warm milk/herbal tea, massage, relaxation music Cluster care and avoid unnecessary awakening; maintain quiet at night Avoid caffeine and excessive IV/PO fluids after 6 pm
Activity	Progressively mobilize to maximal potential and encourage self-care in ADLs, as appropriate Ensure/assist patient out of bed for all meals unless contraindicated Discourage napping during the day Ambulate every shift with goal to regain prior level of function as possible Review for removal of unnecessary lines (catheter, telemetry, IV lines, restraint, etc.) every shift; avoid/minimize restraints Engage in age-appropriate, meaningful activities; enlist involvement of family/identify patient-specific routines/interests and incorporate into care plan as possible Use familiar, calm music and relaxation techniques
Communication enhancement	Assess for communication deficits and provide assistive devices as needed Compassionate communication Approach in a calm, nonthreatening manner; call person by name; introduce self with each encounter Set the stage for positive interaction; smile Use active listening and one task/command/step at a time; repeat information using exact words; allow patient time to respond Search for the meaning/emotion in patient's message and respond to patient's feelings Respond to paranoid or delusional thoughts/expressions by providing comfort to the emotions (i.e., "you sound angry/scared/sad. I'm here to help, to keep you safe."); avoid arguing and rationalizing and do not take it personally Redirect agitated patient with validation and distraction (e.g., reminiscence, walk, sweets)

Table 17.6 (continued)

Identification of risk for delirium	
Reality orientation	Reorient patient frequently within normal conversation; do not quiz patient Provide simple explanation of nursing care and all activities with each encounter Foster familiarity: encourage family/friends at bedside; familiar items from home; consistent caregivers and routine as possible; minimize relocations, especially at night Clock and updated care board with date/orienting information; be sure patient can see it
Sensory stimulation regulation	Optimize sensory stimulation: ensure patient can see and hear with hearing aid/amplifier, glasses, and communication board Ensure quiet room with good lighting to differentiate day from night (blinds open in the day and close at night) Turn off TV if patient not engaged; use familiar music or relaxation tapes Limit visitors as needed; minimize noise, interruptions, and distractions Cluster care to limit unnecessary awakening, especially later in the day when patient is fatigued

From: *On-Call Geriatric Psychiatry book*, 2016, Chapter 18: Acute inpatient medical settings, Table 18.1. Identification and non-pharmacological management of delirium; used with permission of Springer Nature

(OR 0.44, 95% CI 0.28–0.70) [64]. Although olanzapine significantly reduced the incidence of postoperative delirium, patients randomized to olanzapine who went on to develop delirium experienced a greater severity and duration than the placebo group. Haloperidol used in elective hip surgery patients in a randomized, placebo-controlled trial failed to show a significant difference in the incidence of delirium but did show a reduction in the number of days with delirium, the overall severity of delirium, delirium duration, and hospital length of stay [65]. However, in a 2016 systematic review and meta-analysis comparing antipsychotics with placebo or no treatment for delirium prevention after surgery, there was no significant effect on delirium incidence across the groups (OR 0.56, 95% CI 0.23–1.34) [66]. Antipsychotic use was not associated with change in delirium duration, severity, or hospital or ICU length of stay, and no association with mortality was detected (OR 0.90, 95% CI 0.62–1.29). The authors of this review concluded that the evidence did not support the use of antipsychotics for prevention or treatment of delirium at that time [66]. Of note is that there have been substantial confounders and heterogeneity across studies, with marked uncertainty over drug selection, dosing, and duration of use, and therefore, further methodologically rigorous studies using standardized outcome measures are needed to inform care.

Cholinesterase inhibitors Cholinesterase inhibitors are a class of cognitive enhancers used in major neurocognitive disorders. Given the cholinergic deficit hypothesis in delirium, prophylactic use of cholinesterase inhibitors theoretically could reduce the incidence of delirium. A systematic review of the cholinesterase inhibitor trials found no consistent benefit of either donepezil or rivastigmine for delirium prophylaxis in older surgical patients, but the results are inconclusive because of study design limitations and methodological heterogeneity that precluded a valid meta-analysis [67]. Youn et al. randomized 62 patients with baseline cognitive impairment (MMSE scores 10–26) and an acute fragility hip fracture to receive rivastigmine 4.6 mg patch or placebo, from 3 days before to 7 days after the operation [68]. In the rivastigmine group, 16.1% developed postoperative delirium, compared to 45.2% of the control group [68]. Further randomized controlled trials of efficacy of cholinesterase inhibitors in preventing and treating delirium in both surgical and medical settings are needed before definitive conclusions can be drawn. Because Alzheimer disease is characterized by reduced cholinergic transmission, it is plausible that the benefits of cholinesterase inhibitors in delirium may not be detectable without preexisting cholinergic deficits of the central nervous system.

Other medications Melatonin (a naturally occurring hormone secreted by the pineal gland) modulates the circadian rhythm and arousal and has been tried as a means to promote normal circadian rhythms and prevent delirium. In 452 hip fracture patients (aged 65 years and older), prophylactic postoperative melatonin 3 mg versus placebo did not prevent delirium [69]. A randomized, placebo-controlled trial of 145 medical inpatients (mean age, 85 years) taking a low dose of melatonin (0.5 mg) or placebo for 14 days or until discharge has shown that the melatonin group had a significantly lower incidence of delirium (12% vs 31%, $p = 0.014$) [70]. More definitive conclusions about melatonin as prevention strategy for delirium are awaited; however, melatonin has an excellent safety profile, and it is reasonable to prescribe melatonin in older patients in whom non-pharmacological sleep promotion interventions have been unsuccessful.

In an open-label, randomized clinical trial of cardiac surgery patients, postoperative sedation with dexmedetomidine (an α-2 adrenergic receptor agonist) compared with propofol or midazolam was associated with significantly lower rates of postoperative delirium [71]. Patients who developed postoperative delirium experienced significantly longer intensive care length of stays and longer total hospitalization. However, other findings have shown that dexmedetomidine reduces intensive care length of stay and duration of mechanical ventilation [72].

17.1.11 Post-delirium, Aftercare Interventions

Post-delirium debriefing after recovery gives the patients the opportunity to communicate their distress about the delirium experience. Patients may fear that their delirium-related hallucinations might represent the onset of a psychotic disorder. Education about the possibility of recurrence of delirium is essential in advising the patients and their family members to watch for recurrent symptoms and seek emergency medical care at that time. Advising patients to maintain a normal sleep-wake cycle is important. Healthcare systems with integrated electronic medical records (EMRs) should list a diagnosis of "delirium, resolved" on the patient's medical history or problem list and prompt the primary care physician to follow-up post-hospitalization and assume an active role in post-delirium care, including implementation of serial cognitive assessments, risk factor management, and surveillance.

17.2 Case Studies

Geriatric psychiatry plays a key role in the diagnosis and management of delirium. This section is a case-based review that will focus on integrating elements of the diagnosis, evaluation, and evidence-based guidelines for the management of delirium in older adults with relevance to the geriatric psychiatry.

17.2.1 Case 1

Case 1 History

Mr. A., a 74-year-old man with Parkinson disease and mild neurocognitive disorder, was admitted for an acute onset of confusion, visual hallucinations, persecutory delusions, agitation, sleep-wake cycle disturbance, and aggressive behavior shortly after optimizing his oral treatment with carbidopa-levodopa 25–100 mg from 1 tablet three times daily to 1½ tablets three times daily. Other medication recently started was a dopamine antagonist metoclopramide 10 mg three times daily for its antiemetic effect. His psychiatric and family history were unremarkable.

Shortly after admission, his carbidopa-levodopa dose was decreased to one tablet twice daily to reduce his confusion, psychosis, and agitation, believed to be side effects. Additionally, he was started on quetiapine 25 mg qhs to manage his psychotic symptoms and agitation. His psychotic symptoms improved after titration of quetiapine to 50 mg bid over the following 72 hours, but his confusion worsened, and he became lethargic. By day 3, hyperthermia of 39.4 °C (102.9 °F), diaphoresis, severe muscle rigidity in all extremities, lethargy, and fluctuating vital signs were noted. Laboratory investigations revealed an elevated serum creatine kinase and leukocytosis. Troponin level was normal. EEG showed generalized slow waves without a seizure focus. The MRI of his brain, cerebrospinal fluid studies, and chest radiograph were unremarkable. The Confusion Assessment Method (CAM) [42] algorithm had been performed by the nursing staff once a day and had identified delirium.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What were the causes of delirium and the management required in this case?

Question 2. What further clinical assessment should the medical team undertake?

Question 3. What are the discharge planning and prognostic implications in this case?

Case 1 Answers

Case 1 Answer 1 (Question 1—What were the causes of delirium and the management required in this case?)

Mr. A.'s dopamine antagonist medication, metoclopramide, had likely worsened his Parkinson disease-related motor symptoms, for which the antiparkinsonian medication (carbidopa-levodopa) was then increased. An initial hyperactive delirium in this patient was likely triggered by the increase in the dosage of carbidopa-levodopa, in a patient with several predisposing risk factors (advanced age, male sex, and comorbid cognitive impairment). Subsequently, this clinical presentation had progressed to hypoactive delirium and delirium associated with neuroleptic malignant syndrome (NMS) because of abrupt dopamine system hypoactivity, caused by both the decrease of the carbidopa-levodopa and the use of the dopamine antagonist, quetiapine (although quetiapine has less dopamine blockade properties than most antipsychotics and was prescribed at a low dose).

The management of the NMS in this case included discontinuation of the dopamine antagonists (quetiapine and metoclopramide), continuation of the same dosage of carbidopa-levodopa, optimal hydration, and serial monitoring of complete blood count, renal function, and creatine kinase, with gradual normalization of his serum creatine kinase levels (see ► section Neuroleptic malignant syndrome in Chap. 5). Judicious use of lorazepam on prn (on-demand) basis controlled his occasional agitation. Hospital staff sitters closely monitored for his unsafe behaviors; they gave clear instructions to him, provided adequate lighting in his hospital room, and minimized noise level in his nearby environment to promote good sleep hygiene especially at nighttime. By week 2, Mr. A.'s delirium symptoms fully remitted.

Multicomponent intervention program to prevent recurrence and reduce incidence of delirium in this at-risk patient was recommended. In this case, a baseline geriatric or geriatric psychiatry consult should focus on assessing and addressing risk factors such as visual and hearing impairment, sleep deprivation, immobility, and dehydration [73]. These approaches are based on the Hospital Elder Life Program (HELP) that added further essential rehabilitation protocols based on three risk factors: early mobilization (functional

status), oral and nutritional assistance (nutritional status), and communication/orientation (cognitive status) [73]. He was subsequently transferred to a rehabilitation unit to address his physical deconditioning.

Case 1 Answer 2 (Question 2—What further clinical assessment should the medical team undertake?)

It is important to obtain collateral history from a knowledgeable informant to determine the patient's baseline cognitive status. Mr. A. was known to have a mild neurocognitive disorder likely related to his Parkinson disease. Cognitive impairment is one of the most common and significant aspects of non-motor symptoms of Parkinson disease. The cognitive deficits such as executive and visuospatial disturbances can significantly affect the quality of life, reduce life expectancy, increase caregiver burden, and prolong the duration of hospitalization [74]. Major neurocognitive disorder due to Parkinson disease is a key component of survival in Parkinson disease. A 12-year prospective longitudinal cohort study found that a 70-year-old man with Parkinson disease without neurocognitive disorder has a life expectancy of 8 years, of which the latter 3 years would be expected to be comorbid with major neurocognitive disorder (dementia) [74]. Women with Parkinson disease apparently live longer than men and spend more years with major neurocognitive disorder [74]. It would be important to note whether or not Mr. A. had experienced visual hallucination before increasing his dose of antiparkinsonian medication, which could have been a side effect. Visual hallucinations are common in delirium but also can occur in numerous other medical conditions, including Parkinson disease (see ▶ Sect. 17.1.7, Gold Standard: Psychiatric Evaluation). Hallucinations are noted in 74% of patients with Parkinson disease [75]. The challenge is to understand the pathophysiological mechanisms underlying the diverse features of Parkinson disease that go far beyond a lack of dopamine [75].

In this case, performing a cognitive screening test such as the MoCA to confirm a drop in score from the patient's baseline is advisable. Because of confusion and disorientation, perceptual disturbances, altered sleep-wake cycle, and psychomotor changes, the CAM screen is indicated. Questions such as the following are critical elements to address: "Is there evidence of an acute change in mental status from baseline? Has the patient had difficulty focusing attention? Is the patient easily distractible? Can the patient keep track of what was said? Does this fluctuate during the interview? Is the patient's thinking process disorganized, illogical, or incoherent? Is the patient's level of consciousness alert, hyperalert, easily startled, lethargic, or drowsy?" Other bedside screening tests for delirium-related attention deficits have been described previously (see ◘ Table 17.4). For example, attention and awareness can be assessed directly by administering simple bedside tests that include asking the patient to count backward from a specific number and enunciate days of the week backward or months of the year backward. Repeating the cognitive assessments post-delirium aftercare is recommended to ensure adequate monitoring of cognitive status.

Case 1 Answer 3 (Question 3—What are the discharge planning and prognostic implications in this case?)

Clearly indicating the diagnosis of delirium in medical records and ensuring an optimal handover of post-delirium care to the primary care physician is crucial. Because many patients will eventually recover to premorbid cognitive levels, as in this case, at least in the short term, routine inpatient referral to an outpatient memory clinic is not warranted upon hospital discharge.

However, delirium can indicate a fragile "delirium-prone" brain and constitutes a high risk for developing a major neurocognitive disorder. Therefore, the primary care physician should target longitudinal cognitive assessment of this patient with a recent episode of delirium. Moreover, debriefing with primary care physician is warranted since acute stress disorder in hospital and subsequent posttraumatic stress disorder have been reported post-delirium. Post-delirium debriefing with Mr. A. and his wife and educating them about early identification and the recurrence nature of delirium are unequivocally important. Follow-up psychiatric consultation to monitor cognitive status and to diagnose and manage other psychiatric comorbid illnesses should also be considered.

Case 1 Analysis This case illustrates how the emergence of antipsychotic-associated NMS can complicate antipsychotic treatment of delirium in an older medical patient, although delirium is also a common presentation in NMS [76]. Carbidopa-levodopa has central dopaminergic activity, and an increase in the dose, particularly in a geriatric patient with preexisting mild neurocognitive disorder, precipitated a syndromal delirium. Further complicating this patient's presentation was the development of NMS, which had a multifactorial causation, such as the use of dopamine antagonists (i.e., quetiapine, metoclopramide), and the abrupt decrease of a dopaminergic agent (i.e., carbidopa-levodopa), all eventually leading to a central dopamine hypoactivity.

17.2.2 Case 2

Case 2 History

You were the psychosomatic medicine (consultation-liaison) psychiatrist asked to assess Mr. B., an 85-year-old man on the orthopedic unit. He underwent a scheduled elective hemiarthroplasty procedure 3 days previously, and his recovery initially went well. However, 2 days after the surgery, he had developed urinary incontinence and displayed daytime drowsiness alternating with disorientation and stupor, whereas at night, he experienced visual hallucinations and paranoia, was agitated and aggressive, and had pulled out two intravenous (IV) lines. Medical history indicated hypotension, hypothyroidism, Parkinson disease, constipation, and osteoarthritis. He had no prior history of psychiatric illness. Medications included aspirin 81 mg daily, levothyroxine 75 mcg daily, carbidopa-levodopa 25–100 mg qid (increased from 25–100 mg bid 5 days previously), senna 17.2 mg daily,

and acetaminophen 1000 mg q 6 hours. Oxycodone 10 mg po q 4 hours had been added during the postoperative period. His social history revealed that he had been living with his wife at home and he had been independent with his basic activities of daily living but required assistance with several of his instrumental activities of daily living. Upon admission to the hospital, his MoCA was documented to be 17 out of 30 points, with 4 items lost on delayed recall and the remaining points lost on naming, language, and visuospatial/executive function tasks.

On mental status examination during your psychiatric assessment, you noted that the patient was disoriented to person, place, time, and circumstances. He was incoherent and appeared to have talked to his wife who was not present at the time. He was picking at the air and bedclothes, was restless, and attempted to get out of the bed. The MoCA test scored 0/30 at this time. His chest was clear and his abdomen was soft and mildly tender. The rest of the physical examination was difficult to complete due to his agitation and lack of cooperation, but you grossly determined that there were no overt focal neurological signs. Vital signs showed a heart rate of 98 beats/minute with blood pressure, respiratory rate, and oxygen saturation within normal limits. Recent abdominal X-ray showed moderate fecal load in the transverse and descending colon. The operation wound was healing well. The previous day, the surgery team had started oral antibiotic empirically for a presumed urinary tract infection due to new-onset incontinence while awaiting urinalysis results, but there had been no improvement in his mental status.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What is the most likely diagnosis and the differential diagnosis in this case?

Question 2. What is the first step in the management of delirium?

Question 3. What is the treatment of delirium in this case?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is the most likely diagnosis and the differential diagnosis in this case?

In this case, the new onset, abrupt change in attention, and other cognitive features, as well as the fluctuating course, are hallmarks of delirium. He presented with new-onset urinary incontinence which could have indicated the presence of a subsyndromal delirium, which subsequently developed into a syndromal delirium. Mr. B. had a number of risk factors for delirium. Centrally acting medications and substances of abuse can produce delirium, as can polypharmacy, severe systemic medical illnesses, recent surgery, and preexisting cognitive impairment (see Fig. 17.3). His predisposing risk factors consisted of his advanced age, male sex, and preexisting neurocognitive disorder. Other risk factors were constipation (probably induced or worsened by oxycodone), possible urinary tract infection (manifested as urinary incontinence), osteoarthritic pain, Parkinson disease, general anesthesia, and medications (levodopa, oxycodone). Unlike Case 1, there was no evidence for neuroleptic malignant syndrome (NMS) caused by the acute dopamine hypoactivity because his carbidopa-levodopa dose was not decreased but was, rather, increased.

As in this case, multiple etiologies can be present simultaneously in a patient with delirium. Along with a fluctuation in the level of attention or awareness, other symptoms such as disorientation, perceptual disturbances, visual hallucinations, paranoia, or urinary incontinence can be present. His urinary incontinence could have been caused by a urinary tract infection, delirium, or both, and a urinalysis would help with diagnostic clarification. The resulting behavioral problems can interfere with the patient's care, such as pulling out intravenous lines or catheters and displaying disruptive agitation and wandering, which can pose significant risk to the patient and/or others. Therefore, Mr. B.'s working diagnosis was delirium due to multiple etiologies (constipation, urinary tract infection, pain, and medications—levodopa, oxycodone, anesthetic agent). His fluctuating clinical features from hypoactive to hyperactive subtype indicated a mixed form of delirium.

Teaching Point

The hallmark of delirium is a fluctuation in attention, with easy distractibility (e.g., inability to pay attention) or perseveration (e.g., inability to release attention and move on to something else).

Mr. B. did not have a known preexisting diagnosis of major or mild neurocognitive disorder due to Parkinson disease. Having a major neurocognitive disorder increases the risk of developing delirium, but delirium should not be diagnosed if the current condition is better explained by a (separate) major neurocognitive disorder. This difficulty is compounded because both delirium and major neurocognitive disorder can exhibit similar symptoms (e.g., memory impairment, cognitive disturbances, behavioral problems). Several key characteristics help distinguish between these two conditions:

- The onset of delirium is short (hours to days), whereas the onset for major neurocognitive disorder is prolonged (months to years).
- The course of delirium fluctuates over the day, whereas that of major neurocognitive disorder remains relatively stable hour to hour.
- The level of alertness is altered in delirium, whereas in major neurocognitive disorder, it is not.
- Delirium is usually reversible, whereas major neurocognitive disorder is usually irreversible (see Table 17.3 summarizing these characteristic features).

Other diseases in the differential diagnosis for delirium include psychiatric disorders such as schizophrenia and mania; however, such patients usually maintain an intact level of alertness. As previously described in ▶ Sect. 17.1.7, Gold Standard: Psychiatric Evaluation, psychotic disorders are more frequently characterized by auditory hallucinations and systematized delusions, in comparison with delirium where visual hallucinations and transient, simple delusions are more common.

In conclusion, Mr. B.'s impaired baseline cognitive performance (e.g., MoCA score in the mild to moderate impairment range upon admission) coupled with his impaired baseline functional level (e.g., impairment in multiple instrumental activities of daily living) indicated the presence of a preexisting major neurocognitive disorder, possibly due to Parkinson disease that predated the episode of delirium.

Case 2 Answer 2 (Question 2—What is the first step in the management of delirium?)

The cornerstone of treatment for delirium is identification and correction of the underlying abnormality. A cause of the delirium should be sought immediately. A physical examination should be performed. The patient's medication list (e.g., new additions, withdrawals, dose adjustments) should be examined. Common iatrogenic causes for delirium should search for newly started deliriogenic medications including benzodiazepine, anticholinergic, antihistamine, or narcotic medications. Antiparkinsonism medications such as levodopa and dopamine agonists can contribute to delirium in a dose-dependent fashion. For these typically necessary medications, a dosage reduction may be helpful. Generally, if dopaminergic medications are suspected of causing confusion, anticholinergic medications (e.g., trihexyphenidyl) should be the first to discontinue, followed by selective monoamine oxidase inhibitor-B (selegiline) and direct-acting dopamine agonists (e.g., pramipexole, ropinirole) and finally by tapering levodopa. Opioid analgesics are independent risk factors for delirium. Meperidine is often avoided in older adults due to accumulation in those with impaired renal function. All other opioids can cause delirium, especially if high doses are used. In older patients with major neurocognitive disorder and comorbid bipolar disorder, even lithium can cause delirium and even at usually "therapeutic serum levels" with normal renal function [77].

In this case, laboratory studies and radiographic studies should be undertaken to evaluate other common causes of delirium including electrolyte imbalances, hypo/hyperglycemia, pneumonia, urinary tract infection, constipation, hypercapnia, and hypoxia. Additionally, the patient's family members should be interviewed about alcohol and other substance misuse and the possibility of withdrawal.

Teaching Point

The most important management approach for a patient with delirium is to detect and correct the underlying condition(s). Medications can be a significant cause of delirium.

Case 2 Answer 3 (Question 3—What is the treatment of delirium in this case?)

The approach to identification and correction of the underlying abnormality usually results in reversal of the delirious state, usually over several days to a week in acute delirium. However, it is not uncommon for patients to show subtle signs of delirium for weeks or months after hospital discharge (persistent delirium), which can verge with progression of a comorbid major neurocognitive disorder. In addition to treating the underlying causes of delirium, symptomatic pharmacological management for the severe behavioral disturbances can usually be accomplished with low doses of high-potency antipsychotics (such as haloperidol), given their lower incidence of orthostasis and anticholinergic side effects, which can worsen the patient's condition. However, Mr. B. had a history of orthostasis and parkinsonism, and thus, the preferred choice of an atypical antipsychotic as a therapeutic agent for his delirium is quetiapine (due to its much lower level of dopamine blockade), initiated in small doses and up-titrated to effect and tolerance to manage his behavioral disturbance. Although there was no evidence of a substance misuse or a NMS in this case, a short-acting benzodiazepine such as lorazepam can be helpful where the delirium is caused by withdrawal from benzodiazepines or alcohol or is due to NMS. Otherwise benzodiazepines should be avoided because they may themselves precipitate delirium.

Non-pharmacological approaches for treating delirium should always be implemented and involve strategies to help facilitate the orientation of the patient, such as a calendar or clock, access to a window during the day, a television set or a radio playing during the day, family pictures, sleep-wake cycle regulation, and familiar faces such as those of relatives or friends as sitters (see ◘ Table 17.6 for non-pharmacological management).

Teaching Point

Symptomatic management can be accomplished with a low dose of a high-potency typical antipsychotic or an atypical antipsychotic or a short-acting benzodiazepine depending on the cause of delirium.

Case 2 Analysis This patient with a previously unrecognized cognitive impairment, who had no history of psychiatric disorders, began having visual hallucinations and paranoia 3 days after undergoing an elective hip replacement surgery. The short-term nature of the event and the fluctuations in cognition and alertness were consistent with a diagnosis of delirium. (See ◘ Fig. 17.1 for highlights of DSM-5 criteria for delirium of any cause.) As in Mr. B.'s case, major surgical procedures are risk factors for delirium, especially in older patients. However, multiple other factors could have contributed to his presentation of delirium. His recent increase in antiparkinsonian medication (levodopa) could have induced delirium. Further blocking dopamine activity with an antipsychotic (quetiapine) could eventually lead to developing a

clinical picture of delirium due to neuroleptic malignant syndrome. His delirium was also possibly caused by a urinary tract infection (acute onset of urinary incontinence) and constipation (as evidenced by medical investigations). The complexity of this case reflects the fact that delirium in older adults is often multifactorial and identification and management always involve a multifaceted approach.

17.3 Key Points: Delirium in Older Adults

- The core diagnostic symptom of delirium is a problem with attention/awareness. Delirium assessment includes examining levels of arousal, psychomotor activity, cognition, and perceptual disturbances.
- Subsyndromal delirium predicts a poorer outcome than the absence of delirium, yet the fluctuating course of delirium makes subsyndromal delirium difficult to diagnose and can be missed.
- Delirium can be categorized into one of three motor subtypes: hyperactive, hypoactive, and mixed subtype.
- Delirium complicates the hospitalizations of up to 54% of older medical inpatients.
- Delirium incidence can be predicted by the presence and burden of risk factors.
- Delirium is not always transient and reversible, and it can result in long-term cognitive changes.
- To date, no pharmacological agent can be recommended as effective prevention strategy of delirium, although melatonin has a high potential benefit to risk profile in medical patients, while dexmedetomidine is associated with significantly lower rates of postoperative delirium in surgery patients.
- Non-pharmacological approaches to prevent and manage delirium are best implemented through standardized protocols and guidelines, such as HELP and NICE.
- Clinicians play an essential role in identifying previously unrecognized cognitive impairment, as well as identifying and treating depressive disorders, and other medical disorders including metabolic disturbances that may contribute to delirium.

17.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which one of the following statements is correct?

A. Medications for symptomatic treatment of delirium should be stopped immediately after the cause of delirium has been identified and treated.
B. Symptomatic treatment of delirium should not be continued on a long-term basis to prevent recurrence of delirium.
C. Post-delirium recovery should involve assessment of cognition only in pre-delirium cognitively intact patients.
D. Psychiatric complications of delirium are rare and do not warrant routine case finding.
E. Post-delirium debriefing with the patient and family members is offered on a case by case basis.

Answer: B

Medications for symptomatic treatment of delirium usually can be tapered and discontinued once the episode has resolved and the patient is symptom free for approximately 1 week [78]. It should be noted that the underlying illness(es) causing delirium may respond quickly to a treatment regimen, but improvement in mental status (especially cognitive performance) may lag behind, especially in older adults; thus, statement A is incorrect. Some patients with protracted and severe systemic medical diseases (e.g., end-stage liver disease, metastatic cancer) may be prone to recurrent, prolonged, and/or chronic delirium. In such cases, a period of post-recovery treatment with antipsychotics could be considered; otherwise, symptomatic treatment to prevent delirium should not be continued indefinitely (statement B is correct). As discussed previously, in a 2016 systematic review and meta-analysis, the evidence to date did not support the use of antipsychotics for prevention or treatment of delirium, but additional methodologically rigorous studies using standardized outcome measures to inform care are needed [66]. After clinical recovery from delirium, current cognitive status must be assessed in all patients (see Table 17.4 for assessment scales in delirium), regardless of pre-delirium cognitive state, because patients may have persistent cognitive decline compared with pre-delirium state (statement C is incorrect). The psychiatric complications of delirium are distressing to the patient and the caregiver and include acute stress disorder, which may predict the later development of posttraumatic stress disorder [79]. Early recognition and treatment of posttraumatic stress disorder in all patients with delirium are essential and may improve long-term outcomes [79] (statements D and E are incorrect).

MCQ 2. An 85-year-old man is admitted to your psychiatric unit on Monday morning with major depressive disorder and deconditioning. At that time, he is awake, alert, and oriented to place, time, and person. While you are rounding on Tuesday morning, you notice that he falls asleep several times during your exam and is slightly difficult to arouse. When you ask for the date, he tells you his birthdate. When you ask again for the current year, he tells you it is "May." He cannot tell you the name of the city. He believes he is at home in his living room. Later in the morning, you noticed that he is more awake and is oriented to the correct place and time. Which of the following options in this scenario is a characteristic of the criteria from the Confusion Assessment Method (CAM)?

A. Acute onset and fluctuating course
B. Advanced patient age
C. Inattention
D. A and B
E. A and C

Answer: E

Advanced patient age is a risk factor for delirium but is not a characteristic element of the CAM. The CAM diagnostic algorithm is based on four cardinal features of delirium: (1) acute onset and fluctuating course, (2) inattention, (3) disorganized thinking, and (4) altered level of consciousness. A diagnosis of delirium according to the CAM requires the presence of features 1, 2, and either 3 or 4 [42].

MCQ 3. Which of the following is a feature of delirium that can help differentiate it from major neurocognitive disorder?

A. Memory impairment
B. Inattention
C. Disorientation
D. Disorganized thinking
E. Sleep-wake cycle disturbances

Answer: B

Memory impairment, disorientation, disorganized thinking, and sleep difficulties are common in both delirium and major neurocognitive disorder. However, inattention is a core symptom of delirium (see Table 17.3 for characteristic features of medical conditions that mimic delirium). Therefore, statement B is the correct answer.

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Major or Mild Neurocognitive Disorder Due to Alzheimer Disease

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18.1 Background

18.1.1 Definitions, Diagnostic Criteria, and Reclassification Systems

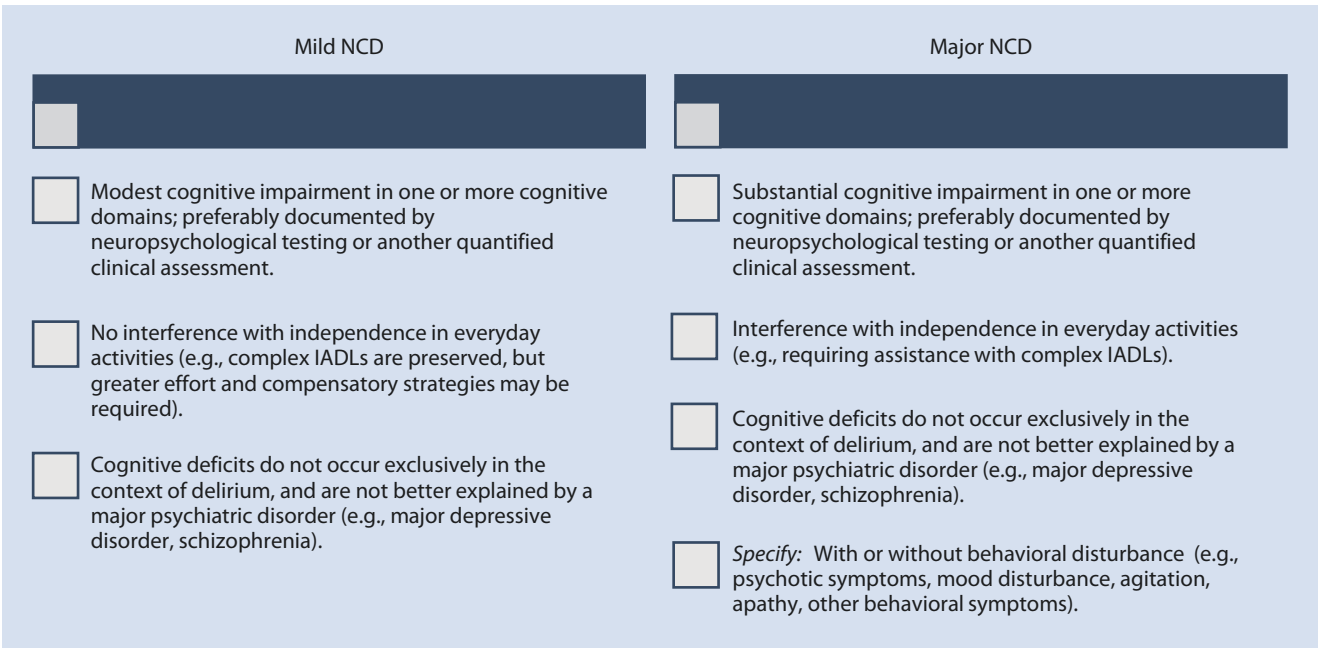
Major or mild neurocognitive disorder (NCD) due to Alzheimer disease is a neurodegenerative disease with an insidious onset and gradual progression of cognitive, behavioral, and functional impairment beyond what might be expected from normal aging [1]. It affects memory and learning, thinking, orientation, language, comprehension, calculation, and judgment. Consciousness is not affected. The cognitive impairment is commonly accompanied, and occasionally preceded, by neuropsychiatric symptoms, manifesting as depression, elation, anxiety, apathy, delusions, hallucinations, and agitation [2]. Neuropsychiatric symptoms have serious adverse consequences including greater impairment in activities of daily living, hastened cognitive decline, worse quality of life, earlier institutionalization, and greater caregiver depression [2]. The assessment and management of neuropsychiatric symptoms are discussed elsewhere in this volume. (See ▶ Chap. 22.)

A decline in the ability to perform daily activities, defined as functional impairment, is a required criterion for the diagnosis of all-cause major NCD [1, 3] (see ◘ Fig. 18.1 for diagnostic criteria for all-cause major or mild NCD). Basic activities of daily living (ADLs) are impaired in the moderate to severe stages of major NCD due to Alzheimer disease and include eating, dressing, grooming, bathing, toileting, and ambulating [4]. Instrumental activities of daily living (IADLs) typically begin to decline at the stage of mild NCD and include shopping, household chores performance, meal preparation, driving, using public transportation, and management of finances [4].

In typical Alzheimer-related NCD, the core clinical criterion consists of episodic memory deficit characterized by impaired free recall that is not normalized by cueing. Episodic memory is the collection of past personal experiences that occurred at a particular time and place. Amnestic mild NCD is generally viewed as the precursor stage to major NCD due to Alzheimer disease and its diagnostic criteria allow for mild difficulties in IADLs [3, 4]. This particular element often leads to an arbitrary distinction between mild NCD and very mild stage of major NCD due to Alzheimer disease, which has been a source of controversy in the literature. Some experts recommend the elimination of the construct of mild NCD due to Alzheimer disease altogether [4].

The precision and confidence of the accuracy of currently employed clinical diagnostic methods for Alzheimer disease is critical for clinical and research areas. The most accurate and definite diagnosis is typically obtained from the histological examination through biopsy; however, biopsy is not indicated for Alzheimer disease due to a high risk/benefit ratio [5]. Despite the emergence of new diagnostic markers, biomarkers have considerable overlap among NCD due to Alzheimer disease, other types of NCDs, and cognitively normal older adults [5]. Therefore, brain autopsy still serves as the "gold standard" for the definite diagnosis of Alzheimer disease [5].

The contemporary revisions for the diagnostic guidelines for Alzheimer disease have incorporated the scientific knowledge and technological advances to reflect the current state of understanding the detection and diagnosis of the cognitive impairment due to Alzheimer disease, which are further reviewed in this section.



◘ **Fig. 18.1** Highlights of the diagnostic criteria for all-cause major or mild neurocognitive disorder according to DSM-5 and NIA-AA classifications [1, 3]. *Note*: *DSM* Diagnostic and Statistical Manual of Mental Disorders, *IADLs* instrumental activities of daily living, *NCD* neurocognitive disorder, *NIA-AA* National Institute on Aging-Alzheimer's Association

NIA-AA Criteria

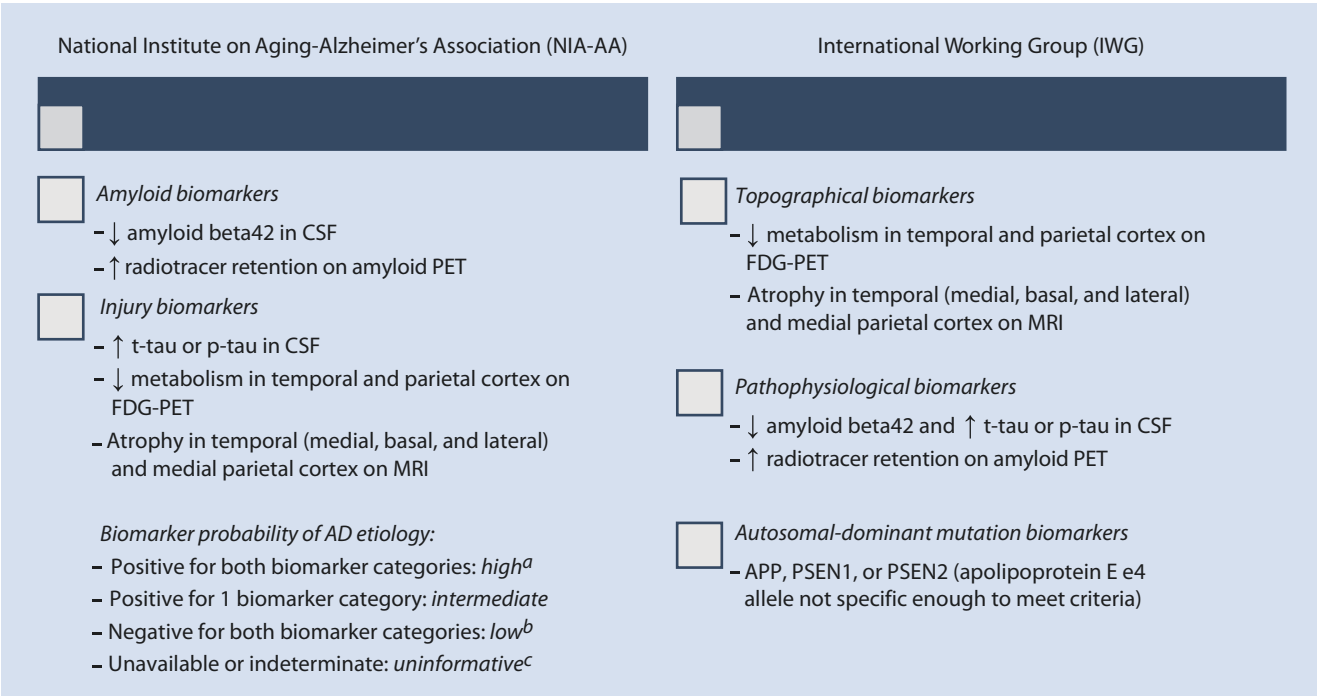
In 2011, after 27 years from the initial publication of the guidelines, the US National Institute on Aging and the Alzheimer's Association (NIA-AA) updated the clinical diagnostic criteria, with novel features including the recognition of a preclinical stage of Alzheimer disease and the incorporation of neuroimaging and laboratory-based cerebrospinal fluid biomarkers. These clinical criteria are seen as a continuum between early phases of Alzheimer disease, including asymptomatic patients and those with mild NCD (or preclinical Alzheimer disease) and those with major NCD due to Alzheimer disease [6]. The NIA-AA recognizes that Alzheimer disease may also have non-amnestic presentations. To diagnose Alzheimer disease in asymptomatic adults, the NIA-AA criteria rely on biomarkers, which will be described later in this chapter. Biomarkers of brain beta-amyloid deposition and those indicative of neuronal injury are the basis for dividing preclinical from clinical stages of Alzheimer disease [6]. Patients with subtle cognitive changes not yet meeting standardized criteria for mild NCD are included in the stage of "preclinical Alzheimer disease" when biomarkers are positive [6]. Although these recommendations for preclinical stage were intended initially for research purposes, they lead the way to diagnosing Alzheimer disease before the onset of symptoms. In symptomatic patients, biomarkers are used to indicate the probability (high, intermediate, or low) of etiology of Alzheimer disease. However, the NIA-AA does not currently advocate for the use of biomarker tests for routine diagnostic purposes [6].

DSM-5 and ICD-11 Criteria

In 2013, with the publication of the 5th edition of the American Psychiatric Association *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), dementia was renamed "major neurocognitive disorder," and earlier stage of cognitive impairment, formerly termed mild cognitive impairment, was renamed "mild neurocognitive disorder" in order to reduce stigma associated with the term "dementia." The introduction of terminology of "neurocognitive disorders" does not mean that "dementia" will no longer be used. In this view, the DSM-5 includes the term "dementia" in parentheses when referring to major NCDs, in recognition of dementia's history and familiarity. Another major diagnostic classification system is the *International Classification of Diseases* (ICD), published by the World Health Organization, and its 11th edition (ICD-11) is currently in development and likely due for release in 2018 [7]. Whether the ICD-11 will also adopt the terminology "neurocognitive disorders" and whether the diagnostic criteria will be similar to those of the DSM-5 remains to be seen.

IWG Classification

In 2014, the International Working Group (IWG) recognized well-defined atypical Alzheimer disease phenotypes and introduced a new conceptualization of the biomarkers defined as topographical biomarkers which are contrasted to pathophysiological biomarkers, which identify Alzheimer disease's signature in the brain [3, 6, 8]. (See ◘ Fig. 18.2 for



◘ **Fig. 18.2** Biomarkers used to define Alzheimer disease [3, 6, 8]. [a]Possible major NCD with evidence of AD pathophysiology does not preclude the presence of another pathophysiological process. [b]Unlikely due to AD. [c]Diagnosis is based on clinical criteria. *Note*: *AD* Alzheimer disease, *APP* amyloid precursor protein, *CSF* cerebrospinal fluid, *FDG-PET* fluorodeoxyglucose positron emission tomography, *MRI* magnetic resonance imaging, *PSEN* presenilin, *t-tau or p-tau* total tau or phosphorylated tau

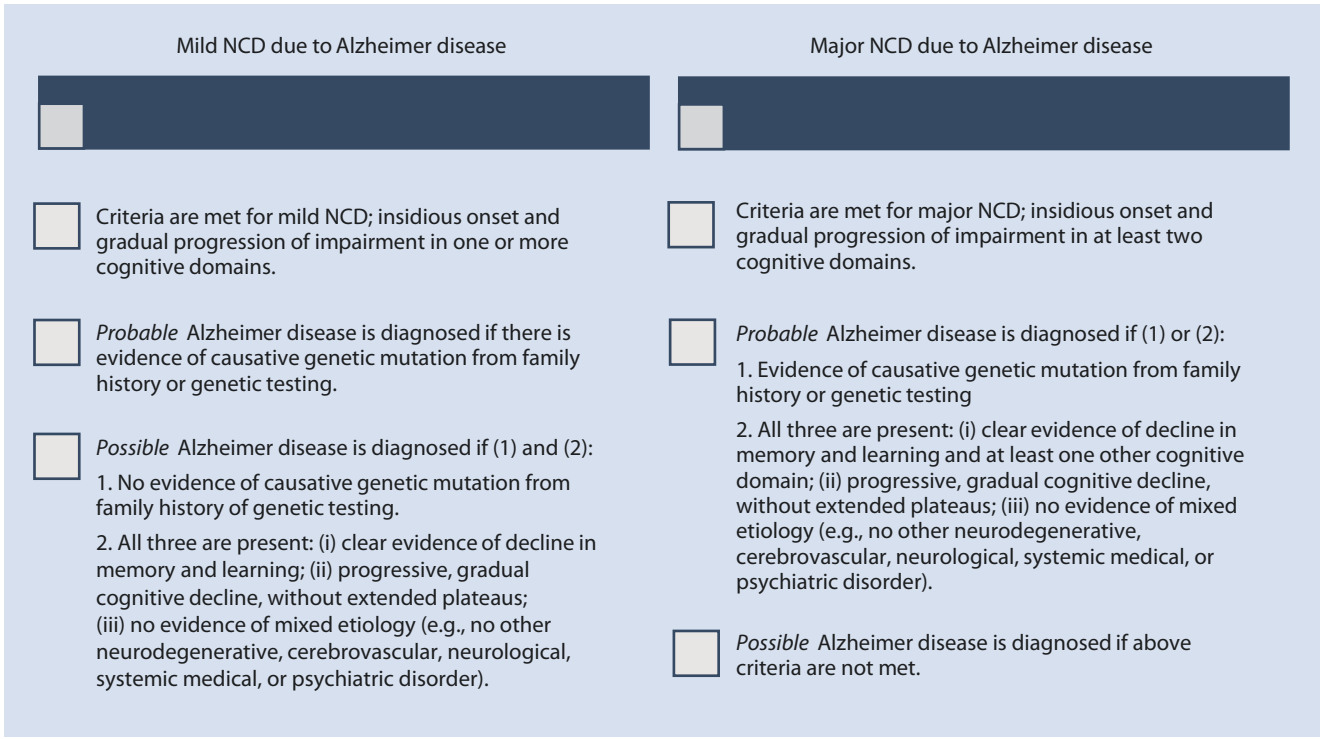


Fig. 18.3 Highlights of the diagnostic criteria for major or mild neurocognitive disorder due to Alzheimer disease according to DSM-5 and NIA-AA classifications [1, 3]. *Note*: *DSM* Diagnostic and Statistical Manual of Mental Disorders, *NCD* neurocognitive disorder, *NIA-AA* National Institute on Aging-Alzheimer's Association

biomarkers used to define Alzheimer disease.) According to the IWG, the pathophysiological biomarkers are largely static, at least in the symptomatic stage of the Alzheimer disease, and used to diagnose Alzheimer disease at any point on the disease continuum. In contrast, topographical biomarkers change and measure disease progression [6].

In summary, Fig. 18.3 presents elements for the diagnostic criteria for major or mild NCD due to Alzheimer disease according to the classification systems previously described [1, 3]. Classification criteria for *probable* versus *possible* Alzheimer disease are also summarized in Fig. 18.3. For a complete review of the DSM-5 diagnostic criteria for major or mild NCD due to Alzheimer disease, the reader is referred to the DSM-5 manual [1].

18.1.2 Epidemiology

Prevalence and Incidence Rates

Alzheimer disease is the most common cause of major NCD, with a rising prevalence that imposes substantial challenges for patients, families, and societies [9]. It was estimated that in 2010, 35.6 million persons worldwide suffered from major NCDs, with numbers expected to almost double every 20 years, to 65.7 million in 2030 and 115.4 million in 2050; of these, 58% are living in low- or middle-income countries, with anticipated increase in proportion to 63% in 2030 and 71% in 2050 [10]. However, future projections of numbers of persons with major NCDs may be substantially modified by lowering the incidence through preventive interventions and prolonging survival through advances in treatment, particularly disease-modifying interventions [10].

The estimated prevalence of the general population aged 60 years or older with all-cause major NCDs is 5–7% in most world regions, with a higher prevalence in Latin America (8.5%) and a lower prevalence in four sub-Saharan African regions (2–4%) [10]. Moreover, the prevalence of major NCDs rises substantially with age as the average life expectancy increases and nearly doubles every 5 years, from approximately 1–4% at age 65 or younger to as high as 30% by age 85 [11]. In the high-income countries, major NCD overall ranges from 5–10% in the seventh decade to 25–45% thereafter [11]. Interestingly, a recent study looking at the participants in the Framingham Heart Study shows that the incidence of major NCD, in fact, has declined over the course of three decades, although the factors contributing to this decline have not been fully identified [11]. At the mild NCD phase, Alzheimer disease is also likely to represent a substantial proportion of mild cognitive impairment, ranging from 2–10% at age 65 to 5–25% by age 85 [11]. This is important because clinical studies have shown that up to 80% of patients with mild NCD develop major NCD after 6 years [6].

Age at Onset and Subtypes of Alzheimer Disease

The onset of major NCD due to Alzheimer disease is at age 65 years or older (late onset) in the majority of patients, but 1–6% of all patients with this type of NCD have an onset before age 65 years (early onset), of which approximately 60% is

familial, with 13% appearing to have an autosomal-dominant inheritance (i.e., defined by some as the occurrence of at least three early-onset cases in three generations) [12, 13] (see Table 18.1). High-penetrant mutations in three genes, such as the gene for amyloid precursor protein (mapped to chromosome 21), presenilin 1 (on chromosome 14), and presenilin 2 (on chromosome 1), cause early-onset autosomal-dominant Alzheimer disease [13, 14]. Presenilin 1 is the most frequently implicated mutation with a frequency of 18–50% [15].

From the discovery of high-penetrant mutations in these three genes as a cause of early-onset autosomal-dominant Alzheimer disease, the identification of another gene, namely, the apolipoprotein E (mapped to chromosome 19), and its epsilon4 allele as a strong genetic risk factor for both early-onset and late-onset Alzheimer disease, to the recent discovery of at least 21 additional genetic risk loci for the genetically complex type of Alzheimer disease, all underscore the likely multifactorial nature of Alzheimer disease [13–15]. The distinction between early-onset familial subtype (younger than age 65) and late-onset familial subtype (older than age 65) is somewhat arbitrary, since early-onset cases can also occur in families with late-onset disease [16].

Nevertheless, it is important to emphasize that the vast majority of patients with Alzheimer disease represent non-familial (or sporadic) cases and do not have a family history consistent with autosomal-dominant inheritance [13] (see Table 18.1). Sporadic cases (defined as a patient with Alzheimer disease and no known family history of Alzheimer disease) represent approximately 75% of patients with Alzheimer disease and appear to have the same clinical and pathological phenotypes as familial cases (defined as two or more family members who have Alzheimer disease) [17]. Therefore, patients with sporadic Alzheimer disease meet the diagnostic criteria for Alzheimer disease and have a negative family history and an age onset at any time during adulthood. A common hypothesis is that sporadic Alzheimer disease is multifactorial and results from a combination of aging, genetic predisposition, and exposure to one or more environmental agents, ultimately leading to cognitive decline in Alzheimer disease. Some researchers believe that a large majority of Alzheimer disease cases may eventually prove to have underlying genetic causes, many of which may appear as polymorphic alleles that predispose to the disease [14]. The recognition that polymorphic alleles of apolipoprotein E (which will be discussed later in this chapter) can strongly predispose to the development of Alzheimer disease in the sixth and seventh decade suggests that other polymorphic genes could predispose to the disease but would be difficult to detect because of not always producing the disease and, therefore, not showing high penetrance [14]. Despite the uncertainty about the degree to which Alzheimer disease is accounted for by genetic factors, the clinical manifestation of familial (autosomal dominant) Alzheimer disease is generally similar to the non-familial (or sporadic) cases, although some familial cases may show early and prominent neurological signs (e.g., myoclonus, seizures, extrapyramidal signs), which will be discussed in later section [14].

Table 18.1 Subtypes of Alzheimer disease [12, 13]

Subtype	Percentage of all cases
Non-familial (sporadic)	75%
Familial	25%
Familial late onset	15–25%
Familial early onset	< 2%; 13% autosomal dominant
Chromosomal (e.g., Down syndrome)	< 1%

18.1.3 Pathophysiology

The pathophysiology of Alzheimer disease is largely unknown; however, the amyloid cascade sequence has been one of the main hypothetical models to explain the Alzheimer disease process [18]. Generally, several pathophysiological hypotheses for Alzheimer disease have been proposed and are summarized below [19]:

- There is universal agreement that alterations in the four confirmed genes discussed earlier predispose to Alzheimer disease, and their relationship to the beta-amyloid phenotype is illustrated in Fig. 18.4 [14].
- The cerebrovascular dysregulation hypothesis proposes changes to the balance between the blood flow delivery and the energy demands for neurons and glial cell activation, which lead to cognitive dysfunction and disease.
- The hypothesis for beta-amyloid and tau misfolded proteins proposes a causal role implicated in the cascade of cognitive decline and clinical presentation leading to the onset of Alzheimer disease.

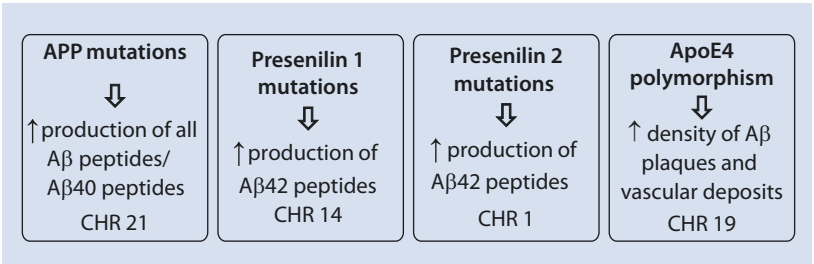


Fig. 18.4 Predisposing genetic factors for Alzheimer disease and relationship to beta-amyloid phenotype [14]. *Note*: *Aβ* beta-amyloid, *ApoE* apolipoprotein E, *APP* amyloid precursor protein, *CHR* chromosome

- The glucose metabolism dysregulation hypothesis suggests abnormal compensatory mechanisms associated with brain energy production in neurons and glial cells.
- The hypothesis for neuronal and synaptic hyperactivity that expands a deleterious effect on contiguous connected neurons and synapses has been postulated to explain the pathology of neuronal degeneration.
- The role of neurodegeneration and associated cortical atrophy, which are common hallmarks of Alzheimer disease progression, hypothesizes that these changes may represent a consequence of antecedent neuropathological factors.
- Recent data on the multifactorial modeling of Alzheimer disease suggest that cerebrovascular dysregulation may be the earliest pathologic factor associated with the onset of Alzheimer disease, followed by beta-amyloid deposition, glucose metabolism dysregulation, cortical atrophy, and functional impairment [19]. This contradicts previous understanding that pointed to an increase in beta-amyloid protein as the first detectable sign of Alzheimer disease [19].
- Recent findings taking into consideration the emerging systems-based conceptualization of Alzheimer disease support a system model characterized by a cascading network failure across the disease spectrum [20]. This model is thought to predict a connectivity "overload" that precedes structural and functional changes and reinterpret the high connectivity from that of a positive compensatory phenomenon to that of a load-shifting process promoting a compensatory role [20]. It remains unknown whether this systems-level pathophysiology is the trigger driving downstream molecular events related to synaptic activity implicated in these systems [20].
- A recent postmortem examination study showed an association of perivascular localization of aquaporin-4 with advancing age and Alzheimer disease [21]. Aquaporin-4 is a key part of the glymphatic system, which allows cerebral spinal fluid from outside the brain to wash away large solutes including beta-amyloid peptide, whose extracellular plaques are the hallmark of Alzheimer-related NCD. This perivascular route for cerebrospinal fluid-interstitial fluid exchange depends on glial cells to perform a "lymphatic" cleansing of the brain interstitial fluid, called the glymphatic system. This system and the failure of the system to cleanse amyloid, tau, and other protein buildup in the brain may be one of the many things that goes wrong in patients with Alzheimer disease; thus, aquaporin-4 might prove to be a useful target in preventing and treating Alzheimer disease [21].

Figure 18.5 depicts a hypothetical model of Alzheimer disease pathophysiology and the interplay with various risk factors, which are further described in the following section [3].

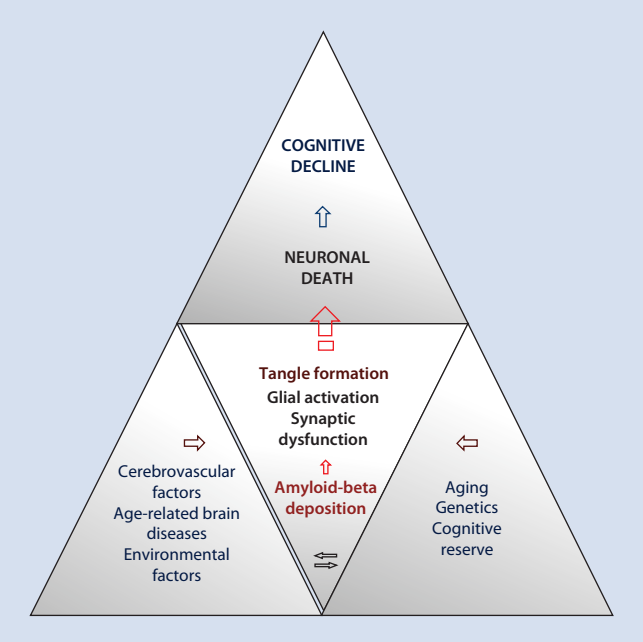


Fig. 18.5 Hypothetical model of Alzheimer disease pathophysiology and the interplay of risk factors [3]

18.1.4 Risk Factors and Prognostic Factors in Alzheimer Disease

Research suggests that the risk of Alzheimer disease is probably not determined in any specific age period but results from the interplay between environmental and genetic factors throughout the life span [22].

Environmental Risk Factors

No environmental agents have been demonstrated to be directly involved in the pathogenesis of Alzheimer disease. However, late-onset Alzheimer disease is often hypothesized to be the result of environmental factors acting on a predisposing genetic background [22]. Other environmental agents which have been implicated to generate Alzheimer disease pathology, including beta-amyloid accumulation, phosphorylation of tau protein, neuronal injury, and apoptosis, include chronic brain infection with herpes simplex virus type 1, *Chlamydophila pneumoniae*, and spirochetes resulting in intricate processes that interact to cause a sequence of uncontrolled neuroinflammation and neurodegeneration [23]. Infections with periodontal pathogens, *Helicobacter pylori*, and *Cytomegalovirus* stimulate production of systemic proinflammatory cytokines that may cross the blood-brain barrier to promote neurodegeneration. Other environmental factors include low education level, traumatic brain injury, toxins, and lifestyle factors such as smoking, physical inactivity, excessive alcohol intake, and poor diet [24].

Genetic Risk Factors

The association of late-onset familial Alzheimer disease with apolipoprotein E epsilon4 (e4) allele is well known [13].

However, late-onset Alzheimer disease is considered to be multifactorial, with a strong genetic predisposition [13]. For many years, apolipoprotein E was the only major gene known to increase Alzheimer disease risk. The apolipoprotein E gene contains three major allelic variants at a single gene locus (e2, e3, and e4), encoding for different isoforms (apolipoprotein E2, E3, and E4) [13]. The apolipoprotein E4 increases risk in familial and sporadic early-onset and late-onset Alzheimer disease, but it is not sufficient to cause the disease [13]. The risk effect is estimated to be threefold for heterozygous carriers (apolipoprotein E3/4) and 15-fold for E4 homozygous carriers (apolipoprotein E4/4) and acts as a potent risk factor by accelerating age of onset, particularly in homozygous persons [13, 25]. The apolipoprotein E2 (5–10% of the population) has a protective effect and delays age of onset [13]. Only about 25% of the general population carries one or more e4 alleles, whereas up to 65% of patients with Alzheimer disease are e4 carriers [13].

Chromosomal Risk Factors

Persons with Down syndrome (trisomy 21) develop the neuropathological hallmarks of Alzheimer disease after midlife. The postulated reason for this association is the lifelong overexpression of amyloid precursor protein on chromosome 21 and the resultant overproduction of beta-amyloid in the brains of persons who are trisomic for this gene [26]. Leverenz and Raskind [26] have demonstrated that there is a substantial variability in the severity of amyloid deposition in Down syndrome and that other factors may be contributing to the timing and severity of amyloid deposition in addition to this chromosomal factor.

Morbidity Risk Factors

Common medical conditions as risk factors for Alzheimer disease include vascular disease, diabetes mellitus, midlife hypertension, midlife obesity, midlife high cholesterol, and late-life depression [24]. These influence the risk for Alzheimer disease and may act by increasing cerebrovascular pathology or through direct effects on Alzheimer pathology. Some evidence indicates that Alzheimer disease may be a microvascular disorder [27]. Chronic, premorbid vascular risk factors in association with advanced aging can contribute to an endotheliopathy (likely due to deficit in basal nitric oxide synthesis) that contributes to regional metabolic dysfunction and progressive neurodegeneration characteristic of Alzheimer disease [27].

Prognostic Factors

Preservation or enhancement of brain, or cognitive reserve, could delay the onset of Alzheimer disease and in some cases prevent the disease from occurring altogether [22]. Non-modifiable and modifiable risk factors for Alzheimer disease are emphasized later at Case 1 (see ▶ section Case 1 Answers, Case 1 Answer 3). Because approximately one third of Alzheimer disease cases worldwide might be attributable to potentially modifiable risk factors, the incidence of this disease might be reduced through improving access to education and reducing the vascular risk factors (e.g., through targeting physical inactivity, smoking, midlife hypertension, midlife obesity, diabetes mellitus) and preventing depression [28]. The current understanding of genetic predisposition to Alzheimer disease and contribution of other risk factors, as well as the overall risks and benefits of strategies for risk modification, remain to be elucidated [24]. ◘ Table 18.2 summarizes the common non-modifiable and potentially modifiable risk factors for Alzheimer disease [6, 24, 29–32].

18.1.5 Clinical Description

Major or mild NCD due to Alzheimer disease affects each patient in a different way, depending upon the impact of the disease and the patient's premorbid personality. Although the threshold between mild and major NCD due to Alzheimer is inherently arbitrary, the mild stage of NCD reveals the first clinical change. The patient and family notice mild changes in memory and other cognitive abilities, but do not interfere with daily activities [3]. A follow-up is essential as even patients with amnestic mild NCD may not all progress on longitudinal performance [33]. It is important to remember that the earlier the diagnosis is attempted the more difficult it becomes and the higher the risk of misdiagnosis, whereas in the moderate to severe stages of major NCD due to Alzheimer disease, the diagnosis can be straightforward.

There is an increasing understanding that other cognitive domains than memory, such as language or complex attention, may be impaired first, or exclusively, depending on which parts of the brain are affected by the underlying Alzheimer disease. According to the DSM-5 classification system, six cognitive domains can be affected in both major and mild NCD, including learning and memory, language, complex attention, perceptual-motor function, executive function, and social cognition [1] (see ◘ Table 18.3).

Mild Neurocognitive Disorder Due to Alzheimer Disease

Diagnosis of mild NCD due to Alzheimer disease requires evidence of *modest* cognitive decline (1–2 standard deviations below norms or 3rd to 16th percentile) from a previous level of performance in one or more of the cognitive domains outlined in ◘ Table 18.3 [1]. These cognitive deficits must not interfere with the independence in everyday activities (e.g., complex IADLs, such as managing medications or finances) which are preserved, but greater effort or compensatory strategies may be required to maintain the level of independence (as illustrated in ▶ Sect. 18.2.1 discussed later). Furthermore, the cognitive deficits must not be attributable to another neuropsychiatric syndrome (e.g., delirium, depressive disorder, schizophrenia). (See ◘ Figs. 18.1 and 18.3 for diagnostic criteria.)

Major Neurocognitive Disorder Due to Alzheimer Disease

Diagnosis of major NCD due to Alzheimer disease requires evidence of *significant* cognitive decline (more than 2 standard

Table 18.2 Non-modifiable and potentially modifiable risk factors for Alzheimer disease [6, 24, 29–32]

Category	Risk factors	Comments
Non-modifiable risk factors		
Age	Increasing age	Age of early onset vs late onset in patient and family members
Sex	Females > males	Doubles the risk
Genetic	First degree relative with AD Down syndrome Early-onset AD: APP, PSEN1, PSEN2 genes Late-onset AD: APOE4 gene Many other genes of little or unknown significance	Increases four times the risk Trisomy 21 Early age at onset: 30–60 years Gene on chromosome 19: 3 alleles: e2, e3, e4 allele e4: 25% of population e4/e4: 50% risk in age 60s e4 heterozygote: 50% risk in age 70s APOE4 screening not recommended in asymptomatic persons due to low sensitivity/specificity and low positive and negative predictive values
Mild cognitive impairment	Mostly amnestic forms	80% develop major NCD after 6 years
Modifiable risk factors		
Morbidity factors	Systolic hypertension Serum cholesterol Head injury Depression Diabetes mellitus	At risk: > 160 mm/Hg At risk: > 6.5 mmol/L (> 251 mg/dL) At risk: moderate/severe, with loss of consciousness Independent risk factor: history of depression Association may be bidirectional
Lifestyle factors	Moderate wine consumption Physical activity Cognitive activity Smoking Diet	Optimal use: 250–500 mL/day At risk: if little/no regular exercise Cognitive training may reduce risk At risk: current use; no conclusive evidence that smoking cessation decreases risk At risk: increased dietary fat intake and reduced omega 3 fatty acids; Mediterranean-style diet associated with better cognitive performance
Sociodemographic factors	Education Occupation	At risk: lower education Inconclusive role; some exposure to environmental toxins (e.g., pesticides, fertilizers, fumigants) increases risk
Statin drugs	Treatment of hyperlipidemia	No evidence of reducing risk of AD; inconclusive results
Other medications and supplements	Nonsteroidal anti-inflammatory drugs, estrogens in women, vitamin B, vitamin C	Studies are inconclusive; no justification for recommending these options; vitamin E dose > 400 IU/d had negative cardiovascular effects

Note: *AD* Alzheimer disease, *APOE* apolipoprotein E, *APP* amyloid precursor protein, *NCD* neurocognitive disorder, *PSEN* presenilin

deviations below norms or less than 3rd percentile) from a previous level of performance in at least two domains outlined in Table 18.3 [1]. The cognitive deficits must interfere with the independence in everyday activities (e.g., at the very least, requiring assistance with complex IADLs such as managing medications and finances). Additionally, the cognitive deficits must not be attributable to another neuropsychiatric syndrome (e.g., delirium, depressive disorder, schizophrenia). (See Figs. 18.1 and 18.3 for diagnostic criteria.) The key distinction between mild and major NCD is the criterion of maintenance versus loss of independent functioning. (See further discussion in ► section Case 1 Answers, Case 1 Answer 5, regarding the role of functional impairment in the clinical diagnosis.)

The signs and symptoms linked to the phases of major NCD can be understood in three stages, as outlined in Fig. 18.6 [1]. The typical form of Alzheimer disease progresses slowly, in which the clinical diagnosis is established approximately 2–3 years after symptom onset and shows a mean cognitive decline of approximately 3 MMSE (Mini Mental State Examination) points per year [34, 35]. Major NCD due to Alzheimer disease is associated with increased mortality. The mean survival estimates among those with major NCD due to Alzheimer disease varies widely because of lack of definitive onset-of-disease dates [34]. In a study, the median survival was estimated at 5.7 years from initial clinical presentation and 11.8 years since retrospectively determined symptom onset [34].

Clinical Categories of Alzheimer Disease

Clinical categories include early-onset, late-onset, familial, and rapidly declining forms [35]. As described previously, the vast majority of Alzheimer disease represent sporadic cases, and only about 25% of all Alzheimer disease cases are familial, of which nearly 95% is late onset (age 65 or older) and 5% is early onset (age 65 or younger). There has been an international effort for judicious identification and treatment implementation of patients who carry mutations for genes causing early-onset familial Alzheimer disease through requests for memory consultations for adults in midlife. The practical message is that patients with major or mild NCD starting before age 65 years should be referred to a clinician with special expertise in this area, preferably in a clinical setting where genetic testing and subtype is the most common form of NCDs and is not causally associated with any unique neuropathological mechanism but rather with multiple concomitant factors [19].

Several risk factors described previously can accelerate deterioration of Alzheimer disease including genetics, comorbidity, and the early occurrence of motor signs [35]. Progressive forms of Alzheimer disease have been reported with rapid cognitive decline and disease duration of only a few years. *Rapid progression* has been defined as an MMSE score decrease of more than 6 points per year [35]. The occurrence of rapid clinical decline in major NCD due to Alzheimer disease necessitates referral to specialty clinics [36]. For patients with Alzheimer disease, a decline of three or more points on the MMSE score in 6 months, which identifies a group with a worse prognosis, is a signal to explore comorbid conditions (e.g., systemic medical and psychiatric disorders) and review of pharmacological management [36].

A comparison between the typical form and rapidly progressive Alzheimer disease is illustrated in Table 18.4 [35].

Table 18.3 Cognitive domains affected in neurocognitive disorder due to Alzheimer disease [1]

Cognitive domains	Examples of symptom domains
Learning and memory	Free recall, cued recall, recognition memory, semantic memory, autobiographical long-term memory, implicit learning
Language	Object naming, word finding, fluency, grammar and syntax, receptive language
Complex attention	Sustained attention, divided attention, selective attention, information processing speed
Perceptual motor	Visual perception, visuoconstructional reasoning, perceptual-motor coordination
Executive function	Decision making, planning, working memory, responding to feedback, inhibition
Social cognition	Recognition of emotions, theory of mind, insight

Teaching Point

Patients with rapidly progressive major NCD where the diagnosis remains uncertain should be referred promptly to appropriate specialty clinics [36]. Patients with known Alzheimer disease who demonstrate faster than expected clinical decline should be reassessed for comorbid conditions. The diagnostic strategy should emphasize the detection of potentially treatable conditions, such as infections, immune-mediated and metabolic causes, major depressive disorder, and other psychiatric syndromes, which cannot be explained by common neuropsychiatric symptoms that occur in existing NCDs and cannot be explained by the typical course of the underlying NCD.

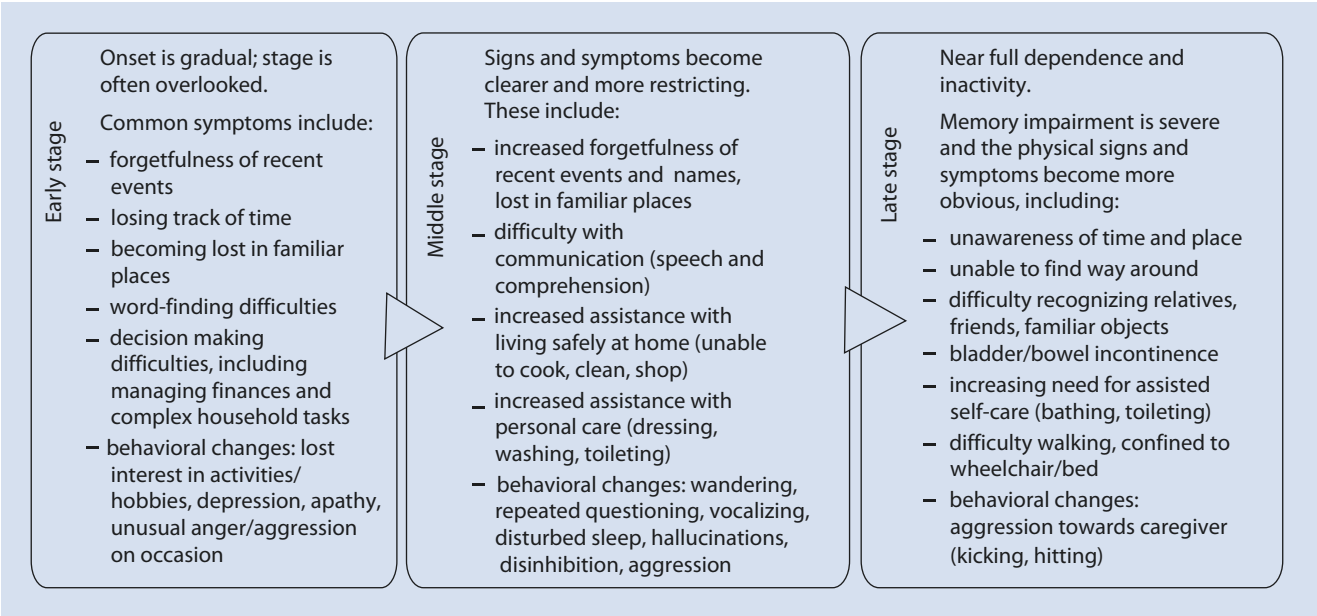


Fig. 18.6 Clinical stages of major neurocognitive disorder due to Alzheimer disease [1]

Table 18.4 Comparison between typical and rapidly progressive Alzheimer disease [35]

Characteristic	Typical Alzheimer disease	Rapidly progressive Alzheimer disease
Onset age	Age 65 (< 65 early onset; > 65 late onset)	Unclear
Rate of decline	3–6 MMSE points/year; gradual	> 6 MMSE points/year; rapid
Survival duration	8–11 years	2–3 years
Focal neurological signs	Late stage	Early stage, extrapyramidal signs
Apolipoprotein E4	Risk factor	Unclear role
CSF biomarkers	↑total tau and p-tau, ↓beta-amyloid1–42, 14–3-3 protein usually absent	↑↑total tau and p-tau, ↓↓beta-amyloid1–42, 14–3-3 protein may be present

Table 18.5 Predictors of Alzheimer disease progression [35]

Predictors of cognitive decline	Rate of progression
Baseline low cognitive status	Rapid/gradual
Male sex	Rapid
Lower education	Rapid
Higher education	Gradual
Apolipoprotein E4 genotype	Unclear
Motor signs (early)	Rapid
Apraxia (constructional)	Rapid
Early MMSE decline (> 4 points/6 months)	Rapid
Seizures	Rapid
Diabetes mellitus	Unclear
Cardiovascular disease	Unclear
Neuropsychiatric symptoms (apathy, psychosis)	Rapid
Increased total tau CSF levels	Rapid

Predictors of Alzheimer Disease Progression

Many factors are contributing to Alzheimer disease progression, including cognitive reserve, educational level, sex, genetics (i.e., apolipoprotein E genotype), and cerebrovascular conditions [35]. Apolipoprotein E is characterized as Alzheimer disease risk modulator, but its importance as a predictor of progression is not well understood [35]. Early MMSE score decline has been shown to correlate with speed of further deterioration, and early loss of at least 4 MMSE points within 6 months predicts poor outcome [35]. Comorbidity with cardiovascular disease and diabetes mellitus generated contradictory findings regarding their influence on Alzheimer disease progression. Certain clinical features such as early motor signs, seizures, apathy, and psychotic symptoms seem to be associated with rapid disease course and poor outcome [35]. Rapid cognitive decline has been associated with high total tau and phosphorylated tau levels, low beta-amyloid$_{1-42}$ level, or a high ratio of total tau to beta-amyloid$_{1-42}$ in cerebrospinal fluid [35]. Particularly, elevated total tau level without a proportionally elevated phosphorylated tau level may predict rapid progression [35]. Table 18.5 gives a summary of predictors of Alzheimer disease progression [35].

Teaching Point

Alzheimer disease presents with the possibility of mixed pathology, such as superadded vascular pathology, which may modify the manifestation of Alzheimer disease phenotype.

18.1.6 Diagnostic Evaluation

The diagnostic evaluation of major or mild NCD due to Alzheimer disease includes a detailed history provided by the patient and a knowledgeable informant, a thorough physical examination, and mental status examination, preferably documented by standardized neuropsychological testing or, in its absence, another quantified cognitive assessment [1]. The diagnosis of major NCD due to Alzheimer disease can be complex, especially when atypical presentations occur. (See ▶ Sect. 18.2.2, for atypical presentations of Alzheimer disease.)

Clinical History

As many patients with major NCD have reduced insight, they may underestimate the problem, and it is important to take a history from a knowledgeable informant as well as the patient. The contrast between the history obtained from the informant and the patient is often the most useful part of the assessment. It is important to exclude whether medication is contributing to their problems. A family history with close attention to the history of persons with NCDs should be obtained. For each affected person, the age of onset of NCD should be noted. The diagnosis of early-onset familial Alzheimer disease versus late-onset familial Alzheimer disease is made in families with multiple cases of Alzheimer disease in which the mean age of onset is before age 65 and after age 65, respectively.

Physical Examination

Physical examination should address weight loss, blood pressure, dehydration, cardiovascular disease, cerebrovascular disease, metabolic illnesses, and nutritional status. Physical examination is typically normal early in the disease course. In later stages myoclonus is common. Neurological examination should include assessment of gait, frontal release signs, focal neurological deficits, movement disorders, and sensory function [37]. For example, a visual field defect or parkinsonian features may suggest a non-Alzheimer NCD such as vascular or Lewy body NCD type. Loss of visual acuity (e.g., cataracts) in those with severe cognitive impairment can increase visual hallucinations, and glasses and cataract surgery need evaluation as prophylactic or adjunctive treatments for visual hallucinations in such patients [38]. Similarly, finding and treating hearing loss may reduce sensory deprivation that may be contributing to cognitive impairment.

Mental status examination includes a formal assessment of cognitive function, which will be described below. Depression rating scales are recommended to assist in differentiating depression from NCD and in monitoring response to antidepressants. Suicide risk assessment (including risk factors such as past suicidal behavior, access to weapons, isolation, and substance abuse) should be integrated in the clinical examination because suicide risk increases in the geriatric population.

Cognitive Assessment

It is essential to the diagnosis of major or mild NCD due to Alzheimer disease that a deficit in cognition is identified. Screening cognitive tests are widely used to assess patients with memory impairment. Although they are a part of the examination of the patient with cognitive impairment, they are not diagnostic tests for major or mild NCD and are not case-finding tools. This misconception about short cognitive tests could lead to over- or underdiagnosis of major or mild NCD. Brief screening tests may overestimate NCD due to Alzheimer disease in patients with less education level, age older than 85, or a history of depression [39]. Serial administrations of the cognitive test can quantify the progress versus stability of the disease process. The typical annual decrease in MMSE score in untreated Alzheimer disease patients has been estimated at 2–4 points per year [40]. While the MMSE is probably the most popular bedside cognitive screening tool widely used by clinicians, an emerging cognitive screening test is the Montreal Cognitive Assessment (MoCA) tool [41]. The MoCA test has been developed, validated, and available in multiple languages. The advantage of the MoCA also includes its examination of multiple cognitive domains such as language, attention, learning and memory, visuospatial, and executive function [41].

Other brief cognitive tests include clock-drawing test, verbal fluency test (e.g., semantic – animals or fruits; or phonemic – words that begin with letter F; and having the patient name as many items as possible in 1 minute), and the "go/no-go" test (e.g., the patient is instructed to tap once if the examiner taps once and to not tap if the examiner taps twice). As discussed later in ▶ section Case 1 Answers, Case 1 Answer 1, a list of the common brief cognitive tests and their utility in Alzheimer disease is presented. In advanced stages of the illness, many patients are unable to complete formal cognitive tests. In such cases, it is important to rely on observations of behavior, speech, and response to stimuli to determine the level of cognitive impairment, emphasizing that a change from baseline is more significant than the absolute test scores.

Investigations

Laboratory investigations are helpful to rule out other contributing or reversible factors of NCD, especially in patients initially presenting with neuropsychiatric symptoms (e.g., apathy, depression, elation, psychosis) early in the course of Alzheimer disease. Neuroimaging (as detailed below) and other investigations can exclude secondary causes of major NCD but may also produce positive support for a clinical diagnosis as is the case, for example, of hippocampal atrophy in Alzheimer disease. This is in support of the previously discussed NIAA-AA guidelines for preclinical Alzheimer disease, which involves the detection of changes in biomarkers that may indicate the very earliest signs of Alzheimer disease in the brain, before any cognitive or behavioral symptoms are noticeable [3]. Electroencephalogram (EEG) has little diagnostic value in Alzheimer disease because of expected diffuse slowing, unless EEG is performed to explain diagnostic targeting (e.g., seizures, Creutzfeldt-Jakob disease).

Biomarkers

Biological markers (or biomarkers) are measurable conditions or naturally occurring substances in the body that act as reliable predictors and indicators of a disease process. These include neuroimaging, cerebrospinal fluid proteins, and substances in blood. While recent research has provided knowledge about the average progression of Alzheimer disease and the subsequent changes in biomarkers, more work is needed to define how this knowledge can be applied to patients for routine clinical diagnosis.

Neuroimaging

Neuroimaging is among the most promising areas of research focusing on earlier diagnosis of Alzheimer disease. It is used in current clinical practice to rule out other causes of cognitive impairment, such as a brain tumor or vascular disease, and to identify characteristic changes that suggest Alzheimer disease or another cause of NCD. (See ▶ Chap. 3.)

Structural neuroimaging Structural neuroimaging provides information about the shape, volume, or position of brain tissue. Structural techniques include computed tomography (CT) and magnetic resonance imaging (MRI). Although more expensive, a brain MRI is preferred over the brain CT scan to better visualize microvascular disease, brain atrophy, and hippocampal volume. Structural imaging studies have shown that degeneration in specific brain regions such as the hippocampus may be an early sign of Alzheimer disease and the brain

regions continue to shrink significantly as the disease progresses. Patterns of atrophy in other brain regions may help identify forms of atypical Alzheimer disease. (See ▶ section Case 2 Answers, Case 2 Answer 2, for further discussion regarding indications for neuroimaging.)

Functional neuroimaging Functional neuroimaging reveals how actively the cells in various brain regions use glucose or oxygen. Functional techniques include single photon emission computed tomography (SPECT), positron emission tomography (PET), and functional MRI (fMRI). The current technique most commonly used in Alzheimer disease is fluorodeoxyglucose (FDG)-PET, which measures the use of glucose by the brain which is often reduced in regions important for learning and memory. Other types of NCDs may be associated with patterns of reduced glucose metabolism in other brain regions. As with the atrophy detected by structural imaging, more work is needed to establish firm criteria for using these general patterns of reduced activity for diagnosis.

Amyloid neuroimaging Radiotracers have been developed for use with PET scans that bind to beta-amyloid in the living brain [42]. Pittsburgh compound B (PiB) was the first radiotracer capable of highlighting the presence of beta-amyloid deposits (one pathological hallmark of Alzheimer disease) during a PET scan. Although PiB has been instrumental in recent knowledge about the development and progression of Alzheimer disease, its short half-life makes it impractical for common use. Other similar radiotracers have been developed that remain stable significantly longer than PiB, potentially increasing the usefulness of amyloid imaging beyond research arena, and become more widely used in the clinical setting in the future. This is not exclusively limited to Alzheimer disease, as for example, PET scans using radiotracers that bind to chemicals in the brain to detect receptors for dopamine may be used to show the reductions in this chemical in Lewy body NCD [42].

Cerebrospinal Fluid Proteins

Research suggests that Alzheimer disease causes changes in cerebrospinal fluid levels of beta-amyloid and tau, two pathognomonic proteins that form abnormal brain deposits. In the early stages of Alzheimer disease, beta-amyloid levels in the cerebrospinal fluid fall, as less of the protein is cleared from the brain and instead gets deposited in the plaques that characterize Alzheimer disease. Levels of phosphorylated tau in the cerebrospinal fluid rise as more of this form of tau is produced in the brain and forms the tangles.

Teaching Point

Cerebrospinal fluid examination is not routinely performed, but would be expected to be acellular and lacking oligoclonal bands in normal persons [36]. Where available, testing for cerebrospinal fluid beta-amyloid$_{1-42}$ (low) and total tau or phosphorylated tau (elevated) supports a diagnosis of Alzheimer disease [36].

The technique using the procedure of lumbar puncture can detect early changes indicating Alzheimer disease is developing before any symptoms are noticeable and is less expensive than amyloid neuroimaging. However, more research is needed to standardize cerebrospinal fluid values for protein levels that establish the significance of specific levels for any individual person at a single point in time. See ▶ Sect. 18.4, MCQ1, at Comprehension Multiple Choice Question Test and Answers for details on how biomarkers correlate with age-related differences in the neuropathological features of Alzheimer-related NCD.

Molecules associated with neurodegeneration and neuroinflammation are also being investigated for characteristic changes in the cerebrospinal fluid in different forms of NCD than Alzheimer disease. For example, tau is also implicated in other NCDs including frontotemporal NCD, and research investigates whether cerebrospinal fluid biomarkers can help detect the earliest signs of neurodegeneration.

Blood Biomarkers

Researchers have investigated whether preclinical Alzheimer disease causes consistent, measurable changes in blood levels of beta-amyloid, tau, or other protein biomarkers. Levels of the implicated proteins tend to be less stable in blood than they are in cerebrospinal fluid, and developing a blood test for Alzheimer disease is proving difficult [36]. As biomarkers of cerebrospinal fluid examination have been proposed for diagnostic purpose or in atypical cases, the plasma beta-amyloid$_{1-42}$ levels are not reliable and are not recommended for clinical practice [36]. Researchers are focusing recently on a protein in the brain called phospho-serine-type 1 insulin receptor substrate that may signal the earliest stages of Alzheimer disease and holds promise [43].

In summary, the basic and more specific laboratory investigations currently performed to diagnose major or mild NCD due to Alzheimer disease are illustrated in ◘ Fig. 18.7 [36, 44].

18.1.7 Comorbidity and Differential Diagnosis

The current diagnostic criteria propose that major or mild NCD due to Alzheimer disease can be diagnosed with different degrees of certainty based on the extent of the cognitive deficits and biomarker abnormalities. The cognitive deficits of Alzheimer disease are typically insidious in onset, with early problems emerging in episodic memory, for example, forgetting conversations and appointments. As the disease progresses, other cognitive domains become impaired, including language, visuospatial, and executive function. The patient with cognitive impairment may have psychiatric illnesses (e.g., major depression) other than Alzheimer disease or concurrent with Alzheimer disease. However, neuropsychiatric symptoms, such as depression and apathy, are common in mild to moderate Alzheimer disease, which complicate the differential diagnosis. Clinical history and examination need

Fig. 18.7 Summary of the diagnostic investigations for Alzheimer disease [36, 44]. *Note*: *AD* Alzheimer disease; *APP* amyloid precursor protein; *CSF* cerebrospinal fluid; *CT* computed tomography; *HIV* human immunodeficiency virus; *MRI* magnetic resonance imaging; *NCD* neurocognitive disorder; *18FDG-PET* 18-fluorodeoxyglucose positron emission tomography; *PSEN* presenilin; *SPECT* single-photon emission computed tomography; *VDRL* venereal disease research laboratory

to consider these other possible diagnostic entities. Therefore, an accurate diagnosis necessitates a comprehensive differential diagnosis, which is important especially because several entities are potentially treatable and reversible conditions. Potentially reversible conditions in the differential diagnosis of Alzheimer disease are shown in Fig. 18.8 [45].

The differential diagnoses to be considered in a patient with Alzheimer disease include psychiatric disorders (such as anxiety, depressive, psychotic, and substance-related disorders), intellectual disability, chronic brain infection, thyroid disease, vitamin deficiencies (especially B_{12} and thiamine), metabolic diseases, brain tumors, and cerebral vascular disease [45]. Other NCDs, such as frontotemporal NCD, Lewy body disease, Parkinson disease, Creutzfeldt-Jakob disease, normal pressure hydrocephalus, and cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), may all be mistaken for Alzheimer disease [46]. Patients with progressive supranuclear palsy often present with cognitive and behavioral changes, which can resemble Alzheimer disease, although the symptoms usually are different. In such atypical cases, the use of Alzheimer-specific biomarkers is emphasized. Structural neuroimaging, such as CT and MRI scan, is valuable for identifying some of these other causes of major or mild NCD including brain tumors, normal pressure hydrocephalus, and cerebral vascular disease. (See later at ▶ section Case 2 Answers, Case 2 Answer 3, for the differential diagnosis and common imitators of Alzheimer disease.)

18.1.8 Treatment

There is currently no cure for Alzheimer disease and the mainstay of treatment remains symptomatic. Novel treatments are being investigated in various stages of clinical trials. In general, affected patients eventually require assisted

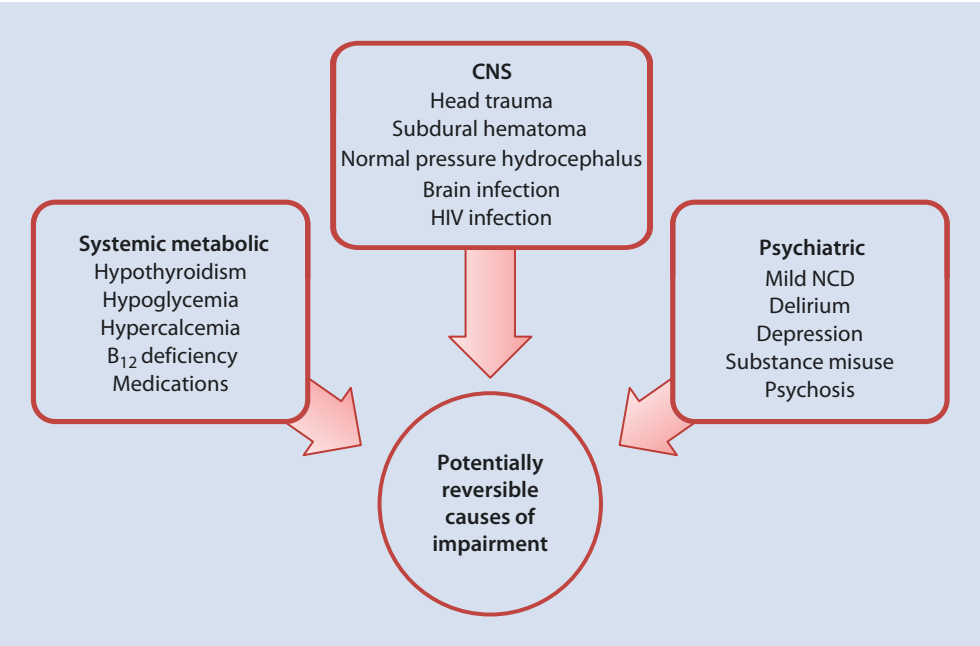


Fig. 18.8 Potentially reversible causes of cognitive impairment [45]

living arrangements or care in a nursing home. The principal goals for the care of patients with major NCDs include:

- Early diagnosis in order to promote early and optimal management
- Identifying and treating challenging neuropsychiatric symptoms (discussed elsewhere in this volume)
- Identifying and treating comorbid systemic medical conditions
- Optimizing physical health, cognition, and well-being
- Providing education and support to caregivers

Non-pharmacological Treatment

Providing early education about diagnosis, prognosis, and treatment, with regular clinical follow-up scheduled at least every 3 months, is advised. Evaluation of whether the patient with a major NCD can still safely live at home is recommended at every visit. More frequent visits may be required to monitor response to non-pharmacological strategies. Psychiatric admission can be considered for severely agitated, aggressive, psychotic, or suicidal patients when complex psychotropic treatment is required.

Supportive therapy helps the patient and the family caregiver manage the loss especially in earlier disease stages. Clinicians should inform primary caregivers of patients with major NCDs of the increased risk of burnout and depression and work closely with caregivers to monitor for and prevent depression by facilitating respite opportunities [47]. These include employing in-home caregiver (e.g., the visiting nurse) model and adult senior center model (e.g., attending a supervised therapeutic program for the business day and returning home at night) [47]. Support and advocacy groups are available such as Alzheimer Society in Canada and Alzheimer's Association in the United States. Although non-pharmacological management of neuropsychiatric symptoms of major or mild NCDs is discussed elsewhere in this book (see ▶ Chap. 22), events that trigger problematic behaviors should be identified and minimized [36].

With the disease progression, power tools, sharp household objects, vehicle keys, firearms, and other weapons should be secured or removed from the home. Legal issues should be addressed early in the disease course when the patient can direct his or her wishes and include discussion for completion of durable power of attorney and advance directives [47]. The physician needs to assess the patient's capacity for medical decision making each time a medical decision is needed to ensure that the patient understands and appreciates the implications of his or her medical choices. Clinicians also need to address the patient's driving ability and emphasize that the driving evaluations may be repeated at 6 month intervals or more frequently if a noticeable decline is observed. A road competency test may be advisable. Clinicians need to comply with the disclosure laws to local motor vehicle departments regarding notification of patients with impaired driving due to a major NCD [36]. Noteworthy, the risk of motor vehicle accidents is statistically increased even in mild stage of major NCD due to Alzheimer disease [48]. Working with family is paramount because car keys may need to be locked up or the automobile removed completely.

The patient may ultimately progress into disease when 24-hour supervision at home to preserve safety is necessary. When placement becomes necessary, a facility (e.g., group home, assisted living facility, skilled nursing facility) that specializes in the care of patients with major NCDs is necessary. Clinicians and family members should clarify the goals of care for the patient at this particular stage and, specifically, what degree of medical comorbidity can be managed in these facilities, because frequent changes in care setting trigger further behavioral disturbance in these patients. Assessing whether there are requirements for a feeding tube, antibiotics, or transfer to emergency department and hospitalization preferences should be addressed at this time.

Pharmacological Treatment

Cognitive Enhancers

Deficiencies of neurotransmitters, such as the cholinergic and glutamatergic systems, are implicated, although the exact biochemical basis of Alzheimer disease is not well understood. There are no randomized controlled trials for approved cognitive enhancers that exceed 12-month duration. The current treatment is symptomatic. Treatment with cholinesterase inhibitors has shown consistent, but modest, clinical effects in late-phase trials and includes donepezil, rivastigmine, and galantamine [13]. Memantine has a low-affinity antagonism to *N*-methyl-D-aspartate (NMDA)-type receptors which may prevent excitatory amino acid neurotoxicity without interfering with the physiological actions of glutamate required for memory and learning. Evidence is lacking for a benefit of memantine in mild stage of major NCD due to Alzheimer disease, and there is a modicum of evidence for its efficacy in moderate stage [49, 50]. Few clinical trials have evaluated combinations of pharmacological treatments. In a study combining memantine to a stable dose of donepezil in moderate to severe NCD due to Alzheimer disease, there were statistically significant additional benefits on measures of cognition, activities of daily living, global outcome and behavior, and it was well tolerated [51]. The three cholinesterase inhibitors are approved by the US Food and Drug Administration (FDA) and Health Canada as monotherapy for the symptomatic treatment of patients with mild to moderate major NCD due to Alzheimer disease and, for the severe stage of illness, donepezil and rivastigmine transdermal system in particular. The UK National Institute for Health and Care Excellence (NICE) approved cholinesterase inhibitors for the treatment of patients with mild to moderate major NCD due to Alzheimer disease. Memantine is approved by the US FDA and Health Canada as monotherapy for the symptomatic treatment of patients with moderate to severe major NCD due to Alzheimer disease. The UK NICE guidance recommended memantine for patients with moderate stage of the illness who are intolerant or have a contraindication to cholinesterase inhibitors and for those with severe stage of the illness. Table 18.6 presents daily doses and characteristics of the approved cognitive enhancers [13, 49].

Other Pharmacological Treatments

A recent systematic review and meta-analysis showed no benefit or harm from selective serotonin reuptake inhibitors in comparison to placebo in terms of cognition, mood, agitation, or global function in the progression of major NCD, although the study included a small number of relatively low-powered studies [52]. Studies evaluating the use of nonsteroidal anti-inflammatory drugs and antioxidants have shown promise in cohort studies, but they have not been proven to delay onset of major NCD in prospective studies [24]. Although epidemiological studies and clinical trials have shown conflicting results for statins to slow the formation of beta-amyloid peptide, new findings showed that the protective effect of statins against Alzheimer disease may vary by sex, race/ethnicity, and drug type [53]. Future clinical trials that include racial and ethnic groups need to confirm these findings. Treatment with estrogens has not been proven

Table 18.6 Cognitive pharmacotherapy for major neurocognitive disorder due to Alzheimer disease [13, 49]

Drug	Initial dose	Maximum dose	Metabolism	Comments
Donepezil	5 mg od	10 mg od[a] 23 mg od[b]	Hepatic: CYP3A4 CYP2D6	Piperidine derivative that inhibits AChE. Approved for mild, moderate, and severe major NCD due to AD. Dose-dependent cholinergic side effects: nausea, vomiting, diarrhea, muscle cramps, dizziness, fatigue, anorexia
Galantamine ER	8 mg od	24 mg od	Hepatic: CYP3A4 CYP2D6	Tertiary alkaloid that reversibly inhibits AChE and binds to nicotinic receptors. Approved for mild to moderate major NCD due to AD. Dose-response is inconsistent. Typical cholinergic side effects
Rivastigmine (oral) (TD)	1.5 mg bid 5 cm^2 od	6 mg bid 15 cm^2 od	Renal	Carbamate derivative that reversibly inhibits AChE and BuChE. Approved for mild to moderately severe major NCD due to AD; benefits at the highest doses. Typical cholinergic side effects. TD formulation: 3 times less GI side effects
Memantine	5 mg od	20 mg od[c] 10 mg bid[c]	Renal	NMDA noncompetitive glutamate receptor antagonist. Approved for moderate to severe major NCD due to AD. Dose-limiting side effects: dizziness, headache, somnolence, confusion

[a]A dose of 10 mg daily is administered after a dose of 5 mg daily for 4–6 weeks; a dose of 23 mg daily is administered after a dose of 10 mg daily for at least 3 months
[b]US FDA approved a once-daily, sustained-release 23-mg tablet
[c]In patients with significant renal impairment (creatinine clearance ≤ 30 mL/minute), the maximum dose should not exceed 10 mg daily
Note: AChE acetylcholinesterase, *AD* Alzheimer disease, *bid* twice daily, *BuChE* butyrylcholinesterase, *CYP* cytochrome P450, *ER* extended release, *od* once daily, *GI* gastrointestinal, *TD* transdermal

beneficial for symptomatic treatment of Alzheimer disease [24]. Vitamins and over-the-counter medications have also been used in the treatment of Alzheimer disease [24].

Disease-modifying and symptomatic treatments for Alzheimer disease have mostly focused on early insights on the molecular mechanisms involved in Alzheimer disease such as the cholinergic, amyloid cascade, and tau hypotheses [13]. Efforts on the amyloid cascade hypothesis led to clinical trials potentially decreasing the production or aggregation of beta-amyloid or enhancing amyloid clearance from the brain [13]. Passive and active anti-tau immunization studies in animal models have been proven effective at preventing and improving tau pathology [13]. Immunization of an Alzheimer mouse model with beta-amyloid has attenuated the pathology and stimulated the search for a possible vaccination approach to the treatment of human Alzheimer disease [49]. A human study of this approach was discontinued because of encephalitis in a few participants [49]. Other similar approaches to this model are under investigation.

Teaching Point
The spread of neurofibrillary tangle pathology in the brain correlates with synaptic and neuronal loss and cognitive decline and makes it a potential therapeutic target to interrupt progression of tau pathology early in disease [36].

The treatment of neuropsychiatric symptoms due to Alzheimer disease is presented elsewhere in this volume (see ▶ Chap. 22).

18.2 Case Studies

The following case-based studies illustrate the various clinical phenotypes of major or mild NCD due to Alzheimer disease and the diagnostic and management challenges that present with these cases.

18

18.2.1 Case 1

Case 1 History

Mr. A., a 74-year-old retired professional, and his wife were both concerned that his memory was not as good as it was the previous year. He returned from the store with the wrong food items, and now he needed to write down a grocery list, although he was previously able to remember it in his head. He continued to pay the bills and do household projects, but these tasks now took him longer to complete and felt as if he lost his confidence. On this visit to his primary care physician, he stated that "I am quite worried about getting Alzheimer disease, just like my mother." Mr. A. stated that his mother had her first symptoms of major NCD at the age of 75 and that her memory was predominantly affected. To his knowledge, no other family members (including grandparents, aunts, and uncles) had been affected by major NCDs. His personal history revealed recurrent episodes of major depression in his midlife treated with ongoing antidepressant medication (sertraline), but denied any current depressive symptoms. On examination, the Geriatric Depression Scale-15 item score was 1 (indicative of no depression) and the Generalized Anxiety Disorder Scale-7 item score was 6 (indicative of mild anxiety). He had never smoked, rarely drank alcohol, and exercised routinely. He had been taking a blood pressure medication (ramipril) for hypertension for many years and had taken simvastatin for hyperlipidemia, which both were well controlled with medication. Memory testing in the office showed that he scored below normal when repeating a brief story containing ten details. His laboratory examination was normal and MRI of his brain showed bilateral hippocampal atrophy in the basal temporal lobe and lateral temporal lobe and atrophy in the parietal lobe. On genotyping test, he had one apolipoprotein E4 copy.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What other information about this patient do you need to make your diagnosis?

? Question 2. What is the utility of apolipoprotein E genotyping in clinical practice?

? Question 3. What are the risk factors of Alzheimer disease and the prevention strategies for this patient? What should the physician have advised Mr. A.?

? Question 4. What are the common mimics of Alzheimer disease? What is the differential diagnosis of Alzheimer disease in this case?

? Question 5. What role does functional impairment play in the diagnosis of Alzheimer disease?

? Question 6. What are the practical issues to consider in this patient's management and what do you advise the family member?

Case 1 Answers

Case 1 Answer 1 (Question 1—What other information about this patient do you need to make your diagnosis?)

A thorough evaluation of the following items is required.

A1.1. *Longitudinal history*. An accurate history from both Mr. A. and his wife, as a knowledgeable informant, is an essential component to determine the cause or precipitant of his cognitive deficits. Important elements of the history should include:

- Chronology and onset of cognitive impairment: Mr. A. had an onset after the age 65 (which defines the late onset) of his episodic memory impairment (e.g., he was unable to freely recall

the elements in the story) and had persisted over the previous year. Taking a longitudinal history will indicate whether there is progressive decline, which defines the diagnosis of Alzheimer disease.

Teaching Point

Episodic memory, the collection of past personal experiences that occurred at a particular time and place, can be tested by repeating a story or learning and recalling of word (the 3-word, as in MMSE, or the 5-word, as in MoCA) lists, for assessing verbal episodic memory, and by copying a figure and then recalling it at a later time, for assessing visual episodic memory. Neuropsychological evaluation done by neuropsychologists is often able to detect deficits that are not captured using gross, neuroanatomical imaging.

- Whether there was a decline from baseline in function of IADLs and basic ADLs: Mr. A. had a preserved function with the use of compensatory strategies.
- Psychiatric history (e.g., depression, anxiety, psychosis) which may represent a recurrence or relapse of underlying primary psychiatric disorder: Mr. A. had a history of recurrent major depression in midlife, which was successfully treated with continued antidepressant treatment (sertraline). While his GDS-15 score was not indicative of current depressive symptoms, he had anxiety symptoms.
- History of substance misuse (e.g., prescription and over-the-counter medications, alcohol, illicit substances), which was not contributory in his case.
- Medication adherence, including review of recent medication changes and withdrawal, which was unremarkable in this case.
- Medical history, especially the presence of delirium, systemic medical, neurologic, cerebrovascular, or metabolic disorders. A medical evaluation (including laboratory studies) will rule out any alternative causes, such as hypothyroidism or vitamin B_{12} deficiency. Mr. A.'s medical history revealed that he had hypertension and hyperlipidemia, for which he took an angiotensin-converting enzyme inhibitor (ramipril) and a statin (simvastatin), respectively. His lifestyle factors were reviewed.
- Family history for NCDs, with onset age for affected family members across multiple generations. The diagnosis of early-onset familial Alzheimer disease versus late-onset familial Alzheimer disease is made in families with multiple cases of Alzheimer disease in which the mean age of onset is before or after age 65. In this case, there was a first-degree relative (mother) with a history of late-onset major NCD of amnestic phenotype that will increase his risk of developing a familial Alzheimer disease.

A1.2. *Physical examination*. Physical examination is necessary to exclude causal factors for the cognitive impairment. This includes a neurological examination to rule out focal neurological signs suggestive of other NCDs than Alzheimer disease. In Case 1, the physical examination was unremarkable.

The mental status examination should include a brief cognitive assessment, with a particular focus on change in performance from previous testing. (See ▶ section Cognitive Assessment, Cognitive Evaluation discussed earlier.) ◘ Table 18.7 summarizes common brief screening cognitive tests for cognitive impairment [54–58]. Although several brief cognitive tests have been utilized for over four decades, the mental test score (MTS), also known as the abbreviated mental test (AMT), and the Mini Mental State Examination (MMSE) have remained popular in the assessment of patients with cognitive impairment despite limitations [55]. Many newer brief cognitive tests have been published, with application to primary care or secondary care, including GPCOG, Mini-Cog, six-item cognitive impairment test (6-CIT), or the seven-minute screen [55]. The Montreal Cognitive Assessment (MoCA) and the Addenbrooke's Cognitive Examination-Revised (ACE-R) are, among several others, validated brief screening tests for major or mild NCDs [56]. Other sensitive screening tools shown to be useful in identifying cognitive dysfunction in medical patients include the Short Blessed Test, Brief Alzheimer's Screen, and Ottawa 3DY [57]. All these performance-based tests require a cooperative patient. It is important to know that the pattern of scoring is often more important than the overall score. Scoring perfectly on any cognitive screening test does not preclude the diagnosis of major or mild NCD due to Alzheimer disease. A single test may not suffice, as a test considerably easy for a graduate with mild cognitive impairment in clinic may be considerably difficult for an older adult with learning difficulties. Highly educated patients with major NCDs may score perfectly but have deficiencies in insight, judgment, and other areas of cognitive function. Conversely, patients may score suboptimally on a screening test because of education level and language barrier, but have good performance when tested in greater depth. Attention and motivation deficits due to anxiety and depressive disorders, as well as physical limitations, may influence results.

A1.3. *Neuropsychological testing*. Neuropsychological testing can establish the pattern and degree of cognitive impairment. Put together, this information will provide the most accurate clinical diagnosis of a potential NCD due to Alzheimer disease versus an alternative diagnosis. This can be a useful tool for helping to quantify impairment and for monitoring for change over time, especially in very early stage of the disease. Like in Case 1, story recall measures listening comprehension and recall of auditory presented and processed information. Studies show

Table 18.7 Common brief screening tests for cognitive impairment [54–58]

Abbreviation	Test name	Time (minutes)	Comments
CDT	Clock-drawing test	2	Quick to administer; limited assessment; less influenced by education and culture than is MMSE/MoCA; detects moderate Alzheimer disease in primary care
VFC	Verbal fluency categories	3	Measure of executive function, language, semantic memory; varies by education
Mini-Cog	Mini-Cog	3–4	It combines 3-term registration and recall with clock drawing; used in primary care practice
MIS	Memory impairment screen	4	Easily administered, even to illiterate patients
MTS	Mental test score	5	Short questionnaire; quick to administer; hard to score
SIS	Six-item screener	5	Telephone or in-person administered; easily scored by summation of errors
GPCOG	General practitioner assessment of cognition	5	Includes informant questions
TMT	Trail making test	5	It reflects cognitive abilities of speed and fluid intelligence
AMT	Abbreviated mental test	5	10-item scale; a short version (the AMT7) was also developed
TICS-M	Telephone interview of cognitive status-modified	5–10	Telephone administered
7MS	Seven-minute screen	7	Highly sensitive to various types of NCD
MMSE	Mini Mental State Examination	8–13	Cutoff score 23/24; takes longer; assesses patients presenting with memory problems, but limited sensitivity to frontal and subcortical changes; varies by age/education
MoCA	Montreal Cognitive Assessment	10–12	Detects mild cognitive problems
ACE-R	Addenbrooke's Cognitive Examination-Revised	16	Sensitive to early cognitive dysfunction

that patients with Alzheimer disease encode and recall less information from the story than patients with frontotemporal NCD, and such patterns of performance can be useful in differentiating memory impairment in these two types of NCD [59]. (See ► Chap. 4.)

A1.4. *Neuroimaging studies.* A brain MRI scan will help to assess the role of strokes, tumors, or other brain pathology. On structural neuroimaging, Mr. A. had a typical Alzheimer pattern of atrophy. While not performed in this case, a PET scan using fluorodeoxyglucose (FDG) could identify the presence of cerebral hypometabolism, whereas amyloid PET scans could identify the presence of amyloid protein.

A1.5. *Laboratory investigations.* There are no specific tests to diagnose Alzheimer disease during life. Laboratory investigations are helpful to rule out other contributing or reversible factors. As discussed previously, Fig. 18.7 offers an overview of the basic and more specific laboratory examinations in the diagnosis of major or mild NCD due to Alzheimer disease [36, 44]. In Case 1, the workup was normal. His apolipoprotein E genotyping test is further discussed below.

Case 1 Answer 2 (Question 2—What is the utility of apolipoprotein E genotyping in clinical practice?)

Clinicians can make a reasonably accurate clinical diagnosis of Alzheimer disease by ruling out other potential causes of NCDs, and checking for a genetic predisposition to Alzheimer disease with apolipoprotein E genotyping, sometimes in conjunction with tau and beta-amyloid testing, is supplemental information. In Case 1, after other causes such as overmedication, thyroid disease, and vascular NCD (caused by strokes) have been ruled out, apolipoprotein E genotyping may have helped to determine the probability that NCD is due to Alzheimer disease. Mr. A. had symptoms of memory impairment that were not yet interfering with daily living. On genotyping test, he had one apolipoprotein E4 copy. However, the utility of genotyping for apolipoprotein E remains under debate (see ► section Genetic Risk Factors). Patients with late-onset NCD and one or two apolipoprotein E4 copies are more likely to have Alzheimer disease [13, 25]. However, this remains equivocal as genotyping for apolipoprotein E was not found to be of significant diagnostic use in identifying Alzheimer disease in a community-based sample with late-onset Alzheimer disease [14]. Not all who have e4 alleles

develop Alzheimer disease, and, even in symptomatic patients, only about 50% of those with late-onset Alzheimer disease have apolipoprotein e4 alleles [13]. It is important to remember that establishing the diagnosis of Alzheimer disease relies on clinical or neuropathological assessment. Neuropathologic findings of extracellular beta-amyloid plaques and tau-containing intraneuronal neurofibrillary tangles remain the gold standard for diagnosis. In summary, the association of the apolipoprotein e4 allele with Alzheimer disease is significant; however, apolipoprotein E genotyping is neither fully specific nor sensitive to be used alone as a diagnostic test for Alzheimer disease [60]. (See ▶ Sect. 18.4, MCQ1, for details on apolipoprotein E and normal aging.)

Case 1 Analysis Mr. A. had subjective concerns about a change in cognition, objective impairment in cognition, and preservation of functional abilities; therefore, he met the criteria for a mild NCD (see ◘ Fig. 18.1). Because his history and cognitive testing were of memory impairment (the main phenotype of Alzheimer disease) and his pathophysiological process of atrophy of the brain was consistent with the Alzheimer disease, he met the criteria for mild NCD due to Alzheimer disease, with an intermediate biomarker probability of Alzheimer disease (see ◘ Figs. 18.2 and 18.3 for highlights of the DSM-5 and NIA-AA diagnostic criteria).

Case 1 Answer 3 (Question 3—What are the risk factors for Alzheimer disease and the prevention strategies for this patient? What should the physician have advised Mr. A.?)

As illustrated earlier in ◘ Table 18.2, there are several non-modifiable and potentially modifiable risk factors for Alzheimer disease, which require review in each individual patient to understand the risks for this disease. Because Mr. A. had a first-degree relative with late-onset Alzheimer disease, and because nothing in his family history suggested an autosomal-dominant multigenerational transmission, he did not require further genetic testing. Although apolipoprotein E is a known risk factor for late-onset Alzheimer disease, data on midlife risk factors for major NCD that have included apolipoprotein E status have not been found to increase the accuracy of the predictive model [24]. A personal history of depression may have increased Mr. A.'s risk for developing Alzheimer disease later in life. His primary care physician should have advised Mr. A. to control his cardiovascular risk factors, including his hypertension and cholesterol levels, using evidence-based strategies (see ◘ Table 18.2 for risk factors). However, Mr. A. should have been informed that there are no high-quality clinical trials that have evaluated the effectiveness of modifying the risk factors and that there are currently no proven therapies that will fully prevent NCD due to Alzheimer disease. Therefore, Mr. A. could not be fully assured that these interventions would decrease his risk of developing Alzheimer disease despite other proven health benefits.

◘ **Table 18.8** Diagnostic entities that mimic Alzheimer disease [45]

Diagnostic entity	Red flags for non-Alzheimer disease
Anxiety	Clinical evidence for anxiety; normal MRI; typical neuropsychological profile
Depression	Clinical evidence for depression; positive personal and family history for depression; presence of stressors; normal MRI; typical neuropsychological profile
Neurodevelopmental and neurocognitive disorders	Onset in the developmental period Non-Alzheimer-like atrophy pattern on MRI, non-Alzheimer-like hypometabolism on functional imaging; abnormal dopamine transporter scan; significant vascular burden or strategic infarcts on MRI; myoclonus, typical EEG pattern, and CSF 14–3-3 protein in Creutzfeldt-Jakob disease
Metabolic diseases	Typical blood screen pattern
Central nervous system infections	Serology testing
Autoimmune encephalopathies	Identifiable antibodies; abnormal MRI; typical neuropsychological profile
Sleep apnea	History of snoring; abnormal sleep study
Epilepsy	Clinical evidence for seizures; transient epileptic amnesia; epileptiform changes on EEG
Brain lesions	Neuroimaging findings; focal neurological deficits
Korsakoff syndrome	History of alcohol misuse; history of Wernicke encephalopathy

Case 1 Answer 4 (Question 4—What are the common mimics of Alzheimer disease? What is the differential diagnosis of Alzheimer disease in this case?)

With nearly half (45%) of older adults aged 85 years and older having major NCDs, it would seem reasonable to assume that cases of presumptive cognitive impairment are actually due to Alzheimer disease. However, this assumption is not always correct, and misdiagnosis can impact management. While many medical conditions can seemingly resemble Alzheimer disease, few are actually true imitators that can confound the differential diagnosis, and these diagnostic entities are further described below (see ◘ Table 18.8) [45].

A4.1. *Anxiety disorder.* It is often challenging to diagnose a geriatric patient presenting with a very mild cognitive complaint, which could potentially represent early Alzheimer disease, but might also reflect an anxiety disorder. Clues to a diagnosis of anxiety disorder rather than major or mild NCD due to Alzheimer disease include the following:

- Impaired performance on bedside cognitive testing despite unchanged performance in everyday activities. Declining occupational or social confidence and early visuospatial deficits in an older adult are red flags for Alzheimer disease.
- Patients may attend the consultation visit alone despite being asked to bring a collateral informant to explain their presenting symptoms [61].
- The anxious patient is more concerned about their deficits than their knowledgeable informant, whereas the opposite is more typical in Alzheimer disease. Nevertheless, concern remains as the evidence suggests that older adults with subjective memory decline, but no objective impairment, may have a higher incidence of subsequent conversion to Alzheimer disease [62]. Mr. A. had evidence of mild anxiety symptoms in the context of objective cognitive impairment, which would warrant ongoing review of this patient.
- Patients with anxiety disorders have specific neuropsychological profile associated with impaired cognitive performance, which may resemble an Alzheimer disease-related profile. (See ▶ Chaps. 4 and 12 .) For example, generalized anxiety disorder in older adults has been associated with deficits in processing speed, inhibition, problem solving, working memory, and immediate and delayed memory, which are associated with functional impairment [63]. In case of diagnostic uncertainty, interval reassessment may help to determine whether there has been objective evidence for decline, which is expected in Alzheimer disease.
- Unlike those with Alzheimer disease, patients with generalized anxiety disorder who either have low cognitive performance or report clinical improvement with anxiety treatment show improvement in multiple cognitive domains [63].

A4.2. *Major depressive disorder.* The pattern of cognitive impairment associated with major depression is often qualitatively different from that seen in Alzheimer disease. Clues to a diagnosis of major depressive disorder rather than major or mild NCD due to Alzheimer disease include the following:

- Clinical interview reveals psychological and neurovegetative symptoms of major depression. Concentration and attention are often impaired, leading to poor registration of information, but the performance may improve dramatically with treatment and when patients are motivated and attend to the task at hand.
- The presence of psychosocial stressors and a personal and family history of psychiatric illness are essential. Attributing cognitive concerns to depression in geriatric patients particularly without obvious stressors or previous psychiatric illness should be carefully reviewed. Additionally, a patient with major depressive disorder will present such features for at least 2 weeks and will not be associated with dramatic changes in episodic memory. (See ◘ Table 18.9 regarding cognitive differentiation between depression and Alzheimer disease [1] and ◘ Table 18.10 regarding differential diagnosis of episodic memory impairment [45].) Although Mr. A. had no current evidence suggestive of major depression to warrant a comprehensive assessment, he did present with a past history of depression. There is a growing evidence to suggest that depression may either be a risk factor for or an early manifestation of Alzheimer disease, consistent with the dysfunction of neuroanatomical limbic structures [64]. (See ▶ Chap. 10.) In equivocal cases, further investigations, treatment of depression, and ongoing review of the patient until the situation is elucidated are recommended.

◘ **Table 18.9** Cognitive differences between Alzheimer disease and major depressive disorder [1]

Alzheimer disease	Depressive disorder
Insidious onset, progressive cognitive loss	Subacute onset, patchy cognitive loss
Patient can minimize cognitive deficit despite objective deficit	Patient with subjective complaints that exceed objective cognitive deficit
Guesses and wrong answers on testing	"I don't know, I can't" responses on testing
Aphasia and apraxia	Language and motor skills intact
Irreversible cognitive loss	Reversible cognitive loss

◘ **Table 18.10** Differential diagnosis of episodic memory impairment [45]

Diagnostic entities	Course and progression of episodic memory
Alzheimer disease, Lewy body disease, frontotemporal NCD	Insidious onset and gradual progression
Vascular NCD, multiple sclerosis	Stepwise progression
Solitary stroke, space occupying lesion, traumatic brain injury, hypoxic or ischemic injury, encephalitis	Static pattern
Concussions, seizures, transient global amnesia	Transient pattern
Medications, hypoglycemia, tumors, Korsakoff syndrome	Variable time course pattern

A4.3. *Substance use disorders.* Substance use disorders can present with significant cognitive impairment, but it is unlikely to produce a clinical syndrome resembling a typical Alzheimer disease. However, episodic memory impairment and confabulation occur in alcohol-related Korsakoff syndrome, although usually without the loss of social confidence (as in Mr. A.'s case) that is typical for Alzheimer disease [45].

A4.4. *Intellectual disability.* Although there was nothing in the Case 1 history to suggest this, intellectual disability is a disorder with onset in the developmental period, which is distinct from NCDs that present with an acquired loss of cognitive functioning. Noteworthy, a major NCD may co-occur with a preexisting intellectual disability (e.g., a person with Down syndrome who develops Alzheimer disease; a person with intellectual disability who further loses cognitive capacity following a traumatic brain injury). In such cases, the diagnosis of NCD and intellectual disability will both be noted.

A4.5. *Metabolic conditions.* It is important to exclude metabolic conditions that may influence Mr. A.'s cognition. As shown in ◘ Fig. 18.7, routine check of serum glucose, B_{12}, folate, calcium, and thyroid function is recommended in all patients [36, 44]. It is important to treat any such abnormalities, as this can lead to dramatic improvements in some patients [36]. However, caution is necessary when attributing progressive episodic memory impairment or other focal cognitive deficits to metabolic conditions, particularly when there is neuroimaging evidence for atrophy, which rather suggest a neurodegenerative process [45].

A4.6. *Infections.* Infections do not usually resemble Alzheimer disease, although several acute infections such as herpes simplex encephalitis may lead to memory impairment, which in the chronic state may mimic clinical and cognitive manifestation of Alzheimer disease [45]. From the history provided in Case 1, there was no indication to screen for infections in this patient, such as HIV infection and syphilis, which could have caused cognitive impairment.

A4.7. *Brain lesions.* Tumors involving the temporal lobe can cause progressive memory impairment resembling Alzheimer disease, but those are uncommon and easily detected through structural neuroimaging.

A4.8. *Autoimmune syndromes.* Several antibodies (e.g., voltage-gated potassium channel complex receptor antibodies, *N*-methyl-D-aspartate (NMDA) receptor antibodies) can cause limbic encephalitis that can affect cognition. These conditions are associated with acute or subacute encephalopathies, seizures, or movement disorders and often with neuroimaging changes of focal hippocampal atrophy, which superficially can resemble Alzheimer disease. Although there was nothing from the history in Case 1 to suggest this, clues to a diagnosis of limbic encephalitis rather than major or mild NCD due to Alzheimer disease include the following:

- The clinical features of anti-voltage-gated potassium channel-associated limbic encephalitis include episodic memory impairment, disorientation, and agitation; however, contrary to Alzheimer disease, there is a subacute onset [65]. Hyponatremia is also noted in most of these patients [65].
- The type of memory loss in patients with encephalitis associated with antibodies to voltage-gated potassium channels is usually different from that seen in Alzheimer disease, with extensive and often temporally ungraded retrograde amnesia for events for many years preceding the acute illness [66].
- Unlike Alzheimer disease, anti-voltage-gated potassium channel-associated limbic encephalitis is potentially treatable with corticosteroid therapy, plasma exchange, and intravenous immunoglobulin, which stresses the importance of accurate diagnosis [65].
- There are anecdotal reports of antibodies in patients with a slowly progressive cognitive impairment and hippocampal atrophy closely resembling Alzheimer disease. A study demonstrated synaptic autoimmunity in a proportion of patients with NMDA receptor antibodies and unexplained slowly progressive cognitive impairment [67]. In view of establishing the differential diagnosis of autoimmunity versus Alzheimer disease, clinicians should consider testing for neuronal-specific antibodies or assessing cerebrospinal fluid for biomarkers of Alzheimer disease.

A4.9. *Seizure disorder.* Seizures and Alzheimer disease can coexist particularly in the late stages of Alzheimer pathology. In the absence of other seizure-related phenomena, medial temporal lobe seizures can manifest with significant memory impairment, described as transient epileptiform amnesia. Although there was nothing from the history in Case 1 to suggest a seizure disorder, clues that should raise suspicion of transient epileptiform amnesia include the following:

- Periods of gaps in the memory record, described as dense amnesia for distinct events with relative preservation at other times, often occurring on waking, and a history of olfactory hallucinations, staring episodes, or automatisms suggestive of epileptic activity [68].
- Prolonged EEG to detect epileptiform activity, along with brain MRI to rule out structural abnormalities, and examining the cerebrospinal fluid to exclude Alzheimer pathology may be considered, especially in someone with attentional deficits or alterations in level of consciousness, even without history of convulsions.

A4.10. *Sleep apnea.* Sleep apnea can manifest with memory complaints that can mimic the clinical manifestations of Alzheimer disease. Patients with Alzheimer disease have a five times higher chance of presenting with obstructive sleep apnea than cognitively normal adults. Progressive changes in sleep quality and structure, cerebral blood flow, and cellular redox status in patients with obstructive sleep apnea may all be contributing factors to cognitive decline, which can further aggravate Alzheimer disease progression [69]. Although there was nothing from the history in Case 1 to suggest sleep apnea, clinicians should consider screening patients at risk for obstructive sleep apnea in those with cognitive impairment. Clues to diagnosis include history of snoring from patients and their partners and abnormal sleep study, where possible to perform.

A4.11. *Other neurocognitive disorders. Delirium.* Although there was nothing from the history in Case 1 to suggest this diagnostic entity, clues to a diagnosis of delirium rather than major or mild NCD due to Alzheimer disease include the following:

- Rapid onset, fluctuations in mental status, and changes in the level of arousal, cognition (i.e., orientation, attention, memory), psychomotor activity, and perceptual abilities are all suggestive of delirium. Falling asleep during the assessment time, staring off into space, decreased motor activity, and lethargy are usually seen in hypoactive delirium and are abnormal to occur in patients with Alzheimer disease. (See ▶ Chap. 17.)
- Because major or mild NCD is a predisposing factor for delirium, a recurrent delirium should raise the suspicion for preexisting NCD. A change from baseline is often key to confirming the diagnosis of delirium in those with preexisting NCDs.
- Patients with a preexisting NCD can present with comorbid depression, who can subsequently develop delirium as a result of "failure to thrive."

A4.12. *Other neurocognitive disorders. Vascular neurocognitive disorder.* As with Alzheimer disease, vascular NCD is common with advancing age and often associated with insidiously progressive rather than the typical stepwise progression [70]. (See ▶ Chap. 21.) Vascular NCD and Alzheimer disease share many risk factors, including hypertension, and commonly coexist. Vascular NCD with an insidious onset and gradual progression is generally due to small vessel disease leading to white matter, basal ganglia, or thalamus lesions. Unlike Alzheimer disease, the gradual progression of vascular NCD in these patients is often marked by acute events that can manifest with subtle neurological deficits. ◘ Table 18.11 depicts the general characteristics of the main types of major NCDs [45]. Clinical clues to a diagnosis of vascular NCD include the following:

- Impaired complex attention, particularly the speed of information processing, relatively preserved episodic memory, executive dysfunction, and subtle personality changes are characteristic for vascular NCD [45].
- The presence of a brisk jaw jerk, facial jerks, and deep tendon reflexes, with extensor, but often flexor, plantar responses, are also suggestive of vascular NCD [45]. On the contrary, early in Alzheimer disease course, the physical examination is typically normal, as in Case 1, but myoclonus is fairly common in later stages.
- Neuroimaging is generally decisive if the scan shows significant vascular damage. Although a small vascular load is common in older adults, the pattern and extent of vascular changes necessitates correlation with the clinical picture. It is often the case that the neuropathology of cognitive impairment in later life is a mixture of Alzheimer disease and microvascular brain damage. On neuroimaging techniques, cerebral amyloid angiopathy emerges as an important risk marker for Alzheimer disease, manifesting as microinfarction, microhemorrhage, and macrohemorrhage of the brain, which need to be differentiated from vascular NCD. Microbleeds in subcortical structures are typical of vascular disease, whereas lobar-specific microbleeds are thought to reflect amyloid angiopathy, which can be a marker of Alzheimer pathology [71]. (See ▶ Chap. 3.)

◘ **Table 18.11** Characteristics of the main types of neurocognitive disorders (NCDs) [45]

NCD type	Characteristics
Alzheimer disease	Progressive cognitive and functional decline, early loss of insight Amnestic and non-amnestic phenotypes Cognitive changes and Alzheimer biomarker evidence required for diagnosis of probable Alzheimer disease
Lewy body disease	Spectrum of disorders with cognitive, movement, visual hallucinations, sleep disturbance, and autonomic changes Alpha-synuclein deposits present in neurons
Frontotemporal lobar degeneration	Focal atrophy of frontal/temporal lobes on MRI Personality and behavior/language changes Younger age at onset, strong familial component
Vascular cognitive impairment	Stepwise progression and focal neurologic signs Complex attentional deficits, slowed processing speed, retrieval difficulties, dysexecutive syndrome, depression Mild motor signs in subcortical subtype Symptoms overlap with Alzheimer disease

- It is important to note the comorbid presence of medial temporal lobe atrophy, which may point to coexistent Alzheimer pathology. A detailed history taking can reveal an acute or subacute decline in vascular NCD patients.

A4.13. *Other neurocognitive disorders. Frontotemporal neurocognitive disorder.* This comprises a group of syndromes with proteinopathies including tau and transactive response DNA-binding protein 43 kDa (TDP-43). Frontotemporal NCD comprises two variants: behavioral-variant frontotemporal NCD and primary progressive aphasia. (See ▶ Chap. 19.) These variants are clinically distinct from typical NCD due to Alzheimer disease, with the following clues to diagnosis:

- Patients with frontotemporal NCD can present with an insidious onset of episodic memory impairment, especially when accompanied by focal medial temporal lobe atrophy, and can resemble Alzheimer disease.
- Anomia due to early semantic-variant frontotemporal NCD can be mistaken for episodic memory impairment due to Alzheimer disease, although the early impairment in verbal and semantic knowledge is more characteristic for frontotemporal NCD variant and not a feature of typical Alzheimer disease [45]. Evidence of amyloid deposition using cerebrospinal fluid measures of beta-amyloid, or performing amyloid PET imaging, may help to distinguish Alzheimer from non-Alzheimer disease pathologies [45].

A4.14. *Other neurocognitive disorders. Lewy body neurocognitive disorder*. This is the second most common cause of late-onset NCD and is typically associated with cognitive fluctuations, parkinsonism, hallucinations, rapid eye movement sleep behavior disorder, or autonomic dysfunction, which are uncommon in Alzheimer disease [45]. Although there was nothing in the history in Case 1 to suggest this entity, clues to a diagnosis of Lewy body NCD rather than NCD due to Alzheimer disease include the following:

- On dopamine transporter neuroimaging, Lewy body NCD often shows evidence of nigrostriatal degeneration [45]. However, in the absence of parkinsonism when patients may have negative dopamine transporter imaging, it may not be possible to distinguish Lewy body NCD from Alzheimer-related NCD during life.
- Because Lewy body disease and Alzheimer disease can coexist at postmortem, even an Alzheimer disease-like cerebrospinal fluid profile (i.e., raised total tau or phosphorylated tau, low beta-amyloid$_{1-42}$, raised tau/beta-amyloid$_{1-42}$ ratio) cannot exclude concomitant Lewy body pathology [45].

A4.15. *Other neurocognitive disorders. Normal pressure hydrocephalus*. This is associated with the triad of cognitive impairment, urinary incontinence, and gait disturbance, which rarely resembles typical Alzheimer disease. However, Alzheimer disease pathology can coexist, and its role in normal pressure hydrocephalus is still debated, but there is evidence to suggest that patients with significant beta-amyloid plaques, neuritic plaques, and neurofibrillary tangles have worse outcomes following shunting, suggesting that Alzheimer disease biomarkers may play a role in selecting patients for surgery [72]. There was nothing in the history in Case 1 to suggest a diagnosis of normal pressure hydrocephalus.

A4.16. *Other neurocognitive disorders. Creutzfeldt-Jakob disease*. Creutzfeldt-Jakob disease is a prion disease. Unlike the typical Alzheimer disease, the diagnosis of Creutzfeldt-Jakob disease is suspected when there are typical symptoms and signs such as rapidly progressing, irreversible NCD with myoclonus, difficulty walking, and mood changes. EEG often shows characteristic generalized periodic sharp wave pattern, cerebrospinal fluid analysis shows 14–3-3 protein, and MRI of the brain often has high signal intensity in the caudate nucleus and putamen on T2-weighted images or diffusion-weighted imaging (DWI). This pattern is distinct from the medial temporal lobe atrophy and bilateral temporoparietal hypometabolism associated with typical Alzheimer disease-related NCD.

Case 1 (Continued)

Three years later, Mr. A. was brought in by his daughter this time. Although he did not believe that anything was wrong, his daughter noted that his father's thinking and memory had slowly deteriorated. He was no longer able to shop as he bought repeatedly the same food items, was getting lost in the store and his familiar neighborhood, was no longer paying the bills, with wife taking over the management of finances, and was no longer driving for concerns of getting lost. Upon interviewing, he had pauses in his speech and his daughter often filled in missing words for him. On a brief cognitive test, he was disoriented to the year, month, day, and date, was unable to name common items, and was unable to recall any of the few items he was instructed to remember. His MRI of the brain showed mild small vessel ischemic disease, read as "average for his age," and bilateral atrophy of hippocampus in the lateral temporal lobes and atrophy of parietal lobes.

Case 1 Answer 5 (Question 5—What role does functional impairment play in the diagnosis of Alzheimer disease?)

Performance-based scales for activities of daily living have mostly been administered to patients with mild to moderate major NCDs, but more recently they have also been used in mild NCDs [4]. Using the impairment of activities of daily living to draw the line between the phase of mild NCD and major NCD has been under debate by many experts [4]. A summary of the IADLs and basic ADLs are listed in ◘ Fig. 18.9 [4].

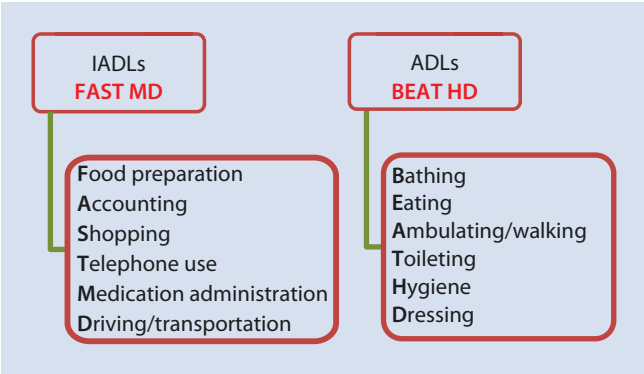


Fig. 18.9 Instrumental activities of daily living (IADLs) and basic activities of daily living (ADLs) [4]

As described previously in the Background section, impairment in activities of daily living can be detected at different stages of Alzheimer disease. Impairment in basic ADLs is detected in the transition from mild to moderate stage of major NCD and beyond, whereas impairment in IADLs is detected at the transition from mild, or even at earlier, stage of the disease to major NCD [4]. It is plausible that changes in activities of daily living will correlate closely with changes in cognition and behavior [4]. If clinical measures used as functional screening tests for early diagnosis are positive, a follow-up with a biomarker test such as an MRI scan, amyloid PET scan, or cerebrospinal fluid analysis for beta-amyloid and tau is helpful.

The short cognitive tests do not evaluate the impact of cognitive impairment on occupational activities of daily living, which are performance-based measures. An example of such test is Kohlman Evaluation of Living Skills (KELS), which is a standardized test designed to determine the patient's ability to function in basic living skills [73]), which distinguishes demented from non-demented populations [57]. There is a great deal of interdependency among patients' social, financial, and functional status, which need thorough evaluation and appropriate attribution. For example, a low socioeconomic status may play a role in inadequate ability to purchase medications and is not a reflection of impaired IADL function. A critical issue in the functional assessment is the concern about driving ability due to cognitive impairment. According to local jurisdiction, physicians have a mandatory or discretionary duty to report patients whom they believe to be unfit to drive to the relevant licensing agency. There is no cognitive test which has sufficient sensitivity or specificity to be used as a single determinant of driving ability. However, abnormalities on the MMSE, MoCA, clock-drawing test, and trail making test Part B should trigger further in-depth testing of driving ability [74].

Case 1 Analysis (Continued) Mr. A. had a clear evidence of decline in his prior abilities that interfered with his function (he was unable to shop, manage finances, and drive). Cognitive impairments in domains of memory and language were present. Therefore, Mr. A. met criteria for a major NCD (see Fig. 18.1). His cognition deteriorated slowly over 3 years and suggested a gradual onset, whereas worsening of his memory indicated an amnestic presentation. His brain MRI scan showed typical cortical atrophy (a biomarker) and ruled out a vascular NCD. There was nothing in the history to suggest another type of NCD or a systemic medical condition that could have had a substantial effect on cognition. Therefore, Mr. A.'s presentation met the criteria for the amnestic type of probable major NCD due to Alzheimer disease with the atrophy on the MRI suggesting an intermediate biomarker probability of Alzheimer disease (see Fig. 18.2). There was nothing in the history to suggest possible instead of probable Alzheimer disease (see Fig. 18.3).

Case 1 (Continued)

Five years later, you saw Mr. A. and his daughter again in your office, this time for his agitation. A neurologist already started Mr. A. on donepezil 10 mg daily and subsequently added memantine 20 mg daily 1 year previously. His MMSE score was now 5 out of 30 (severe stage), with 6 points decline in the previous 12 months. He was incontinent and required assistance with bathing. He lost significant weight due to anorexia since donepezil was started, was dizzy, had several falls, and had difficulties with swallowing his medications. He was irritable and agitated and was only able to use single words. His daughter also wanted you to address the perceived loss of response to treatment and wished to discontinue his medications.

Case 1 Answer 6 (Question 6—What are the practical issues to consider in this patient's management and what do you advise the family member?)

There are four main areas that clinicians need to discuss with the patient or substitute decision maker when prescribing cognitive enhancers for major NCD due to Alzheimer disease:

1. Set realistic treatment expectations
2. Address possible side effects
3. Consider when to switch medications
4. Consider when to discontinue medications

Providing early education to Mr. A. and his family that all available pharmacological treatments are symptomatic and do not alter the progression of Alzheimer disease is imperative and helps with adjusting their treatment expectations. In mild to moderate stages of major NCD, patients show greatest improvement on cognitive measures usually at 6 months and cross baseline at 9–12 months, whereas the most benefit on global measures is observed at 3 months and cross baseline performance at 6 months [49]. On functional measures, patients would rather show stabilization that lasts for an average of 6 months; for example, managing one's finances or driving should not be expected to significantly improve with treatment. Regarding non-cognitive symptoms such as apathy, irritability, and agitation, cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) usually prevent new neuropsychiatric symptoms (in those with mild to moderate disease stages), but also may help improve some of these symptoms (especially in those with moderate to severe disease stages). In moderate to severe cases, memantine tends to stabilize cognitive and functional manifestations of

Table 18.12 Potential contraindications to using cognitive enhancers [49]

	Cardiac disease	Renal disease	Liver disease	Other diseases	Medications
Cholinesterase inhibitors	Bradycardia (< 50 bpm) Left bundle branch block Syncope (rivastigmine, galantamine)	Renal insufficiency (rivastigmine)	Liver disease (galantamine)	Peptic ulcer disease COPD (no evidence in mild/moderate) Seizure disorder	Anticholinergics Beta-blockers
Memantine		Creatinine clearance < 30 mL/minute (max daily dose 10 mg)			

Table 18.13 Strategies for side effects, lack of response, and treatment discontinuation of cholinesterase inhibitors [49]

Approach to GI side effects	Approach to lack of treatment response	Approach to treatment discontinuation
Wait: GI side effects are more common at treatment initiation/at dose increase, tend to be transient Slow titration rate by no less than 4-week intervals to the minimally effective dose Lower the dose Caregiver administration (if evidence of unintentional misuse) Take with food (esp. for rivastigmine per os) Switch to rivastigmine patch (3 times fewer GI side effects) If GI intolerance: wait for complete resolution of side effects before switching to second agent Discontinue	Ensure previous compliance Ensure trialed max dose for at least 3 months Ensure lack of response is well defined: > 2 MMSE points/year decline; documented decline in functional autonomy or behavior during prior 6–12 months Switching to second agent: likely done overnight, initiate at recommended dose, increase twice as fast (in 2-week intervals) to avoid possible deterioration during switch	Stop if: Patient/caregiver wants to, and understands risks/benefits of continuing/stopping Rate of decline greater than before treatment Global Deterioration Scale of 7 (see Table 18.14) Patient experiences dysphagia Significant GI adverse events Do not stop if: Based on MMSE alone Patient is institutionalized Based on adverse events (e.g., falls) that may have other causes

Note: *ChEIs* cholinesterase inhibitors, *GI* gastrointestinal, *MMSE* Mini Mental State Examination

the disease for an average of 6 months [49]. Based on Mr. A.'s stage of illness, a standard approach was to offer Mr. A. at least a trial of a cholinesterase inhibitor and, subsequently, memantine. Regarding reasonable options, Mr. A. and his daughter needed to know that all three cholinesterase inhibitors are modestly efficacious for mild to moderate stage of NCD due to Alzheimer disease [49], with donepezil being approved for mild to severe stages.

All three cholinesterase inhibitors are associated with cholinergic side effects (e.g., anorexia, nausea, vomiting, diarrhea, abdominal discomfort, fatigue, muscle cramps, dizziness) and are dose dependent. Table 18.12 shows the most common contraindications to using cholinesterase inhibitors and memantine [49]. Switching agents for loss of response after several years of treatment with a cholinesterase inhibitor is not recommended because this usually indicates the natural progression of the disease stage rather than loss of response [49]. In Mr. A.'s case, addition of memantine, rather than switching to a second cholinesterase inhibitor, had been a reasonable option. Some evidence shows that in patients with moderate to severe major NCD due to Alzheimer disease, combination treatment with donepezil and memantine slowed cognitive and functional decline and produced consistent benefits that appear to increase over time, and that are beyond those expected of cholinesterase inhibitor treatment alone, although the additive benefit of these two agents has not been conclusively demonstrated [36]. Table 18.13 summarizes some approaches to minimizing side effects, especially the gastrointestinal side effects of cholinesterase inhibitors, the approach to lack of response, and reasons to discontinue treatment [49]. The titration schedule and total daily dose of cognitive enhancers are shown in Fig. 18.10 [49]. The clinicians need to provide information that discontinuing cholinesterase inhibitors in patients with moderate to severe Alzheimer disease may lead to worsening of cognitive and functional impairment as compared to continued treatment, and this must be reevaluated according to the risk for known side effects if treatment continues [36]. The patient or their substitute decision maker must be informed of the risks and benefits of continuation versus discontinuation of treatment. When a medication is discontinued because of a perceived lack of effectiveness, it is suggested that the dose be tapered and stopped, with monitoring over the following 1–3 months. If there is evidence of an observable decline in some cases, reinstating treatment may be considered if feasible [36].

Case 1 Analysis (Continued) Mr. A. had an optimal medication trial for both donepezil and memantine. He had anorexia

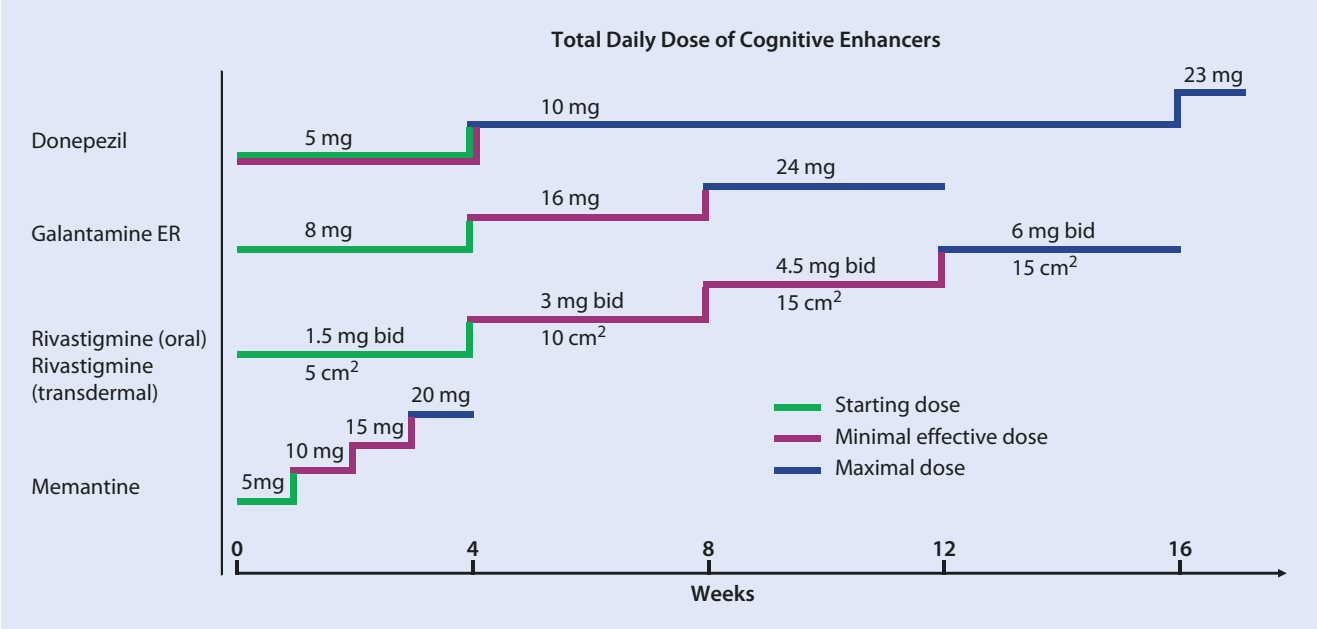


Fig. 18.10 Titration schedule and total daily dose of cognitive enhancers

Table 18.14 Key elements of the Global Deterioration Scale [75]

Stage of cognitive decline		Patient's abilities
1	None	No problems in daily living
2	Very mild	Forgetting names and locations of objects, trouble finding words
3	Mild	Difficulty traveling to new locations, handling problems at work
4	Moderate	Difficulty with complex tasks (e.g., finances, shopping, planning events)
5	Moderately severe	Requires assistance to choose clothing, prompting to bathe
6	Severe	Loss of awareness of recent events; requires assistance with bathing; incontinent
7	Very severe	Limited vocabulary; use of single words; inability to walk and sit; requires assistance with eating

with weight loss, possibly as a side effect from donepezil treatment. He experienced dizziness possibly due to the use of donepezil and memantine. His falls may have been adverse events from cognitive enhancers but may have had other plausible causes, including the progression of his disease. He had a rapid decline on MMSE score of 6 points during the previous 12 months, which may have suggested a lack of response to trial of memantine. Some clinicians use the Global Deterioration Scale to measure the progression of Alzheimer disease [75]. This scale divides Alzheimer disease into seven stages of ability (see Table 18.14) [75]. Mr. A.'s disease progressed to more advanced stage (i.e., Global Deterioration Scale stage 7) where there would be no clinically meaningful benefit for the patient to continue treatment. Most importantly, he already experienced dysphagia, which made continued use of the oral treatment risky and ineffective. After reviewing the treatment expectations, his daughter, now the substitute decision maker, made the decision to taper off and discontinue treatment of both his cognitive enhancers, donepezil and memantine. She was agreeable to bring her father for a follow-up visit in 1 month time after treatment discontinuation to monitor his cognition and behavior.

18.2.2 Case 2

Case 2 History

Mrs. B., a 56-year-old married, right-handed female, with grade 12 education, was brought to the ophthalmologist by her husband for a 2-year history of visual impairment not associated with anterior visual pathology, described as difficulties with reading (particularly following the lines of text while reading) and writing, and blurred vision, but nonvisual aspects of language were preserved. She had increased sensitivity to bright light and shiny surfaces, double vision, difficulty seeing clearly in low light conditions, problems with depth perception when climbing stairs, and difficulty reaching out to pick up an object. She relied more on her touch than on eyesight. She was anxious but denied any depressive symptoms.

Three years later, she began to show progressive spatial disorientation, getting lost in familiar places, affecting her ability to drive a car. She had begun having difficulty in performing household tasks. She needed help with IADLs, for instance, she was unable to use the telephone because she

did not see the numbers. She became confused with right and left hands. She had no family history of major NCDs. On examination, Mrs. B. scored 18 out of 30 points on the MoCA. She had difficulty in performing manual tasks under visual guidance bilaterally (optic ataxia), had jerky intrusions when attempting to perform smooth pursuit eye movements (ocular apraxia), and could not see two pen of different colors on the table (simultanagnosia). She had brisk symmetric tendon reflexes, but normal optic fundi, no frontal release signs, and no other neurological signs. Her insight was intact. The remaining physical exam was unremarkable.

For diagnostic clarity, a neuropsychological evaluation was requested, which revealed visuospatial deficits. She could not perform either the short form of the Hooper Visual Organization Test (a 15-item test of visual spatial ability that presents subjects with a line drawing of a common object that has been broken into fragments and asks patients to name what the object would be if reassembled [76]) or the Raven's Progressive Matrices (a 60-item test used in measuring abstract reasoning and regarded as a nonverbal estimate of fluid intelligence [77]). Her visual impairment precluded the evaluation of the other cognitive domains, especially language functions. She performed poorly on the trail making test part B (a test of visual attention and task switching) and Stroop test (a test of attentional capacity and flexibility, related to the ability to read words more quickly and automatically than naming colors). Laboratory screening tests for major or mild NCD were unremarkable. Her brain MRI scan showed focal atrophy featured by prominent bilateral parieto-occipital involvement. The FDG-PET showed prominent bilateral hypometabolism of parietal and occipital regions. A diagnosis of posterior cortical atrophy was eventually made based on the clinical and neuroimaging grounds.

On subsequent examination 3 years later, her visual and language functions, especially reading and writing, naming, and fluency, further deteriorated. She presented bilateral inability to distinguish the fingers on the hand (finger agnosia) and difficulty in performing computations (acalculia), in keeping with spatial disorders [78]. She had difficulty on confrontation field examination, because most of the time she could not see the target (due to simultanagnosia and ocular apraxia). A neurologist treated Mrs. B. with donepezil 10 mg daily and, subsequently, with addition of memantine 20 mg daily. She further deteriorated and presented with worsened decision making. She had to be assisted with her basic ADLs such as dressing and bathing. Two years later, Mrs. B. died and autopsy showed an abnormal accumulation of the proteins amyloid and tau that formed plaques and tangles, as is seen in Alzheimer disease.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What is posterior cortical atrophy?

Question 2. When is neuroimaging indicated in the diagnosis of Alzheimer disease?

Question 3. What are the other atypical presentations of Alzheimer disease? Why is it important to recognize these atypical variants?

Question 4. What is the treatment of posterior cortical atrophy?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is posterior cortical atrophy?)

Posterior cortical atrophy is the visual variant of Alzheimer disease, causing a progressive decline in vision. As in Mrs. B.'s case, patients with posterior cortical atrophy may initially see an ophthalmologist. Although visual impairment commonly develops with age, in patients with posterior cortical atrophy, the visual deficits are due to problems with cortical processing of the information received from the patient's eyes. As the disease progresses, word finding, episodic memory, and other cognitive functions become impaired, and patients eventually develop the symptoms of typical Alzheimer disease [79]. Visual hallucinations occur in about 25% of patients with posterior cortical atrophy [79]. In the later stages of the disease, patients can experience seizures.

In the vast majority of cases of posterior cortical atrophy, the underlying cause is Alzheimer disease, but it can also be due to Lewy body NCD, corticobasal degeneration, and Creutzfeldt-Jakob disease [80]. Although it has been underrecognized, posterior cortical atrophy affects less than 5% of patients with Alzheimer disease [80]. Posterior cortical atrophy tends to affect patients at an earlier age than typical Alzheimer disease, often in their mid-50s or early 60s when they experience the initial symptoms. Patients often experience a considerable delay in the time to diagnosis owing to the unusual presenting symptoms and younger age of onset than the typical Alzheimer disease. Life expectancy is approximately similar to patients with typical Alzheimer disease or longer [79]. While there is no definitive test for posterior cortical atrophy, a neurological exam, neuropsychological evaluation, blood tests, and brain scan may help to exclude potentially treatable causes such as infection, inflammation, or brain tumor.

Case 2 Answer 2 (Question 2—When is neuroimaging indicated in the diagnosis of Alzheimer disease?)

Molecular neuroimaging in Alzheimer disease has advanced over the past decade in the detection of brain beta-amyloid deposition during life by using PET. This has improved the understanding of beta-amyloid as a therapeutically targetable component of Alzheimer pathology, because beta-amyloid plaques are one of the defining pathological features of Alzheimer disease. However, many otherwise normal older adults have elevated levels of beta-amyloid, as do patients with clinical syndromes other than Alzheimer disease (see Sect. 18.4, MCQ1, regarding biomarkers and aging). Therefore, the potential clinical utility of amyloid PET requires careful consideration so that its

Table 18.15 Recommendations for appropriate use of neuroimaging in neurocognitive disorders [36, 81]

Consider performing CT or MRI, if:	Consider performing PET or SPECT, if:
Age < 60 years Unexplained neurological symptoms (e.g., new onset of severe headache, seizures) New localizing sign (e.g., hemiparesis, Babinski response) Rapid unexplained decline in cognition or function (< 2 months) Short duration of major NCD (< 2 years) Unusual or atypical presentation (e.g., progressive aphasia) Urinary incontinence and gait disorder early in the course of major NCD (e.g., rule out normal pressure hydrocephalus) History of cancer with potential for brain metastases History of anticoagulant use or bleeding disorder Recent and significant head injury Gait disturbance Need to identify unsuspected cerebrovascular disease that could change the management	Underlying pathology remains unclear after routine evaluation, preventing diagnostic certainty (18F-FDG-PET). If 18F-FDG-PET is unavailable, consider SPECT rCBF Amyloid PET is *appropriate* for: (1) persistent or progressive unexplained mild NCD, (2) criteria for possible Alzheimer disease due to unclear presentation because of either atypical clinical course or etiologically mixed presentation, and (3) early onset (< 65 years) and progressive course Amyloid PET is *inappropriate* for: (4) probable Alzheimer disease with typical age of onset; (5) determining NCD severity; (6) differentiating Alzheimer disease from other amyloid-associated NCD, Alzheimer clinical variants, and non-Alzheimer causes of NCD; (7) solely based on positive family history of major NCD or apolipoprotein E; (8) cognitive complaint unconfirmed on clinical examination; (9) in lieu of genotyping for suspected autosomal mutation carriers; (10) asymptomatic persons; and (11) nonmedical use

role should be placed in the proper clinical context [81]. The Society of Nuclear Medicine and Molecular Imaging and the Alzheimer's Association have jointly developed the appropriate use criteria for amyloid PET in order to offer clinicians the information necessary to provide their patients with optimal care while also considering the cost-effective use of limited health-care resources [81]. Recommendations for performing brain CT, MRI, FDG-PET, and regional cerebral blood flow (rCBF) SPECT imaging are summarized in Table 18.15 [36, 81]. Magnetic resonance spectroscopy shows promise for predicting which patients with mild NCD are likely to progress to major NCD, but it is not currently recommended for clinical use [36]. Although there is growing evidence supporting the use of dopamine presynaptic imaging agents for differentiating Lewy body disease from Alzheimer disease, these imaging agents are not yet recommended for clinical practice [36].

The patient in Case 2 presented with an early onset (younger than age 65) and a progressive, unexplained atypical clinical course of major NCD, with brain MRI showing focal atrophy featured by prominent bilateral parieto-occipital atrophy and FDG-PET showing prominent bilateral hypometabolism of parietal and occipital regions. There were no parkinsonian signs, fluctuations in cognition, or visual hallucinations at any stage during the disease to suggest a diagnosis of Lewy body NCD. The diagnosis of posterior cortical atrophy in this case was made based on the clinical and neuroimaging grounds. Several years later, at postmortem examination, this clinical diagnosis was corroborated with the pathological diagnosis of major NCD due to Alzheimer disease because of abnormal accumulation of amyloid plaques and neurofibrillary tangles, as is seen in Alzheimer disease. This case demonstrated the difficulties of early clinical diagnosis of atypical Alzheimer disease based on clinical phenotype and emphasized the value of neuroimaging, which may be particularly helpful in the context of atypical clinical presentation of Alzheimer disease.

Teaching Point

The practical message is that structural neuroimaging is not required in all (although will be indicated in most) patients with cognitive impairment [36]. Although more costly and less available, brain MRI is preferable to CT. 18F-FDG-PET or amyloid PET imaging, where available, can be used for clinical purpose in patients with atypical Alzheimer disease.

Case 2 Answer 3 (Question 3—What are the other atypical presentations of Alzheimer disease? Why is it important to recognize these atypical variants?)

Alzheimer disease typically presents with episodic memory impairment progressing over time to impairment in other cognitive domains, but a small proportion of patients present with atypical phenotypes. Table 18.16 summarizes the common atypical presentations of Alzheimer disease and characteristics for identifying these variations [35, 45]. Some practical considerations for recognizing these atypical variants consist of situations including:

1. Justification for referral to specialized clinics for a more in-depth evaluation.
2. The clinician feels less knowledgeable about their management.
3. Rationale for genetic testing (especially the early-onset types) and family counseling.
4. Rationale for considering treatment with cognitive enhancers.

Case 2 Answer 4 (Question 4—What is the treatment of posterior cortical atrophy?)

There is no evidence to indicate the effectiveness of cholinesterase inhibitors (e.g., donepezil, rivastigmine, galantamine) and *N*-methyl-D-aspartate receptor antagonist

Table 18.16 Atypical variants of Alzheimer disease [35, 45]

Atypical Alzheimer disease	Characteristic features
Posterior cortical atrophy	< 5% of Alzheimer disease cases; early anxiety, deficits in visual processing, praxis, calculation, and spelling, in various combinations; early preservation of memory, naming, and executive function Parieto-occipital atrophy with relative sparing of medial temporal lobes Low incidence of family history, present in middle age Pathology: > 80% Alzheimer disease; some corticobasal atrophy, Lewy body disease or prion disease
Frontal Alzheimer disease	Frontal more than posterior deficits: more behavioral changes Frontal, anterior temporal atrophy Onset at younger age
Language-associated Alzheimer disease	Progressive language decline Language-associated syndromes: Alzheimer-associated logopenic aphasia, progressive nonfluent aphasia, or semantic variant Asymmetrical atrophy Biomarkers can confirm Alzheimer pathology
Young-onset Alzheimer disease	< 5% of Alzheimer disease cases; includes autosomal dominant Onset age < 65 years More rapid progression usually More non-amnestic phenotype (visuospatial, attention, executive deficits); early prominent myoclonus
Familial Alzheimer disease	< 2% of Alzheimer disease cases Early-onset, familial autosomal dominant: APP, PSEN1, PSEN2 genetic mutations Onset at younger age (e.g., fourth decade) Myoclonus, seizures: more common than in sporadic form
Rapid Alzheimer disease	10% of Alzheimer disease cases > 6 points down/year on MMSE Predictors of rapid decline (see also Background section): low education, younger age, male, severe cognitive impairment at onset, focal signs, seizures, psychotic symptoms (e.g., delusions, primarily visual hallucinations), cortical signs (e.g., apraxia), subcortical signs (e.g., apathy, executive dysfunction), behavioral changes (e.g., aggression, agitation, wandering), biomarkers (e.g., positive PSEN1 and other genes, high CSF tau)
Corticobasal syndrome due to Alzheimer disease	20% of cases have Alzheimer pathology Medial perirolandic dysfunction: asymmetric, akinetic-rigid, levodopa-resistant syndrome Atrophy extends into temporoparietal cortex and precuneus

(e.g., memantine) in posterior cortical atrophy. However, clinical experience and case reports suggest some clinical benefit with these medications, particularly in patients with underlying Alzheimer or Lewy body pathology [82]. Case 2 demonstrates the value of trials of cognitive enhancers, which may be helpful in the context of neuropathology where Alzheimer disease is possible. Patients experiencing depression or irritability may also benefit from an antidepressant trial. (See ► Chap. 22.) Levodopa/carbidopa trials in patients with parkinsonism may also be considered [82].

Due to limited recognition of the syndrome, these patients often receive limited or inappropriate care and advice, which should center on critical perceptual difficulties (e.g., many activities in day centers and nursing homes are visually mediated and often not focused on atypical impairments of Alzheimer disease but rather on the typical memory decline). The relative preservation of memory, language, and insight in posterior cortical atrophy, especially in the mild to moderate stages, allows patients to attend support group meetings and psychotherapies where appropriate [82]. These patients often benefit from resources designed primarily for persons with visual impairment, such as talking books and watches, task (or directed) lighting, voice recognition software, or mobile phones with simplified displays [82]. Referral to an occupational therapist to maximize function is recommended. An occupational therapy assessment of patients with posterior cortical atrophy can also determine whether there is a prominent visual disturbance, which renders them as inappropriate to drive a car [82]. Referral to an ophthalmologist to register as partially sighted and provide access to financial and social benefits and services is essential [82]. Referral to a physical therapist can benefit patients with parkinsonism and gait disturbance [82]. Limited data indicate that compensatory strategies and cognitive exercises may produce small improvements in visuoperceptual functioning [82].

Case 2 Analysis Mrs. B.'s visual impairment was initially attributed to an ophthalmologic problem. She presented with visuospatial, visuoperceptual, and visual orientation deficits, with presenting complaints such as "difficulty following the lines of text while reading." These symptoms initially suggested

an ophthalmologic condition. As in this case, patients with posterior cortical atrophy, as in other atypical forms of Alzheimer disease, rarely present initially with memory impairment, which may not prompt the diagnosis of a major or mild NCD, thus delaying an accurate diagnosis and treatment. It is essential for eye specialists to rule out posterior cortical atrophy in patients presenting with specific ophthalmologic symptoms.

18.3 Key Points: Major or Mild Neurocognitive Disorder Due to Alzheimer Disease

- Alzheimer disease is the most common cause of major or mild NCD.
- Clinical categories include early-onset, late-onset, familial, and rapidly declining forms.
- The typical form of Alzheimer disease progresses slowly, with a median survival of 11.8 years since retrospectively determined symptom onset, and a cognitive decline of approximately 3 MMSE points per year.
- Different rates of progression have been observed among patients with Alzheimer disease. Risk factors that accelerate deterioration of Alzheimer disease have been identified, such as genetics, comorbidity, and the early appearance of motor signs. Progressive forms of Alzheimer disease have been reported with rapid cognitive decline and disease duration of only a few years. *Rapid progression* has been defined as an MMSE score decrease of 6 or more points per year.
- Clinicians need to remain vigilant that Alzheimer disease can mimic a range of other conditions, and, in particular, it is always important to consider reversible or treatable conditions, even if they are rare.
- Alzheimer disease presents with the possibility of mixed pathology, such as superadded vascular pathology, which may modify the manifestation of Alzheimer disease phenotype.
- History taking and bedside assessment can help to define atypical cases, but standard investigations, particularly neuroimaging and neuropsychological testing, can be useful in assessing the likelihood of Alzheimer disease versus other conditions.
- Current treatments remain symptomatic.

18.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. How do age-related differences in the neuropathological features of Alzheimer-related NCD correlate with biomarkers? Choose the most appropriate statement.

A. The biomarkers' ability to distinguish cognitively normal persons from Alzheimer disease patients decreases with age.
B. The diagnostic accuracy of brain morphometry biomarkers of Alzheimer disease increases with age.
C. The diagnostic accuracy of cerebrospinal fluid biomarkers of Alzheimer disease increases with age.
D. Amyloid PET positivity increases with age in those with Alzheimer disease, whereas it decreases in cognitively intact adults.

Answer: A

Despite similar levels of cognitive impairment, the typical MRI pattern of Alzheimer-related brain changes seen in the young-old patients (aged 60–75 years) appears to be less noticeable in very-old patients (aged 80–91 years) [6]. Therefore, mild NCD due to Alzheimer disease may go undetected in the older patients if diagnosis relies on brain morphometry markers. Thus, statement B is incorrect.

Cerebrospinal fluid biomarkers show significant overlap with non-Alzheimer-related NCDs, such as Lewy body NCD and vascular NCD, which are more likely to be found as coexisting pathologies in older adults [6]. There is also an age-dependent increase in Alzheimer-type brain pathology in cognitively unaffected older adults [6]. Therefore, while cerebrospinal fluid biomarkers may be useful to rule in Alzheimer disease in younger adults, their specificity for controls may be problematic in older adults. Furthermore, the density of neuritic plaques and neurofibrillary tangles can rise by more than tenfold as function of the severity of major NCDs in patients aged 60–80 years old [6]. However, this difference is surprisingly absent in patients over 90 years old, reflecting a lower density of Alzheimer disease lesions in brains of oldest-old patients with major NCD compared to non-demented controls [6]. Therefore, the diagnostic accuracy of cerebrospinal fluid biomarkers of Alzheimer disease decreases, and not increases, with age [6], and so statement C is incorrect.

Two meta-analyses found that the prevalence of amyloid PET positivity decreases with age in those with Alzheimer disease, whereas it increases in most non-Alzheimer-related NCDs and in cognitively intact adults [83, 84]. To exemplify, the prevalence of amyloid positivity increases from 10% to 44% in those aged 50–90 years among cognitively normal adults, and it decreases from 86% to 68% in Alzheimer patients [6, 83, 84], questioning the diagnostic utility of such biomarker. Therefore, statement D is incorrect.

The high degree of overlap in neuropathology between cognitively normal and cognitively impaired persons aged over 90 years makes it appropriate for clinicians to be cautious about for the use of biomarker strategies in the aging population. Therefore, the biomarkers' ability to distinguish cognitively normal persons from those with Alzheimer disease decreases with age, and so statement A is the correct answer.

MCQ 2. A 68-year-old man presented with difficulty recalling names of places and people he used to know. He was able to care for his own dressing and hobbies and continued to drive. He continued to manage his own

finances, although he had always received assistance from his wife. According to his wife, he had always had difficulty with names, but this seemed to have gotten worst since he retired from his job as a corporate executive about 6 months prior.

His past medical history was remarkable for hypertension and remote tobacco use until 20 years ago when he smoked 1 pack per day for 30 years. His only medications were aspirin 81 mg daily and lisinopril 20 mg daily. His physical examination was unremarkable. He did not have any tremor, rigidity, or gait abnormalities. His MoCA was 26 out of 30 points, missing 1 point for day of the week, 2 points for delayed recall, and 1 point for naming. In addition to making a diagnosis of possible mild NCD due to Alzheimer type (or amnestic type), what else should you have on your differential diagnosis?

A. Mild NCD, Lewy body type
B. Vitamin B_{12} deficiency and hypothyroidism
C. Mild NCD, frontotemporal type
D. B and C
E. A and B

Answer: D

Both vitamin B_{12} deficiency and hypothyroidism are possible "reversible" causes of cognitive impairment. However, other associated symptoms of "reversible" causes of cognitive impairment such as blood dyscrasia (for vitamin B_{12} deficiency) and fatigue and weight gain (for hypothyroidism) were not reported in this patient. Nevertheless, it is not unreasonable to check for thyroid-stimulating hormone and vitamin B_{12} level in this patient as an initial workup.

This patient was not reporting symptoms of altered level of consciousness, hallucinations, or parkinsonian symptoms to suggest a Lew body NCD, and, therefore, statement A was incorrect.

Although this patient was not displaying any changes in personality, apathy, executive dysfunction, or hyperorality to suggest a frontotemporal NCD, a variant of frontotemporal NCD, termed primary progressive aphasia of semantic variant, should be considered in the differential diagnosis. As discussed previously, anomia due to early semantic-variant frontotemporal NCD can be mistaken for episodic memory impairment due to Alzheimer disease, although the early impairment in verbal and semantic knowledge is more characteristic for frontotemporal NCD variant and not a feature of typical Alzheimer disease [45]. PET imaging may help to distinguish Alzheimer from non-Alzheimer disease pathologies [45]. Also, a more in-depth neuropsychological battery of tests would be indicated, especially those involving testing of language deficits, as well as episodic memory, to further characterize deficits in language and memory. Studies show that patients with Alzheimer disease encode and recall less information from the story than patients with frontotemporal NCD, and such patterns of performance can be useful in differentiating memory impairment in these two types of NCDs [59]. Therefore, the correct answer is D.

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Major or Mild Frontotemporal Neurocognitive Disorder

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19.1 Background

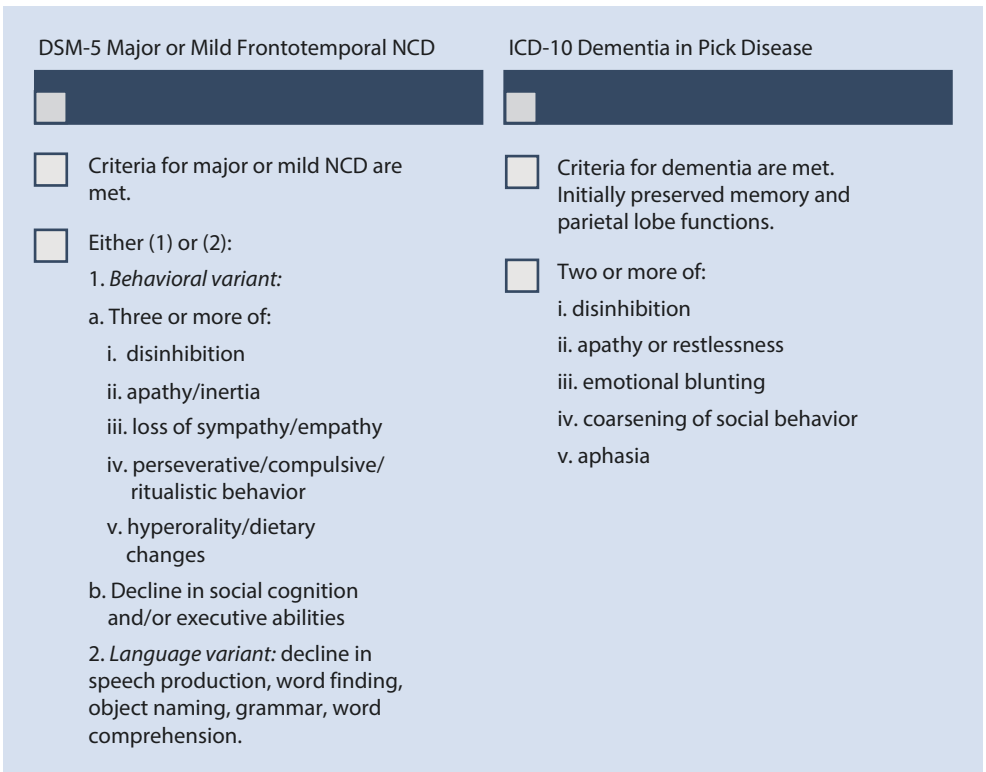
19.1.1 Definition

Major or mild neurocognitive disorders (NCDs) have been traditionally defined as an impairment in intellectual function, with distinct neurocognitive profiles which reflect the distribution of pathological changes within the brain. Typical major or mild frontotemporal NCD is a family of early, slowly progressing, primary neurodegenerative disorders, affecting primarily the frontal and temporal lobes. It comprises a spectrum of syndromic variants characterized by the progressive development of behavioral changes, executive dysfunction, and/or language impairment, along with other cognitive deficits. Concomitant motor signs can occur and include parkinsonism and motor neuron disease. Frontotemporal NCD presents with either sporadic forms or familial variants with the expression of multiple genetic mutations. The behavioral variant and three language (nonfluent/agrammatic, semantic, and logopenic) variants of frontotemporal NCD present with distinct clinical features, patterns of brain atrophy, and corresponding neuropathology.

According to the *Diagnostic and Statistical Manual of Mental Disorders*-fifth edition (DSM-5), diagnostic criteria must be met for either the behavioral or the language variant, but many patients can present features of both [1]. Another major diagnostic guideline is provided by the *International Classification of Diseases*-tenth revision (ICD-10) published by the World Health Organization [2], which uses the term "dementia in Pick disease" instead of frontotemporal NCD. As is shown in ◘ Fig. 19.1, the key criteria for the DSM-5 frontotemporal NCD and ICD-10 dementia in Pick disease overlap and contain many of the same elements but are not identical [1, 2]. ICD-11 is currently in development and is due for release by 2018. It will remain to be seen whether ICD-11 will also adopt the terminology "neurocognitive disorders" and whether diagnostic criteria will become similar to those of the DSM-5. The current DSM-5 terminology of "neurocognitive disorders" still allows "dementia" as an acceptable term in clinical practice in recognition of its familiarity. For a complete review of the diagnostic criteria for major or mild frontotemporal NCD, the reader is referred to the DSM-5 and ICD-10 manuals [1, 2].

19.1.2 Epidemiology

Major or mild frontotemporal NCD represents about 10% of all patients diagnosed with major or mild NCDs [3]. Its prevalence ranks after Alzheimer disease, vascular NCD, and Lewy body NCD. However, major or mild frontotemporal NCD remains the leading cause of early-onset NCD in patients younger than age 65 and, of these patients, 60% are diagnosed between ages 45 and 64, with an additional 10% presenting in those younger than age 45, whereas about 30% occur in patients older than age 65 [3–5]. Cases of frontotemporal NCD with onset after the age of 70 are occasionally reported at autopsy [6]. In a retrospective cohort study, 3.2% of all patients with late-onset NCDs proved to have frontotemporal NCD pathology at autopsy [6]. Among all variants of frontotemporal NCD cases, the behavioral variant accounts for nearly 60% [7]. Prevalence rates of behavioral



◘ Fig. 19.1 Highlights of the DSM-5 diagnostic criteria for major or mild frontotemporal neurocognitive disorder (NCD) and ICD-10 dementia in Pick disease [1, 2]

variant and semantic language variant are higher among males, whereas the rates of nonfluent language variant are higher among females [4].

19.1.3 Etiology

The etiology of frontotemporal NCD is unknown, although genetic associations have been suggested. The most prominent risk factor is a positive family history of frontotemporal NCD. In some studies, a family history of early-onset NCD with language and/or behavioral symptoms has been found in approximately 40% of index cases of major or mild frontotemporal NCD [3, 8]. An autosomal-dominant inheritance was reported in 27–40% of cases [3, 8, 9]. The remaining patients did not have clear evidence of a genetic abnormality, and the molecular basis of these cases remains poorly understood. A spectrum of genetic factors have been associated with autosomal-dominant frontotemporal NCD, with common mutations occurring in the genes encoding the microtubule-associated protein tau (MAPT), progranulin (PGRN), chromosome 9 open reading frame 72 (C9ORF72), transactive response DNA-binding protein of 43 kDa (TDP-43), and valosin-containing protein [3, 10]. The genetic and molecular biology of major or mild frontotemporal NCD will be discussed later.

19.1.4 Clinical Description

Behavioral-Variant Frontotemporal NCD

Behavioral variant (also called frontal variant) has a subtle onset with progressive deterioration in behavior and function [11]. Frontal lobe-associated behavioral changes involve alterations in personality and social conduct [3]. To meet the DSM-5 diagnostic criteria, three or more of the behavioral symptoms described in ◘ Fig. 19.1 must be present and persistent, along with a decline in social cognition and/or executive abilities. The behavioral disturbance must have an insidious onset and gradual progression. Patients may become disinhibited or become apathetic, abulic, and inattentive to personal hygiene and interact little with others in their environment. Disinhibition may manifest as socially inappropriate behavior, loss of manners, and impulsive actions [11]. Apathy presents with varying degree of diminished interest, initiation, or engagement in previously satisfying activities [11]. Caregivers and family members may note a disinterest in daily activities, including personal hygiene. Loss of sympathy and empathy may also occur, with a noted indifference for other people's feelings. Repetitive and stereotyped behavior can manifest as simple, repetitive gestures or more complex behaviors, mimicking obsessive-compulsive disorder. Verbal repetition can present as repeating words and phrases. Hoarding, impaired persistence on tasks, and utilization behavior (e.g., the patients grab and play with objects in their visual field and within reach) can develop [3]. Dietary changes and hyperorality are common manifestations presenting as excessive compulsions to place items in their mouth [11]. Carbohydrate and sweet cravings, in addition to binge behavior with food, tobacco, or alcohol, are common. Deficits in executive tasks, such as planning and problem solving, along with poor judgment and insight, are common [3]. The disease has a median survival of 3–4 years from the time of diagnosis, which is shorter than in typical Alzheimer disease [5].

Primary Progressive Aphasia

The second major clinical syndrome of frontotemporal NCD is primary progressive aphasia characterized by subtle onset and gradually progressive changes in both expressive and receptive language abilities [12]. Difficulty expressing oneself and naming objects is common [12]. Language can lack proper grammar, and speech becomes hesitant, slow, sometimes "telegraphic," and effortful. Language impairment can manifest as a loss of the ability to recognize, comprehend, and retrieve words. Aphasia is generally the most prominent symptom and the major cause for limitations in daily living, such as the inability to communicate via telephone [12, 13]. As the disease progresses, difficulties in reading, writing, planning, and attention may develop, while language progressively deteriorates until the patient becomes virtually mute [12]. Early on, learning, memory, and perceptual-motor functions remain preserved [3], a key distinction from Alzheimer disease. Patients with primary progressive aphasia initially can have a high degree of functional independence, and may be able to continue gainful employment, pursue hobbies, and travel independently, provided that they do not depend on language skills for these tasks. Later on, they may develop symptoms of major or mild NCD. Primary progressive aphasia is slowly progressive, and whether all patients with this syndrome eventually develop a generalized major NCD remains controversial. By one estimate, the incidence of major or mild NCD in patients with primary progressive aphasia probably reaches 50% over several years [3].

Primary progressive aphasia has been subcategorized based on the type of language deficit into three separate syndromes, which are presented in briefer form here and will be discussed later in the chapter [3, 12] (see also ▶ section Case 2 Answers, Case 2 Answer 1):

- Nonfluent language/agrammatic variant (previously known as progressive nonfluent aphasia), involving effortful and agrammatic speech
- Semantic variant, involving impaired single-word comprehension
- Logopenic variant, involving impaired word retrieval and repetition

19.1.5 Diagnostic Evaluation

Behavioral-variant frontotemporal NCD and primary progressive aphasia are *clinical syndromes, not pathological diagnoses*. The distinct behavioral and language characteristics of these variant syndromes permit an accurate diagnosis

if a comprehensive clinical history, physical examination (including a comprehensive neurological and mental status evaluation), and targeted laboratory testing are performed.

Clinical History

Obtaining a thorough personal and family history is necessary. Family members may not have been formally diagnosed with frontotemporal NCD, and inquiring about unusual but persistent maladaptive behaviors that are not isolated or rare events may provide an indication for the presence of familial frontotemporal NCD. In obtaining a clinical history, it is often difficult to attribute symptoms to a frontotemporal NCD versus other types of NCD. Although the significant behavioral changes and deficits in both expressive and receptive language are common presentations in frontotemporal NCD, the diagnosis is typically ambiguous and difficult to make due to the heterogeneity of the associated symptoms. For example, typical manifestations of the "cortical" frontotemporal NCD, such as personality changes, depression, apathy, and irritability, are also common in "subcortical" (e.g., Parkinson disease-related) NCD, in which memory and judgment impairment may arise relatively early in the course of the disease. Toward the end stages of illness, all major NCDs converge on the same pattern of global cognitive dysfunction, thereby impeding clinical distinction from one another. Within the spectrum of frontotemporal NCDs, the clinical phenotypes described previously may overlap as the diseases progress. Therefore, obtaining an accurate history is essential but also challenging, where a strong family history and specific phenotypic presentation may point to a particular NCD and familial subtype.

Studies suggest that frontotemporal NCD in geriatric patients may be under-recognized and should be considered in those presenting with an "atypical" Alzheimer disease phenotype. The age of onset at which frontotemporal NCD would be considered unlikely has been debated. In a retrospective cohort study, features of frontotemporal NCD in geriatric patients (age older than 65 years) differed from those of "typical" cases presenting before age 65, which may suggest that they represent separate disease processes [6]. This study showed that the main clinical and neuropathological features of the frontotemporal NCD phenotype in geriatric patients included prominent memory loss, behavioral changes, and hippocampal sclerosis, but less pronounced language dysfunction and cortical lobar atrophy [6].

Cognitive and Functional Assessment

Cognitive Assessment

In the early stages of frontotemporal NCD, standard cognitive screening usually shows few deficits, and recognition requires more formal cognitive testing that can identify lack of planning and organization, difficulties with abstract reasoning and response inhibition, distractibility, and poor performance on tests of mental flexibility. Learning and memory, along with perceptual-motor abilities, are generally preserved in early stages [3].

Brief Cognitive Instruments

Brief cognitive instruments commonly used for detection of the major or mild NCDs are also the best aids in the differential diagnosis of frontotemporal NCD and include the Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE). However, the MMSE does not assess frontal *executive* skills and therefore has low sensitivity for detecting early frontotemporal NCD, particularly the behavioral variant. With a cutoff below 17 out of 30 points, the MoCA results for sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of the behavioral-variant frontotemporal NCD were found to be superior to those of the MMSE [14]. Broadly used scales specifically developed to detect frontotemporal NCD include the Frontal Assessment Battery (FAB), Frontal Behavioral Inventory (FBI), and Middelheim Frontality Scale (MFS) [15–17]. The FAB is a tool which is easy to use at the bedside, takes approximately 10 minutes to administer, and is sensitive to frontal lobe dysfunction [15]. FAB is a brief battery of six neuropsychological subsets, which explores (1) conceptualization, (2) mental flexibility, (3) motor programming, (4) inhibitory control, (5) sensitivity to interference, and (6) environmental autonomy [15]. Some of these items are often incorporated into a neuropsychological examination and are deemed as complementary. The FBI is a tool that asks caregivers about frontal lobe deficits in the patient such as apathy, personal neglect, and loss of insight and evaluates changes in behavior over time [16]. The MFS is a clinician-administered scale that measures key frontal lobe deficits including apathy and stereotyped behavior [16, 17]. The Boston Naming Test (BNT) is an assessment tool to measure confrontational word retrieval in patients with language disturbance caused by anomic aphasia. The BNT short forms in older adults are useful as screening instruments and as alternate forms for clinical protocols, pre-post experimental designs, and longitudinal research [18]. Facial emotion recognition is a test in which impaired performance of emotion recognition is a relatively specific feature of behavioral-variant frontotemporal NCD and can assist in differentiating it from Alzheimer disease [19]. Because patients with frontotemporal NCD typically have preserved cognitive abilities in early stages, the use of these cognitive tests may help rule out other NCDs. The challenge in applying these tools in clinical practice is that these instruments require a cooperative patient. ◘ Table 19.1 summarizes broadly used scales utilized in diagnosis and differential diagnosis of frontotemporal NCD [15–20]. These tools do not assess the impact of cognitive dysfunction on social or occupational activities of daily living, which are tested with performance-based instruments [21].

It is important to know that scoring perfectly on any one cognitive screening test does not preclude a diagnosis of a NCD. Highly educated patients with a major NCD, including those with frontotemporal NCD, may score within normal range at early stages of illness, but have deficiencies in insight, judgment, and other areas of cognitive function. It is important to note that a change from baseline is more significant than the absolute test scores.

Table 19.1 Brief cognitive tests for frontotemporal NCD [15–20]

Abbreviation	Test	Admin time (minutes)	Comments
MoCA	Montreal Cognitive Assessment	10–12	Less ceiling effect than MMSE Poor at discriminating between frontotemporal and Alzheimer-related NCD; more testing is required
MMSE	Mini Mental State Examination	8–13	MMSE score of 24 is equivalent to MoCA of 18 to detect mild NCD cases [20] Used for initial screening; more testing is required
FAB	Frontal Assessment Battery	10	Developed for frontotemporal NCD Brief battery of six subsets: conceptualization, mental flexibility, motor programming, inhibitory control, sensitivity to interference, and environmental autonomy
FBI	Frontal Behavioral Inventory	20–30	Developed for frontotemporal NCD; useful in early stages. Asks caregivers about apathy, personal neglect, and loss of insight; it measures changes in behavior over time
MFS	Middelheim Frontality Scale		Clinician-administered scale; it detects frontal lobe features scored on ten items: initially spared memory and spatial abilities, personality and behavioral changes/impaired insight and judgment, disinhibition, dietary hyperactivity, changes in sexual behavior, stereotyped behavior, impaired control of emotions, aspontaneity, speech disturbances, and restlessness
BNT	Boston Naming Test	15	It measures confrontational word retrieval in patients with language disturbance caused by anomic aphasia
ERT	Emotion Recognition Task	10	Emotion recognition impairment is a feature of behavioral-variant frontotemporal NCD. It can assist in differentiating from Alzheimer disease

Neuropsychological Testing

Neuropsychological testing is recommended when the history and mental status examination cannot provide a clear and accurate diagnosis. (See ▶ Chap. 4) Although neuropsychological testing is a useful tool for helping to quantify impairment and for monitoring changes over time, it is resource intensive and not recommended on a routine basis. In patients with frontotemporal NCD, the neuropsychological test results can be variable, inconsistent, and patchy due to the patient's impulsive, amotivational, or echolalic responses. The patients may be uncooperative and testing may thus be incomplete. Although some studies have shown variable memory performance in patients with behavioral-variant frontotemporal NCD, episodic memory and orientation are thought to be relatively preserved, and these patients tend to benefit from multiple-choice options [22]. Perseveration on the Wisconsin Card Sorting Test, impaired word fluency, and impaired performance of Trail Making Tests are commonly observed frontal lobe deficits. Whereas utilization behavior (described previously) and echopraxia (i.e., abnormal repetition by the patient of the actions of another person) can also be present during neuropsychological testing, visuospatial function and memory are generally preserved in patients with behavioral-variant frontotemporal NCD. Some patients have relatively normal scores on frontal lobe function measures despite severe behavioral disturbances, thus complicating the differential diagnosis of frontotemporal NCD. Moreover, there is a significant overlap in the test performance of patients diagnosed with frontotemporal NCD and those with Alzheimer disease, especially in the moderate and severe stages. In this view, the most discriminating cognitive tests have been measures of orientation, language, memory, visuomotor function, and general cognitive function [23]. In a meta-analytic review of the neuropsychological profiles, Hutchinson and Mathias [23] have suggested that cognitive tests should be used cautiously when making differential diagnoses and be applied only in conjunction with a medical history, behavioral observations, neuroimaging, and collateral data from knowledgeable informants [23].

Functional Assessment

Acquired functional impairment defines a major NCD, and determining the areas of functional impairment helps with the diagnosis. A decline in the ability to perform daily activities is a required criterion for the diagnosis of all-cause major NCD [1, 2]. (See Figure 18.1 in ▶ Chap. 18) Mild and major NCDs exist along a continuum and the distinction between them is arbitrary. Therefore, complete history taking, observation, and integration with other findings are necessary. Patients with mild frontotemporal NCD may have preserved daily functioning, although there may be subtle interference with function such as tasks requiring more effort, taking more time than previously, or the loss of compensatory strategies in problem solving. Work performance in more demanding jobs may deteriorate, as may the quality and

extent of extracurricular activities. Patients with major frontotemporal NCD will have impairment of sufficient severity that others will have to assume responsibility for tasks that the patients were previously able to complete on their own.

Because of the typical early age at onset, frontotemporal NCD often affects workplace and family life. The involvement of behavior changes leads to function often being more severely impaired early in the disease course. Behavioral changes such as impulsive wandering, hyperorality, and other disinhibited behaviors may cause strained relationships with family and friends and ultimately may lead to institutionalization. These behaviors can be disruptive particularly when patients are otherwise healthy, non-frail, and ambulatory. As previously stated, patients with primary progressive aphasia who do not depend on language skills for functional tasks initially can have a high degree of functional independence; however, they subsequently may develop symptoms of major NCD, including behavioral disturbances more typical of a behavior-variant frontotemporal NCD.

Instrumental activities of daily living typically begin to decline at the stage of mild NCD and include shopping, performance of household chores, meal preparation, management of finances, driving, and using public transportation [24]. Basic activities of daily living are generally preserved early in the illness, although the quality may decline; e.g., patient's grooming, hygiene, and appearance may deteriorate. Inability to independently perform basic activities of daily living such as bathing, dressing, and grooming characterizes the moderate to severe stages of frontotemporal NCD and other major NCDs, with loss of independent toileting occurring along with incontinence. Loss of mobility, including transferring, develops late, with self-feeding usually being the last basic activity of daily living to be lost [24]. (See ◘ Fig. 18.9 for a list of daily activities in ► Chap. 18.)

Physical Examination

Along with a thorough history, a comprehensive physical examination with neurological examination is critical for clinical diagnosis. Patients with frontotemporal NCD are typically physically well early in the disease course, but neurological signs may develop later. In behavioral-variant frontotemporal NCD, neurological abnormalities may be limited to frontal release signs, such as positive glabellar sign, grasp, snout, and palmomental response, while other patients may show evidence of motor neuron disease, with muscle weakness, fasciculations, muscle atrophy, bulbar signs such as dysphagia, and hyperreflexia [3]. In primary progressive aphasia, extrapyramidal features may be prominent in some cases, with clinical and pathological overlap with syndromes of progressive supranuclear palsy and corticobasal degeneration [3]. Rarely, features of motor neuron disease may be present in primary progressive aphasia. The overlap of neurological abnormalities can sometimes cloud the differentiation of the frontotemporal NCD subtypes. (See ► section Case 2 Answers, Case 2 Answer 3.)

Investigations

Laboratory Tests

Laboratory investigations are generally unrevealing in major or mild frontotemporal NCD, except for genetic tests. In familial cases of frontotemporal NCD, the identification of genetic mutations may help confirm the diagnosis. However, laboratory testing is useful in ruling out systemic medical causes for impairment. Basic tests should include thyroid-stimulating hormone and free thyroxine to rule out thyroid disorders and a complete blood count with a vitamin B_{12} level to rule out anemia and B_{12} deficiency. Additional laboratory testing should be reserved for situations when other contributors to cognitive impairment, such as alcohol abuse, are suspected. Other congenital diseases that can cause NCDs, such as Wilson disease, usually cause signs and symptoms at a much earlier age.

Neuroimaging Tests

Further testing may include neuroimaging with magnetic resonance imaging (MRI) or computed tomography (CT) scan. Focal atrophy of the frontal and/or temporal lobes of one or both hemispheres is a characteristic feature of frontotemporal NCD. Patients with frontotemporal NCD may show distinct patterns of focal cerebral atrophy, in contrast to Alzheimer disease, which may show widespread cortical atrophy [3]. Patterns of atrophy also differ across groups of patients with tau, progranulin, and C9ORF72 mutations and those with sporadic forms [25] (see ◘ Fig. 19.2). In the behavioral variant, frontal lobes and the anterior temporal lobes are predominantly atrophic, unilaterally or bilaterally [3]. The nonfluent language variant has a perisylvian left hemisphere atrophy, involving predominantly the left frontal cortex. The semantic language variant has middle, inferior, and anterior temporal lobe atrophy, often bilaterally [3]. The logopenic variant is associated with posterior temporal and parietal atrophy, often bilaterally, sometimes predominantly left sided [3]. Because structural changes are typically not seen in the early stages of frontotemporal NCD, patient history and clinical presentation become essential to the clinician for early recognition. However, when the clinical diagnosis remains unclear, and in the absence of structural abnormalities, functional neuroimaging can demonstrate hypoperfusion and cortical hypometabolism in the corresponding brain regions. Biomarkers of Alzheimer disease, such as cerebrospinal fluid beta-amyloid and tau levels, and amyloid imaging, may help in the differential diagnosis by exclusion of Alzheimer disease, but they remain largely experimental diagnostic studies that are not generally available in clinical practice, with additional importance as research findings accumulate over time [1]. However, the distinction of frontotemporal NCD from Alzheimer disease may remain difficult since the logopenic variant is often a manifestation of Alzheimer disease [3]. (See ► Chap. 18, Case 2 Answers, Case 2 Answer 3 for atypical Alzheimer disease.)

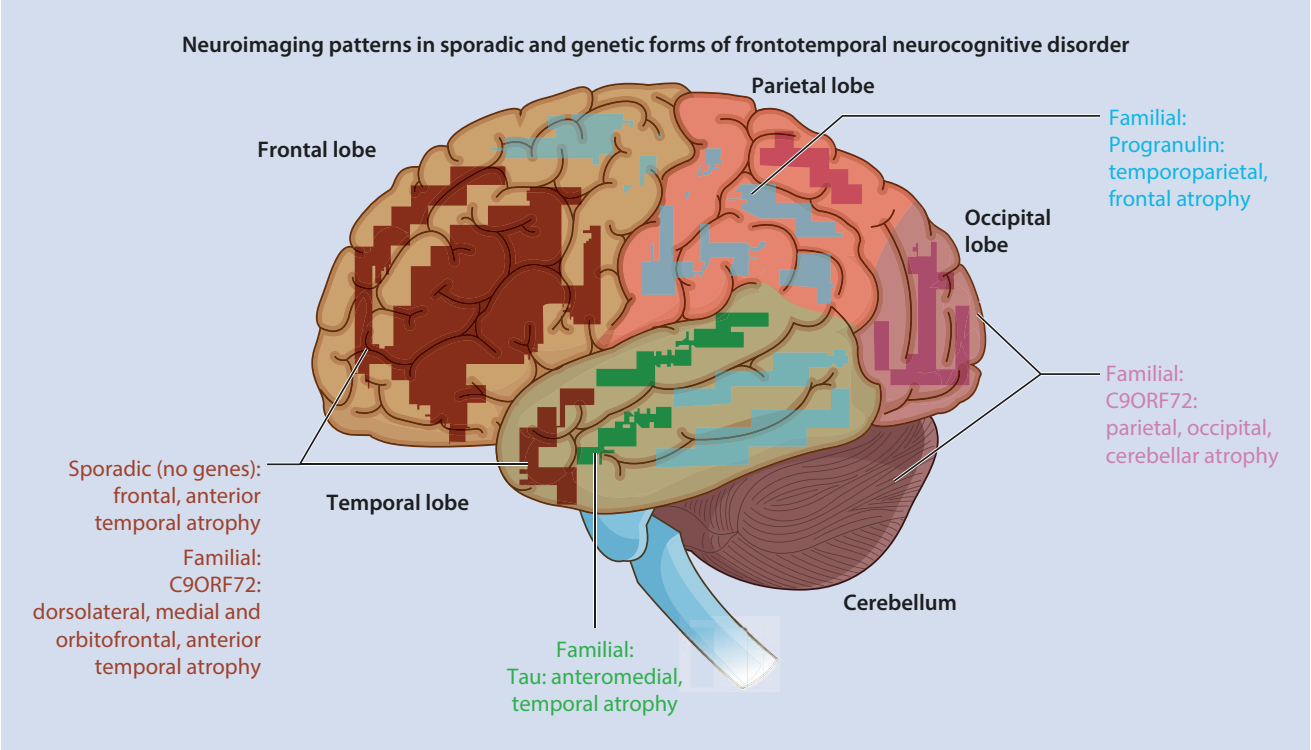


Fig. 19.2 This figure demonstrates the relative distribution of brain involvement and corresponding regional atrophy of the four main types of frontotemporal neurocognitive disorder (C9ORF72, tau, progranulin, and sporadic forms), based on findings from volumetric MRI [25]. All four disease groups present some involvement of the frontal lobes, but the absence of early frontal atrophy points toward a tau mutation and striking frontal atrophy suggests a sporadic form, whereas the C9ORF72 mutation is associated with predominant frontal lobe atrophy, with involvement of the anterior temporal, parietal, and occipital lobes and cerebellum

Focal atrophy in the anteromedial temporal lobes corresponds specifically to the behavioral variant of frontotemporal NCD that is predominantly associated with the MAPT gene mutation. If atrophy primarily involves the lateral temporal and parietal lobes, then either a progranulin or C9ORF72 mutation should be suspected, since atrophy in sporadic forms of frontotemporal NCD generally does not involve these regions. There is an overlap in the atrophy pattern observed between patients with progranulin and C9ORF72 mutations, which makes the differentiation between these two groups rather challenging. However, atrophy predominantly of the parietal lobe would be more suggestive of progranulin pathology, whereas relatively greater atrophy of the sensorimotor cortices and occipital lobe would suggest C9ORF72 pathology [25].

It is essential to assess the relative involvement of each region in comparison with other regions of the brain. All four frontotemporal variants have shown some involvement of the frontal lobes; therefore, it may be difficult to differentiate variant types based only on the effect on this brain region. However, striking dorsolateral frontal atrophy would point toward a sporadic form of frontotemporal NCD, whereas the absence of early frontal atrophy would suggest a MAPT mutation [25]. Early in the disease course, a patient with progranulin mutation may have the same degree of parietal atrophy as a C9ORF72 patient later in the disease course; however, progranulin patients would still have relatively greater atrophy of the parietal lobe compared with other brain regions [25]. Differentiation is likely to be more difficult in patients with advanced disease, where there is a less focal pattern of atrophy. Neuroimaging is therefore most likely to be helpful early in the disease course. Optimum diagnostic prediction is likely to require both neuroimaging and clinical information. Younger age at onset would be particularly suggestive of a MAPT mutation, while older age of onset is more consistent with progranulin mutations [25].

Teaching Point

Neuroimaging is most likely to be useful early in the disease course. This is because, in more advanced stages of the disease, brain regions that were previously unaffected may start to "catch up" to the regions that showed greater atrophy early in the disease process, resulting in a less focal pattern of atrophy and, therefore, making the differentiation more difficult [25].

Molecular Pathology Examination

Focal atrophy of the frontal and/or temporal lobes, along with neuropathological changes including gliosis, microvacuolation of the neuropil, and loss of neurons, are characteristic features of frontotemporal NCD. A positive family history in patients with frontotemporal NCD accounts for a large proportion of cases, suggesting an autosomal-dominant inheritance. The most implicated genetic signatures are

mutations in MAPT and progranulin, both located on chromosome 17, and mutations in C9ORF72, genetically linked to chromosome 9 and the most common genetic abnormality both in familial frontotemporal NCD and amyotrophic lateral sclerosis [25]. Mutations in MAPT are associated with deposition of the hyperphosphorylated protein tau, whereas progranulin and C9ORF72 gene mutations are associated with deposition of transactive response DNA-binding protein of 43 kDa (TDP-43) [25]. Mutations occurring in the gene encoding valosin-containing protein on chromosome 9 are less frequent and cause a progressive aphasia associated with inclusion body myopathy and Paget disease; some patients with this mutation have TDP-43 protein accumulation [3, 26]. The C9ORF72 mutation is not only associated with amyotrophic lateral sclerosis, but is also commonly associated with the behavioral variant [25]. MAPT and progranulin mutations have been associated with behavioral variant as the most common clinical phenotype, although progranulin mutations have been associated with a more variable clinical spectrum, including primary progressive aphasia and corticobasal syndrome [8, 25]. Mutations in the MAPT gene are considered tauopathies. Other tauopathies include progressive supranuclear palsy and corticobasal degeneration [3]. Genetic testing for frontotemporal NCD can confirm autosomal-dominant progranulin and MAPT mutations when the clinical presentation and neuroimaging are inconclusive, usually very early in the course. Although identification of tauopathies and abnormalities of ubiquitin presently does not provide a therapeutic pathway, it does provide an opportunity for patient and family counseling.

As mentioned earlier, the syndromes of progressive supranuclear palsy, corticobasal degeneration, and motor neuron disease are underlying disorders in frontotemporal NCD [3]. Particularly, some patients with frontotemporal NCD appear to develop motor neuron disease as their illness progresses [3]. Some cases have been noted to have ubiquitin immunoreactive neurites, initially referred to as frontotemporal NCD-ubiquitin. The progranulin gene has been associated with mutations in frontotemporal NCD-ubiquitin. The binding protein in progranulin mutations is TDP-43, which aggregates in neurons and glia and is a major component of the ubiquitinated inclusions in frontotemporal NCD-ubiquitin. Most cases of major or mild frontotemporal NCD with motor neuron disease show ubiquitin staining (sometimes called frontotemporal NCD-motor neuron disease). As shown previously, mutations on chromosome 9 have been associated with frontotemporal NCD-amyotrophic lateral sclerosis; most such cases are associated with ubiquitin inclusions and TDP-43 accumulation [3]. At postmortem, most familial cases of frontotemporal NCD have either a tau or progranulin mutation [3].

It has been shown that the genetic mutations leading to autosomal-dominant frontotemporal NCD can give rise to a multitude of clinical phenotypes even within the same family pedigree and, neuropathologically, they are diverse [27]. Therefore, the behavioral variant is predominantly associated with MAPT mutations and usually with more symmetrical, bifrontal atrophy. Mutations in the progranulin gene are associated with more asymmetrical atrophy. Nonfluent language-variant major or mild frontotemporal NCD is associated with MAPT mutations and left frontal convexity atrophy. Semantic-variant major or mild frontotemporal NCD is associated with progranulin mutations and bitemporal atrophy. Logopenic-variant major or mild frontotemporal NCD is associated with Alzheimer pathology and temporoparietal atrophy (see Fig. 19.3). As previously discussed, Fig. 19.2 portrays the main neuroimaging signatures in sporadic forms and those with associated genetic mutations in frontotemporal NCD [25].

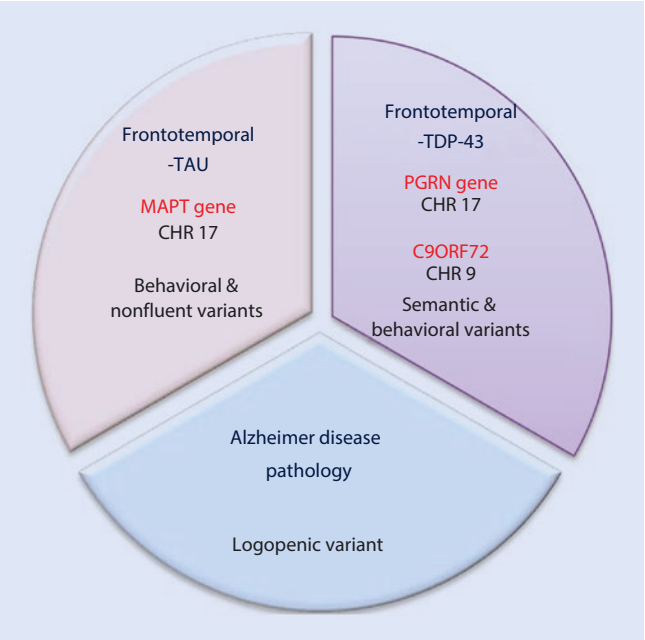


Fig. 19.3 Main neurogenetic variants of the frontotemporal neurocognitive disorder. *CHR* chromosome, *C9ORF72* chromosome 9 open reading frame 72, *PGRN* progranulin, *TDP-43* transactive response DNA-binding protein of 43 kDa

Teaching Point

The absence of early frontal atrophy would suggest a MAPT mutation, whereas prominent dorsolateral frontal atrophy would likely suggest a sporadic frontotemporal NCD [25].

19.1.6 Differential Diagnosis

The diagnosis of frontotemporal NCD can be difficult to make, as this syndrome shares important similarities with other more common causes of major or mild NCDs. Frontotemporal NCD, especially the behavioral variant, can present with neuropsychiatric symptoms that may mimic and thus be initially attributed to other psychiatric disorders. Interestingly, Lopez et al. [28] found more symptoms of major depression, irritability, mood lability, disinhibition, agitation, inertia, and social withdrawal in patients

with frontotemporal NCD when compared to those with Alzheimer disease who, instead, displayed more psychotic symptoms such as delusions. When frontotemporal NCD is suspected, other neurodegenerative, vascular, and psychiatric disorders and other conditions affecting the brain must first be ruled out. The differential diagnosis includes cerebrovascular accident, prolonged delirium, encephalitis, hypothyroidism, vitamin B_{12} and other vitamin deficiencies, traumatic brain injury, and brain tumor. Other psychiatric disorders such as bipolar disorder, major depressive disorder, obsessive-compulsive disorder, schizophrenia, substance use disorders, personality disorders, and other major or mild NCDs must be excluded [11]. Table 19.2 lists conditions to consider in the differential diagnosis of frontotemporal NCD.

In summary, making the diagnosis of frontotemporal NCD and the differential diagnosis depends on a comprehensive history from the caregiver. The emergence of poor judgment, disregard for social norms, indifference, hoarding, and senseless joking in a person with relatively preserved memory should raise suspicion of the diagnosis. The clinical quantification of behavioral abnormality and confirmation with neuroimaging are necessary in establishing a diagnosis of frontotemporal NCD. Diagnostic criteria delineate different levels of diagnostic certainty. "Probable" is distinguished from "possible" frontotemporal NCD by either the presence of characteristic atrophy or reduced activity in associated brain regions on structural or functional neuroimaging or by the presence of causative genetic mutations (e.g., MAPT) from either family history or genetic testing [1]. A "definite" diagnosis is reserved for cases with positive autopsy findings or a proved genetic mutation [3]. A summary of the clinical syndromes of major or mild frontotemporal NCD, how they differ clinically, genetically, and in neuroimaging patterns, is presented in briefer form in Table 19.3; these elements will be explored later in the case-based discussions [3, 29].

Table 19.2 Differential diagnosis of major or mild frontotemporal neurocognitive disorder

Category of disorder	Diagnostic entity
Neuropsychiatric and substance-related syndromes	Schizophrenia Major depressive disorder Bipolar disorder Obsessive-compulsive disorder Substance-related disorders (e.g., prescription, chemotherapies, opioids; alcohol misuse, Wernicke-Korsakoff syndrome; illicit drugs) Personality disorders
Neurocognitive disorders and encephalopathies	Delirium Alzheimer disease; Lewy body disease; Parkinson disease; Huntington disease; vascular neurocognitive disorder Creutzfeldt-Jakob disease Normal pressure hydrocephalus Multiple sclerosis Adult-onset leukoencephalopathy with axonal spheroids and pigmented glia (ALSP) Adult metachromatic leukodystrophy Mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) Radiation-induced cognitive impairment Prolonged refractory status epilepticus Fragile X-associated tremor/ataxia syndrome (FXTAS) Cerebral autosomal-dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Cerebral autosomal recessive arteriopathy with subcortical infarcts and leukoencephalopathy (CARASIL)
Infections and inflammatory diseases	Meningoencephalitis: herpes simplex, syphilis, HIV Cerebral vasculitis Temporal arteritis Neurosarcoidosis
Immune diseases	Rheumatologic diseases: systemic lupus erythematosus
Traumatic brain injuries	Neurocognitive disorder due to acute and chronic traumatic brain injury (e.g., dementia pugilistica, chronic traumatic encephalopathy)
Tumors and tumor-like formations	Meningioma Brain metastases Paraneoplastic syndrome Cerebral tuberculoma
Metabolic disorders	Metabolic syndrome Mitochondrial disease Glucose metabolism disorders Calcium metabolism disorders Hyper- and hypothyroidism Vitamin B_{12} and other nutritional deficiencies

19.1.7 Treatment

The current treatment approaches in major or mild frontotemporal NCD focus on symptom identification and management, irrespective of genetic status, and not on slowing the disease progression [30]. The non-pharmacological interventions for behavioral disturbance should be considered alone or in combination with pharmacological agents for the identified target symptoms. Primary care physicians can refer patients with frontotemporal NCD to a geriatric psychiatrist, geriatrician, or neurologist to identify or confirm the diagnosis and to assist in coordinating a plan of care for patients, their caregivers, and their primary care clinicians.

Non-pharmacological Treatment

There are no systematic studies of non-pharmacological interventions in frontotemporal NCD. Nevertheless, behavioral strategies are an important aspect of managing these symptoms and are an essential alternative or supplement to

Table 19.3 Key characteristics of major or mild frontotemporal neurocognitive disorder and its variants [3, 29]

Characteristic	Behavioral variant	Nonfluent/agrammatic variant	Semantic variant	Logopenic variant
Behavior	Aberrant	Preserved (early)	Preserved (early)	Preserved (early)
Fluency	Fluent (early)	Nonfluent, grammatical simplification, speech sound errors, dysarthria	Fluent	Fluent (absence of agrammatism); speech sound errors
Naming	Preserved (early)	Some anomia, word finding	Anomia (poor confrontation naming)	Preserved object knowledge
Repetition	Preserved	Nonfluent	Preserved (fluent)	Impaired repetition of phrases and sentences
Reading	Preserved	Preserved for short items	Surface dyslexia (difficulty with whole word recognition and spelling)	Preserved for simple items
Comprehension	Preserved (early)	Preserved content word comprehension; impaired syntactic comprehension	Impaired single-word comprehension	Preserved single-word comprehension
Visuospatial	Preserved	Preserved (early)	Preserved	Preserved (early)
Motor speech	Preserved	Effortful/halting speech	Preserved	Preserved
Neurological signs (PSP, CBD, MND)	Positive frontal release signs, some parkinsonism, MND	Likely	Likely	Likely
Neuroimaging MRI (atrophy)	Frontal cortex (bi-, unilateral)	Left dorsolateral prefrontal cortex and insula	Anterior and ventral temporal cortex (bilateral)	Left posterior-superior temporal and inferior parietal cortex
PET (hypometabolism)		Left temporal and left frontal lobe (in advanced cases)		
Neuropathology (main)	Tauopathy	Tauopathy	TDP-43 accumulation	Focal presentation of AD pathology TDP-43 accumulation
Genetics	MAPT mutations C9ORF72 mutations	MAPT mutations	Progranulin mutations	AD-related genes

Note: AD Alzheimer disease, *CBD* corticobasal degeneration, *MAPT* microtubule-associated protein tau, *MND* motor neuron disease, *MRI* magnetic resonance imaging, *PET* positron emission tomography, *PSP* progressive supranuclear palsy, *TDP-43* transactive response DNA-binding protein 43

pharmacotherapy. Anecdotal reports suggest that socially disruptive and stereotypical behaviors may be amenable to interventions [15]. Resuming prior hobbies and favorite games as substitutes to distract the patients from more troubling behaviors may reduce disinhibition and socially disruptive behaviors among patients with behavioral-variant frontotemporal NCD [31]. The antecedent-behavior-consequence (ABC) model specifically used to identify triggers and consequences of particular behaviors is another strategy to utilize [32]. (See ▶ Chap. 22.) Executive dysfunction, apathy, and loss of empathy have proven difficult to treat with pharmacotherapy and require behavioral and environmental intervention. Apathy or loss of empathy can be especially distressing to caregivers, which can lead to feelings of isolation. Certain behavioral symptoms may require close supervision. Impaired judgment and impulsiveness in these patients can lead to making reckless purchases or involvement in financial scams and require caregivers to limit access to credit cards and bank accounts. Management of hyperorality may require caregivers to provide dietary supervision to prevent weight gain or the ingestion of inedible objects. Caregivers should be encouraged to keep detailed logs of behavioral symptoms that can be shared with the geriatric psychiatrist, geriatrician, or neurologist as a way of identifying temporal patterns, triggers, and effective behavioral strategies. In patients with the behavioral-variant frontotemporal NCD, fewer behavioral symptoms may be present with disease progression [32].

Because frontotemporal NCD often occurs in middle age, it can critically affect patients and families as the disease occurs at the time of life characterized by industriousness and productivity. Social support can be crucial for the caregivers and includes support from family and friends, healthcare

professionals, and support groups with other caregivers of NCD patients. Caregivers should be encouraged to connect with local, regional, and national organizations, such as the Association for Frontotemporal Dementia (► www.theaftd.org) to obtain education about frontotemporal NCD, support, and appropriate services. Counseling and cognitive behavioral psychotherapy may help patients and families adapt to the neurocognitive and functional impairments of these patients [3]. Psychotherapeutic interventions should be considered as family caregivers struggle to understand and accept the behavioral changes and the impact the behaviors have on the entire family. Caregiver education is, however, key. Providing psychoeducation to caregivers helps them to become partners in monitoring for medication adherence and effects and contributes to optimizing patient and caregiver quality of life [27]. Speech and language therapy is initially helpful in nonfluent-variant primary progressive aphasia. Physical activity may have an important role since exercise for patients with Alzheimer disease may transiently help cognition and has been shown to reduce agitation [33], but this has not been proven as yet in frontotemporal NCD [3].

Pharmacological Treatment

Currently, there is no approved pharmacological treatment for cognitive decline in frontotemporal NCD [30]. The treatment modalities will be presented in briefer form here, but discussed later in the chapter. (See ► section Case 2 Answers, Case 2 Answer 4.) The symptomatic pharmacological management of behavioral symptoms in frontotemporal NCD currently relies on medications used to treat Alzheimer disease-related behavioral symptoms and psychiatric comorbidity. Several medication classes have been employed for the treatment of symptoms in frontotemporal NCD and include antidepressants (e.g., selective serotonin reuptake inhibitors (SSRIs), trazodone), antipsychotics (e.g., risperidone, olanzapine, quetiapine, aripiprazole), psychostimulants (e.g., modafinil, methylphenidate), dopamine agonists (e.g., bromocriptine, levodopa), and oxytocin [3, 30, 34]. Antidepressants can have some efficacy in reducing disinhibition, repetitive behaviors, sexually inappropriate behaviors, and hyperorality. Atypical antipsychotics may decrease agitation and aggression. Although the evidence is lacking in frontotemporal NCD, cognitive enhancers (e.g., donepezil, galantamine, rivastigmine, memantine) have been used to slow the progression of clinical symptoms, analogous to their use for Alzheimer disease. However, studies suggest that cholinesterase inhibitors are particularly not recommended in frontotemporal NCD, especially in the behavioral variant in which worsening agitation may occur with these agents [35]. The lack of evidence for cholinesterase inhibitors points to a serotonergic system abnormality in frontotemporal NCD, unlike the hypocholinergic system implication in Alzheimer disease.

Because there have been no large, randomized double-blind, placebo-controlled studies yet reported, all such treatments should be considered investigational and off-label. Targeting the underlying pathology with disease-modifying treatments will remain the future focus for the treatment of frontotemporal NCD.

End of Life Care

It is typical that these patients reach the end stages of frontotemporal NCD, which include terminal symptoms and comfort measures. Families and caregivers may not know what to expect in the final stages of the disease and need education, support, and guidance in making difficult decisions for palliative care and hospice. Upon the death of the patient, contact with the family may continue to address results of postmortem neuropathology reports and address questions about the genetic implications of the disorder for the next generation. The neuropathological diagnosis may differ from the clinical diagnosis, which families may find difficult to understand. Some families request a final meeting with the clinician to address persistent worries about care planning and decision-making, such as "did I make the right decisions?" (See ► Chap. 33.)

19.2 Case Studies

The complex symptomatology of the clinical variants of major or mild frontotemporal NCD and the intricate neuropathology and comorbidity that may present in such cases are emphasized in this section through the following case-based studies.

19.2.1 Case 1

Case 1 History

Mr. A. a 62-year-old man, treated with sertraline 150 mg daily for major depressive disorder for the previous 2 years, was brought to the emergency department by his wife for a 2-day history of becoming suddenly confused, disoriented, and agitated. He was unable to sleep and attempted to leave the house in the middle of the night, stating that he was in a different place rather than at home. He became physically aggressive with his wife when prevented from leaving the house. Upon evaluation, his wife reported that he was displaying erratic behavior for the previous year, making embarrassing comments in public and downloading pornography onto his computer. He had endorsed that items he had misplaced were stolen by family members and friends and had alienated them because of this. His wife reported that over the previous 6 months, he had progressively lost interest in his family and mostly watched television without speaking when at home. He was driven to eat when seeing food commercials. He developed a strong desire for potato chips and gained 14 lbs. His manners deteriorated, eating food on his plate in a specific order and stuffing his mouth, often choking at the dinner table. All his instrumental activities of daily living, along with bathing, a basic activity of daily living, were impaired. One year earlier, he scored 28 out of 30 points on the MoCA, losing points on attention and executive function tasks. His family history revealed that his father was initially diagnosed with depression, had prominent symptoms of bizarre behaviors and confabulation, and died at age 69 after 5 years of illness, including several

admissions to psychiatric hospitals and later to a nursing home. A paternal cousin had died from amyotrophic lateral sclerosis. Mr. A. social history indicated that he was married once and was the father of one biological and two adopted children. He had a college degree. He was still employed as a teacher at the school where he had worked continuously for two decades, but he had significantly struggled at his job for over a year to the extent that the principal had suggested him to seek medical care or take a leave of absence. He had no encounters with the law and had no substance abuse history. He was generally healthy and took no additional medications until 2 weeks previously, when his primary care physician started him on a cholinesterase inhibitor, donepezil 5 mg po qAM, but his wife had not noted any improvement. A brain MRI report from 1 year prior was read as "age-related atrophy and perivascular patchiness," but no notable changes otherwise. You were the in-house psychiatric consultant and asked to see this patient urgently because he was becoming increasingly agitated during his evaluation in the emergency department.

Case 1 Questions and Answers

Case 1 Questions

- Question 1. What other information about this patient do you need to make an accurate diagnosis?
- Question 2. What is your working diagnosis?
- Question 3. What is the differential diagnosis?
- Question 4. What would your management for agitation be in this patient?

Case 1 Answers

Case 1 Answer 1 (Question 1—What other information about this patient do you need to make an accurate diagnosis?)

Clinicians should perform a thorough evaluation of the following items.

A1.1. Obtain an accurate clinical history from both Mr. A. and his family caregiver, which is an essential component to determine the cause or precipitant for his confusion and agitation. The important elements in Mr. A.'s history should clarify the following:

- Chronology and onset of his cognitive and behavioral symptoms (acute versus chronic). There were chronic personality changes in this patient, which were especially distressing to his family. In determining whether there was a personality change from baseline, a history from family members should include questions such as:
  - Has the patient's attitude or behavior embarrassed other people?
  - Has the patient seemed less affectionate to relatives and pets?
  - Has the patient had a new and altered sense of humor?
  - Have the patient's food preferences changed or table manners declined?
  - Has the patient developed new interests or hobbies, and which are pursued routinely?
- Presence of comorbid illness, especially signs and symptoms of delirium, cerebrovascular event (which can be a risk factor for depression and agitation), infections (including sexually transmitted infections), metabolic changes, pain, or constipation. Mr. A. had a recent, sudden decline from baseline cognition, which suggested an acute illness.
- A history of psychiatric episodes (e.g., depression, mania, psychosis, anxiety), which may indicate a relapse of an underlying primary psychiatric disorder.

A1.2. Determine the current level of function. Prior to diagnostic clarification, there may be significant problems in the workplace, family environment, and legal arena because of persistent socially inappropriate behaviors. Mr. A. had progressively declined in his functional level and manifested impairment in multiple domains of instrumental and basic activities of daily living. Impairment in at least one basic activity of daily living or at least two instrumental activities of daily living indicates, at minimum, a moderate stage of major NCD. Figure 18.9 in ▶ Chap. 18 lists the daily activities that need assessment in patients suspected of all-cause major or mild NCDs. Functional decline can be seen as the final common pathway of major NCDs, but the initial cause can be behavioral (as in the behavioral-variant frontotemporal NCD), from other executive dyscontrol, as an accompaniment to the underlying cortical changes that compromise memory and praxia (as in Alzheimer disease-related NCD), or from loss of motor function (as in Parkinson disease-related NCD). Early loss of activities of daily living suggests a behavioral cause such as indifference to appearance and resulting bodily odor. Numerous diagnostic scales have been developed, including the Functional Assessment Staging Tool. If the loss of activities of daily living appears inconsistent with the pattern typically seen in Alzheimer disease, it is unlikely due to Alzheimer disease.

A1.3. Conduct a careful examination to determine the presence of other neuropsychiatric symptoms. Assess for current psychiatric symptoms (e.g., rate of speech, amount of sleep, energy level) which could suggest a manic, mixed, or depressive episode. Ask the patient about the presence of vivid dreams, nightmares, or poor sleep quality during the previous night, although some patients may have little recollection of the night before if they are cognitively impaired. New-onset incontinence, mild disorientation, hypersensitivity to environmental stimuli, hypervigilance, dysphagia, dysarthria, refusal to mobilize, or falls can represent manifestations of subsyndromal delirium, which then can progress to include more dramatic agitation or psychotic symptoms.

Overall, clinicians need to facilitate assessment for neuropsychiatric syndromes known to precipitate agitation or aggression (e.g., delirium, major or mild NCD, manic episode). Assess whether there was a new, uncharacteristic use of alcohol or illicit substances, particularly if that was hidden from family. A review of substance misuse or withdrawal was noncontributory in Mr. A. case.

A1.4. Review the list of prescription and nonprescription medications, adherence, changes, and withdrawals. If a new medication was recently prescribed or discontinued, drug-drug interactions must be reviewed. (See ▶ Chap. 5.) Donepezil, a cholinesterase inhibitor approved for Alzheimer disease-related NCD, was recently started in this case and would require close monitoring to evaluate adverse events including agitation, symptomatic bradycardia, and/or gastrointestinal distress. As stated previously, patients with behavioral-variant major or mild NCD can experience worsening of symptoms with cholinesterase inhibitors [35].

A1.5. Perform a thorough physical exam, including mental status examination. Physical examination in Case 1 was necessary to exclude infection, pain, constipation, and cerebrovascular or cardiovascular disease as a precipitant for Mr. A.'s recent cognitive and behavioral disturbances. A neurological examination is important in order to rule out focal neurological signs suggestive of stroke, tumor, or subdural hematoma. Physical examination revealed that Mr. A. had pathologically brisk snout, jaw jerks, fasciculations, as well as subtle atrophy and weakness in the upper and lower extremities. Plantar responses were extensor. He had localized inspiratory crackles at the base of the right lung, suggesting a sign of consolidation, pneumonia, or aspiration. His remaining physical exam was unremarkable.

Mental status examination revealed that Mr. A. was apathetic and indifferent and denied any wrongdoing at home, passively shrugging his shoulders when his tearful wife described his problems. However, his affect also became labile, quickly shifting from jocularity to tearfulness. His speech was fluent, and he insisted on telling improper jokes during the evaluation. He was alert and oriented to person and place, but he thought that the date was several months earlier than it actually was. No hallucinations or delusions were noted. He had no insight into his predicament.

The mental status examination should include a cognitive assessment, with a particular focus on change from the patient's previous testing. It was imperative to distinguish an episode of delirium (which was the most likely diagnosis responsible for his current presentation to the emergency department) from neuropsychiatric symptoms due to a major or mild NCD. Poor attention and distractibility during assessment in the context of acute and new-onset behavioral disturbances are helpful features in distinguishing delirium from preexisting major or mild NCD. On cognitive examination, Mr. A. now scored 26 out of 30 points on the MoCA, missing one point each for serial 7 subtraction task and abstraction, made frequent perseverative errors on the Trails-B item, and failed on the language fluency task (he generated only five words that begin with the letter F in 1 minute). On delayed recall, he remembered 5 of 5 words without cueing in 5 minutes. On the Boston Naming Test, he correctly named 55 of 60 words. On the Geriatric Depression Scale-15 items (GDS-15), he scored 1 suggesting no current major depression. However, a MoCA performed by a nurse 1 hour earlier was 5 out of 30 points. The medical chart at that time documented that, on the bedside test of attention, Mr. A. performed poorly on reciting, backward, months of the year, and on serial subtractions of the same number from a starting point. He was also noted to have problems focusing, staring off into space, and losing track of questions and was "picking at the air."

A1.6. Perform targeted laboratory investigations to rule out systemic medical causes. In Mr. A.'s case, the laboratory tests revealed the following (all values within normal limits unless stated otherwise): hemoglobin 132 g/L, white blood cell count 13×10^9/L (elevated), neutrophils 9×10^9/L (elevated), sodium 136 mmol/L (136 mEq/L), potassium 3.9 mmol/L (3.9 mEq/L), urea 7 mmol/L (20 mg/dL), creatinine 68 μmol/L (0.76 mg/dL), estimated glomerular filtration rate (eGFR) 90 ml/minutes/1.73 m^2, thyroid-stimulating hormone (TSH) 1.3 mlU/L, calcium 2.15 mmol/L (8.6 mg/dL), vitamin B_{12} 430 pmol/L (582 pg/mL), and urine dipstick negative. Other investigations included a venereal disease research laboratory (VDRL) test that was nonreactive; electroencephalogram (EEG) with diffuse slow waves; electrocardiogram (ECG) with sinus rhythm, heart rate of 89 beats per minute and QTc of 435 milliseconds; anteroposterior chest X-ray with consolidation at the right lung base, suggesting an aspiration pneumonia, given his history of choking at the table; neuroimaging (MRI) with mild right greater than left frontal atrophy and perivascular patchiness; electromyography (EMG) that was normal; and genetic testing for which blood was sent for tau and progranulin mutations, which were absent.

Teaching Point

In summary, for diagnostic purposes, Mr. A.'s clinician needed to obtain a thorough psychiatric history, medical history, and medication profile to complete the picture as his presentation may suggest various diagnostic possibilities. A sexual history would be important with his history of disinhibited behavior, which may have resulted in unprotected sex causing sexually transmitted infections. The presence of a strong family history argues against sporadic major or mild NCD. Routine laboratory tests as per consensus guidelines could reveal exacerbating factors. The atypicality of this case gives reason to delve into more depth with the evaluation by performing tests more sensitive to frontal changes such as the Trail Making Test Part B or, if available, neuropsychological evaluation. An MRI scan of the brain may be more likely to identify atrophy, and, if available, a SPECT or PET scan could clarify the diagnosis.

Case 1 Answer 2 (Question 2—What is your working diagnosis?)

Mr. A.'s presentation revealed classic symptoms of a behavioral-variant major frontotemporal NCD, including poor judgment and insight, disinhibition, apathy, compulsive overeating, change in eating habits and routines, delusions, and a progressive decline in functional abilities (see ◘ Fig. 19.1 for the DSM-5 diagnostic highlights). Like many patients with frontotemporal NCD, despite a relatively normal MoCA and visuospatial function, he failed severely on tasks of executive function and word list generation. His symptomatology presented at a younger age, as is typically expected in frontotemporal NCD, and in contrast with Alzheimer disease. He had a familial aggregation with a possible autosomal-dominant inheritance, as seen in many reported cases [3].

Because of the acute onset of confusion and agitation, a delirium was also considered. Identifying delirium requires a high index of suspicion, and until a specific cause is identified, the confused patient should be assumed to have delirium, which is often reversible with treatment of the underlying systemic medical condition. Delirium has a myriad of reversible, partially reversible, and irreversible risk factors (see ▶ Chap. 17, ◘ Fig. 17.3). Among those, major or mild NCDs constitute irreversible risk factors for delirium. Differentiating a major NCD from delirium can be challenging in the acute setting or when collateral history is lacking. In these settings, care must be taken not to attribute symptoms of delirium to a known major NCD when the two can be superimposed on one another. In this context, it is essential to recognize and treat potentially reversible causes of delirium occurring "within" an irreversible NCD, characterized by an abrupt change from baseline. Although delirium is described in detail elsewhere (see ▶ Chap. 17), there are several bedside screening tools to help with identifying delirium. The MoCA and MMSE are not by themselves definitive in screening for delirium or differentiating it from major or mild NCDs, because they only offer a cross-sectional assessment of the patient's cognitive status at a particular point in time. The Confusion Assessment Method (CAM) is a tool that can be used to identify the presence of delirium even if a preexisting major or mild NCD is established. The presence of delirium is indicated by a CAM algorithm that includes four features:

1. Acute onset *and* fluctuating course
2. Inattention
3. Disorganized thinking
4. Altered level of consciousness

Features (1) and (2), plus either (3) or (4), suggest delirium [36].

Teaching Point

An acute change from baseline is often key to confirming the diagnosis of delirium in patients with major or mild NCDs.

Mr. A. had an acute onset in disturbances of attention, distractibility, and fluctuating course during assessment, which are hallmarks of delirium [36]. In such patients, it is imperative for clinicians to obtain collateral information from caregivers or staff (e.g., comments of family members, nursing staff, review of medical notes) over the previous 24–48 hours [37]. This will allow clarification whether there was any acute change from baseline in the patient's cognition, behavior, and function. Acute and fluctuating changes in mental status, along with the presence of systemic medical illness (pneumonia) in a patient described as acutely "confused" and "disoriented," were strong indicators of delirium in this case. Moreover, diffuse slow waves on EEG, in a patient without a history of seizure disorder, supported the diagnosis of delirium. Notably, EEG can be useful in differentiating delirium from other conditions. In patients with delirium, EEG shows a diffuse slowing of the background rhythm, except in delirium tremens, where the EEG shows fast activity. EEG is also useful in detecting ictal and postictal seizure activity, as well as nonconvulsive status epilepticus, all of which can present as delirium. Abnormal EEG readings would not be expected in patients with bipolar, major depressive, or psychotic disorders. The positive predictive value of diffuse slow-wave activity is limited, however, as it occurs in patients with more advanced major NCDs. In summary, the EEG should not be used routinely in the evaluation of delirium, but can provide valuable information when trying to distinguish delirium from *early* stages of major NCDs or when there is clinical suspicion of seizures (e.g., when the patient has intermittent, unexplained periods of confusion or has unexplained syncope with post-syncopal cognitive depression). Although EMG was performed in Case 1, this test is not routinely done for patients with major or mild NCD unless they are experiencing other problems such as muscle weakness, myoclonus, or twitching of the muscles. This test is important in the diagnosis of motor neuron diseases such as amyotrophic lateral sclerosis. In summary, Mr. A. had a working diagnosis of behavioral-variant major frontotemporal NCD and a superimposed delirium due to aspiration pneumonia, which precipitated his current presentation to hospital.

Case 1 Answer 3 (Question 3—What is the differential diagnosis in Case 1?)

Diagnosing frontotemporal NCD can be challenging due to multiple factors. The symptom overlap with psychiatric disorders such as depressive, manic, or psychotic episodes can make frontotemporal NCD difficult to distinguish from other conditions, especially early in the disease course. Another factor is the low prevalence of frontotemporal NCD compared to psychiatric disorders. For example, major depressive disorder in adults is approximately 100 times more common than frontotemporal NCD [38]. Therefore, based on the prevalence data, patients with anhedonia, social withdrawal, and apathy are more likely to have a major depressive disorder or have their symptoms attributed to a major depression than frontotemporal NCD.

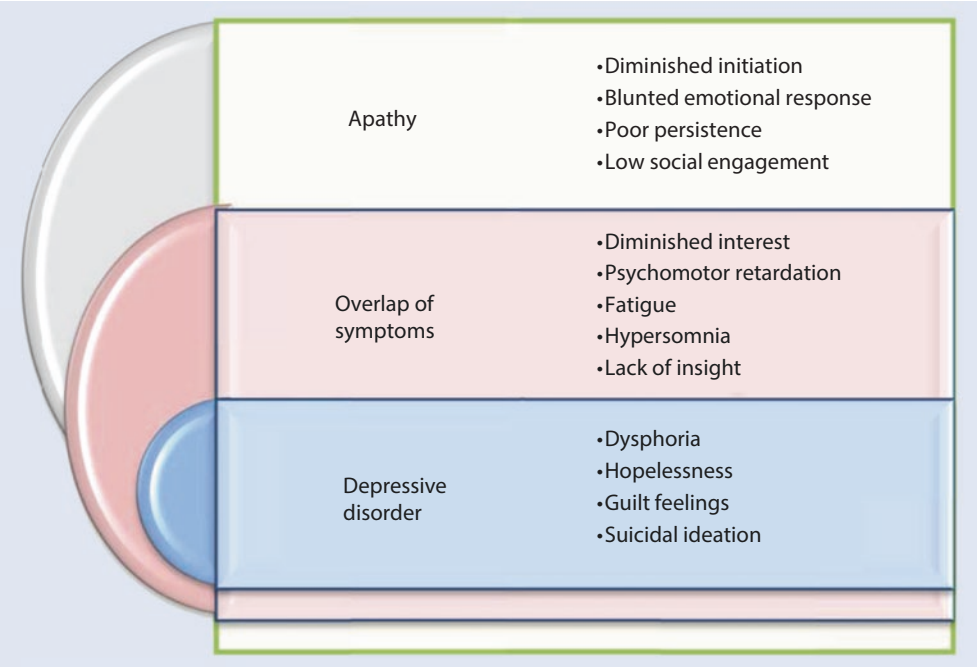


Fig. 19.4 Distinguishing apathy and associated features from major depressive disorder [41]

The main differential diagnoses to be considered in this patient with cognitive impairment exhibiting neuropsychiatric and behavioral symptoms include:

- Bipolar disorder, current manic episode, with psychotic features
- Major depressive disorder, with psychotic features
- Other psychiatric disorders (e.g., obsessive-compulsive disorder, schizophrenia, schizoaffective disorder, delusional disorder)
- Other major or mild neurocognitive disorders (e.g., frontal-variant Alzheimer disease)
- Neurological disorders

A3.1. *Bipolar disorder, current manic episode, with psychotic features.* The manifestation of affect lability, sexual disinhibition, psychotic symptoms (delusions), and diminished judgment and insight, in a patient with a history of major depression and a relatively normal MoCA, calls for a need to consider a diagnosis of a manic episode. Although the associated symptoms for sleep and energy changes in Mr. A. were unknown, his progressive and chronic deterioration in behavior, speech, affect, and functional abilities, along with, now, acute presence of "confusion," or altered level of consciousness, and marked fluctuations in cognition (as documented by his MoCA scores), was unlikely to suggest a current manic episode. There was no evidence from the history, physical examination, or laboratory and neuroimaging investigations to suggest a bipolar disorder due to another medical condition or substance abuse.

A3.2. *Major depressive disorder, with psychotic features.* Upon examination, Mr. A. did not endorse depressed mood that lasted consistently for at least 2 weeks. It remained unclear whether he had anhedonia (defined as loss of interest and enjoyment in life), which is one of the key symptoms of major depression, or apathy (defined as loss of initiative and motivation, emotional indifference, and diminished social engagement). Apathy can be difficult to differentiate from anhedonia. Apathy is a common and significant problem in patients with major or mild NCDs, regardless of etiology. However, apathy is more common in major or mild frontotemporal NCD than in Alzheimer disease-related NCD [39]. An observation of "loss of interest" due to apathy versus depression may be challenging as it can represent the manifestation of both. Apathy is often associated with limited insight, low interest, blunted emotional response, poor persistence, and impaired daily activities [40], as probably was the case with Mr. A.

Figure 19.4 lists the distinguishing and overlapping features between apathy and major depressive disorder [41]. Differential diagnosis of major or mild NCD-associated apathy includes depressive disorder, sedation, drowsiness, delirium, systemic medical illness, and boredom. Although Mr. A. had a history of major depressive disorder, there was no evidence from the history, physical examination, mental status examination, and medical investigations to suggest a decompensation of major depression, a depressive disorder due to another medical condition, or depression associated with substance misuse. On depression screening tool, his GDS-15 scored 1, suggesting no evidence of clinical depression.

A3.3. *Other psychiatric disorders.* Behavioral-variant major or mild frontotemporal NCD may be mistaken for a primary psychiatric disorder, such as obsessive-compulsive disorder, schizophrenia, schizoaffective, or delusional disorder, particularly when patients present with delusions or confabulations as neuropsychiatric manifestations of NCDs [42]. Patients with this variant may often present initially to psychiatric services. Compulsions (defined as repetitive or ritualistic behaviors, which the patient feels compelled to perform) are common in frontotemporal NCD, whereas obsessions

Table 19.4 Red flags for diagnosis of frontotemporal neurocognitive disorder (NCD) vs. psychiatric disorders [38]

Psychiatric disorders	Common symptoms in frontotemporal NCD	Rare symptoms in frontotemporal NCD
Mania	Logorrhea, distractibility, increased goal-directed activities, impulsive behavior, violations of social/personal boundaries	Elevated mood, flight of ideas, decreased need for sleep
Major depressive disorder	Anhedonia, psychomotor agitation or retardation, decreased motivation, decreased energy, decreased concentration and focus	Depressed mood, weight loss, insomnia, feelings of worthlessness or guilt, poor self-esteem, suicidal ideation
Obsessive-compulsive disorder	Compulsions (i.e., repetitive behaviors, which the patient feels compelled to perform)	Obsessions (i.e., unwanted, recurrent intrusive thoughts that cause anxiety)
Schizophrenia	Disorganized speech and behavior, affective flattening, alogia (poverty of speech), avolition (lack of initiative or motivation)	Complex delusions, auditory hallucinations (which are more common in C9ORF72 mutation carriers)

(defined as recurrent, unwanted, intrusive thoughts, which cause anxiety) are less common. In comparison with delusions due to schizophrenia, those related to major NCDs are usually transient, simple, and poorly systematized, as in Mr. A.'s case. Paranoid delusions in major NCD are the most common, with themes of theft, infidelity, and misidentification the most prevalent. Table 19.4 emphasizes clinical features suggestive of a diagnosis of frontotemporal NCD versus other neuropsychiatric disorders [38]. Mr. A.'s progressive neurocognitive difficulties helped to make the diagnostic distinction. A careful medical evaluation in this case excluded treatable causes of neuropsychiatric symptoms, such as metabolic abnormalities and nutritional deficiencies.

A3.4. *Other major or mild neurocognitive disorders (e.g., frontal-variant Alzheimer disease).* Major or mild NCD due to Alzheimer disease presents with an early decline in learning and memory. However, approximately 30% of patients presenting clinically with focal syndromes suggestive of major or mild frontotemporal NCD are found postmortem to have Alzheimer disease pathology [43]. This often occurs in those with logopenic-variant frontotemporal NCD or in those with progressive dysexecutive syndromes in the absence of behavioral changes or movement disorder. However, Alzheimer disease can begin with behavior disturbance or executive dysfunction, suggesting a frontal lobe syndrome, being referred to as the frontal-variant Alzheimer disease [3]. In Mr. A., the presence of impaired social skills, in the context of no prominent memory difficulties, no problems in word retrieval, and no constructional and perceptuospatial difficulties, was suggestive of a non-Alzheimer pathology. Typical Alzheimer disease patients are older at onset than Mr. A., have major memory and visuospatial impairments, and have diffuse cortical atrophy. Review of this patient's recent brain MRI, a diagnostic biomarker of downstream neurodegeneration [44], showed a pattern of bifrontal atrophy, supporting a diagnosis of frontotemporal neurodegeneration. Physical signs of motor neuron disease (such as amyotrophic lateral sclerosis as in Case 1) can be present in frontotemporal NCD [3], but typically are absent in Alzheimer disease.

Teaching Point

Although more expensive, MRI is more sensitive and accurate than CT scan for delineating cortical atrophy. Coronal MRI makes it especially easy to detect temporal lobe atrophy, as well as to look at the medial temporal lobe structures, which are more typically affected in Alzheimer disease. Positron emission tomography (PET) scans, such as fluorodeoxyglucose (FDG)-PET and amyloid PET, are not presently indicated in clinical practice but may become future tools for emerging utilization of computer-assisted diagnosis in the evaluation of patients with major or mild NCDs.

The presence of perivascular patchiness on Mr. A.'s MRI scan was intriguing as it may have indicated segmental deposition of amyloid in the artery walls, termed *cerebral amyloid angiopathy*. Cerebral amyloid angiopathy suggests either an age-related failure of perivascular drainage of soluble amyloid from the brain or an association with Alzheimer disease and with focal intracerebral hemorrhage [45]. (See ▶ Chap. 21.) Cerebral amyloid angiopathy is present in about 30% of the normal older adults and over 90% of patients with Alzheimer disease, in whom cerebral amyloid angiopathy tends to be more severe, with a greater proportion of blood vessels involved and extension into adjacent brain parenchyma. However, Mr. A. lacked prominent deficit in learning and episodic memory (i.e., memory of autobiographical events), a clinical hallmark for Alzheimer disease pathology, whereas he displayed early behavioral and executive function changes—which characterize the behavioral-variant frontotemporal NCD. While a diagnosis of typical Alzheimer disease was improbable, the exclusion of frontal Alzheimer disease remained uncertain. For this, cerebrospinal fluid and amyloid PET biomarkers may prove decisive in differentiating Alzheimer disease from non-Alzheimer pathologies in frontotemporal NCD, but their clinical role is not yet established [46].

Teaching Point
Memory and visuospatial functions are usually preserved in earlier stages of major frontotemporal NCD, in contrast to the clinical presentation in Alzheimer disease.

Mr. A. presented with an insidious onset and progressive course of NCD that, until recently, was not associated with fluctuations in mental status (one of the core features of Lewy body NCD). Moreover, Mr. A. did not present with persistent, well-formed visual hallucinations and spontaneous parkinsonism, which are also pathognomonic core features for Lewy body NCD. (See ▶ Chap. 20.)

Mr. A.'s loss of executive abilities and behavioral changes, including apathy, suggested the need to rule out a major or mild vascular NCD. However, there was no history of a cerebrovascular event that was temporarily related to the onset of his cognitive impairment, and neuroimaging did not reveal infarctions or white matter lesions in expected brain regions sufficient to account for the clinical picture.

A3.5. *Neurological disorders.* Progressive supranuclear palsy, corticobasal degeneration, and motor neuron disease can overlap clinically and pathologically with major or mild frontotemporal NCD. Many patients with behavioral-variant major or mild frontotemporal NCD show features of motor neuron disease, as was in Mr. A.'s case who presented with mixed upper and lower motor neuron disease. Neurocognitive disorder secondary to neurosyphilis was excluded based on his negative VDRL test. Although in later stages of the behavioral variant loss of continence may occur, normal pressure hydrocephalus was ruled out in this patient in the context of no gait or sphincter control disturbances and no enlarged ventricles on the MRI scan. A diagnosis of Creutzfeldt-Jakob disease in this case was excluded based on lack of characteristic clinical findings (e.g., myoclonus, ataxia, seizures), typical EEG pattern (e.g., generalized periodic sharp wave complexes), and MRI of the brain (e.g., high signal intensity in the caudate nucleus and putamen bilaterally on T2-weighted images) often shown in these patients.

Case 1 Answer 4 (Question 4—What would your management for agitation be in this patient?)

A4.1. *Correct the underlying causes for agitation*. Agitation due to delirium will be associated with other typical features of delirium (e.g., altered level of consciousness, fluctuating mental status). Agitation due to a major NCD will typically manifest in clear sensorium and occurs in the moderate to severe stages of the disease. (See ▶ Chap. 22.) In Mr. A.'s case, his newly developed agitation was likely caused by delirium, precipitated by aspiration pneumonia, which required specific treatment. Additionally, checking for pain and constipation should be routine in the management of delirious patients. (See ▶ Chap. 17.) Cautious use of medications, particularly those with known potential for significant adverse events, and review of drug-drug and drug-disease interactions are necessary. In Mr. A.'s case, a review of his medications revealed that donepezil (a cholinesterase inhibitor) was recently started. Patients with behavioral-variant frontotemporal NCD do not appear to benefit from cholinesterase inhibitors, and their agitation may even worsen with these medications [3, 35]. Therefore, discontinuation of donepezil was warranted in this case.

Teaching Point
When there are systemic medical conditions that necessitate review of newly started, or recently increased, delirium-provoking medications, consider dosage tapering, switch, or discontinuation of nonessential medications. (See ▶ Chap. 28, ◘ Table 28.3 on delirium-provoking medications.)

A4.2. *Treat the agitation symptomatically*. When a clinician is asked to evaluate a patient with distressing agitation, aggression, and/or psychotic symptoms, whether due to delirium or major NCD, and in which non-pharmacological approaches solely did not suffice, psychopharmacological treatment may be required. (See ▶ Chaps. 17 and 22 for non-pharmacological management of patients with delirium and those with Alzheimer disease.) Antipsychotic medications are the symptomatic treatment of choice for short-term duration until delirium resolves. Psychosis, agitation, and aggression in patients with major NCDs requiring pharmacotherapy with antipsychotics may respond best to risperidone, olanzapine, and aripiprazole [47], among which the choice should be based on ease of administration and potential side effects, including prolongation of the QTc interval. The use of haloperidol should be limited to addressing agitation and psychosis in delirium, using low doses for a brief period of time until symptoms clear. Black box warnings on the increased risk of cerebrovascular events and mortality in patients with major NCDs taking either typical or atypical antipsychotics have been issued. In 2016, the American Psychiatric Association released evidence-based recommendations on the use of antipsychotics in the treatment of patients with agitation and psychosis related to a major NCD [48]. It is important to know that the functional impairment due to behavioral and language dysfunction in frontotemporal NCD may exceed that due to the cognitive disturbance in other types of NCDs and may lead to earlier hospitalization or nursing home placement.

Teaching Point
The goal for the symptomatic pharmacological treatment of agitation and/or psychosis, be that due to delirium or major NCDs, should be an *alert* patient who is manageable, rather than a sedated patient. The medication should be tapered and discontinued as soon as possible after resolution of symptoms.

Case 1 (Continued)

Within 6 months, Mr. A. became even more apathetic, unable to speak, and exhibited difficulties with swallowing fluids, with frequent aspiration. He died 11 months after diagnosis as a result of aspiration pneumonia. Neuropathology showed loss of neurons, extensive gliosis, and vacuolation of the cortical neuropil in the frontal cortex, a pathology very distinct from the changes of Alzheimer disease, which typically involves neuritic plaques and neurofibrillary tangles [49]. This, once again, excluded a frontal-variant Alzheimer disease. Ubiquitin-positive and tau-negative intraneuronal inclusions were seen in the dentate fascia of the hippocampus.

Case 1 Analysis Mr. A. initially presented with behavioral symptoms as the earliest and most prominent feature. A breakdown in his social behavior, affect, and executive function occurred in the context of preserved perceptuospatial skills. Moreover, the patient's clinical profile was representative of the characteristic neuroimaging pattern of bifrontal atrophy, suggestive of a diagnosis of probable behavioral-variant frontotemporal NCD. Therefore, optimum diagnostic prediction required both clinical and neuroimaging information. The presence of a strong family history in this case argued against a sporadic frontotemporal NCD. With a family history of amyotrophic lateral sclerosis, Mr. A. went on to develop symptoms suggestive of motor neuron disease, with prominent evidence for dysphagia. Genetic testing was negative for tau and progranulin, suggesting the possibility of another gene involvement than those associated with chromosome 17. The genes that cause frontotemporal NCD-motor neuron disease remain unclear, although a locus on chromosome 9 has been identified that will likely explain many cases of frontotemporal NCD-amyotrophic lateral sclerosis, which have a familiar autosomal-dominant pattern and evidence for anticipation [50]. Clinically, features of motor neuron disease, such as amyotrophic lateral sclerosis, may develop in patients with a behavioral or language variant of frontotemporal NCD, and prominent behavioral and language deficits can also emerge in the course of amyotrophic lateral sclerosis. Therefore, frontotemporal NCD and amyotrophic lateral sclerosis can form a clinicopathologic continuum. On postmortem examination, a definite diagnosis of major frontotemporal NCD-motor neuron disease was given in this case. The presence of motor neuron disease has been associated with a more rapid deterioration compared with other frontotemporal NCD variants [3]; Mr. A. had died within 1 year from the clinical diagnosis.

19.2.2 Case 2

Case 2 History

Mrs. B., a 61-year-old bank manager, had slowly started to have difficulty finding words, began to have trouble writing, and became somewhat socially withdrawn and quieter. She took a long time to express her ideas and communicated agrammatically with nouns. She expressed profound frustration regarding her speech, and, subsequently, she developed a major depressive episode. There was no family history of major depressive disorder, bipolar disorder, or major or mild NCD. There was no personal history of illicit drug use or alcohol abuse. She had a supportive husband at home.

You had seen her in your psychiatric clinic for depressive symptoms which had improved on treatment with sertraline 150 mg daily, but her language deficits persisted. On mental status examination, Mrs. B. was well groomed and her social graces were appropriate. Her neurological examination was normal except for minor difficulty looking downward. On cognitive testing, she scored 28 out of 30 points on the MoCA. Her speech was nonfluent, generating only six words beginning with letter F in 1 minute (normal $\geq$ 11 words). She spoke in short phrases and had a stuttering cadence. Her comprehension was normal. Her working memory was slightly diminished, as she could only repeat 4 of 5 listed words. The Trail Making Test Part B was performed slowly, but without errors. On delayed recall (verbal learning), she remembered 5 of 5 words after 5 minutes without cueing. Facial emotion recognition was normal. She correctly named 55 of 60 words on the Boston Naming Test and generated three more words with multiple-choice cueing. Further investigations revealed that MRI of her brain showed asymmetric atrophy, predominantly of the left frontal lobes, and blood tests revealed that progranulin gene mutation was absent, whereas mutation for tau was present. A probable diagnosis of nonfluent/agrammatic language variant of primary progressive aphasia was eventually made.

Subsequently, Mrs. B. had changed her job and was able to work for another year as a downtown courier driver where she learned several delivery routes without any problems. However, within 3 years she became progressively mute and dysphagia emerged. She had recurrent falls, particularly when walking downstairs. On further examination, inability to look up or down was found and axial rigidity was evident. There was no tremor noted. EMG showed a reduced amplitude from the orbicularis oculi muscle. Mrs. B. died within 2 months of aspiration pneumonia. Progressive supranuclear palsy was seen at postmortem neuropathology.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. How would you differentiate language deficits due to nonfluent variant from semantic-variant frontotemporal NCD?

? Question 2. How can you tell if the language impairment is due to language variants of frontotemporal NCD versus Alzheimer disease-related NCD?

? Question 3. What neurological characteristics differentiate frontotemporal NCD and its variants from Alzheimer disease?

? Question 4. What is the evidence-based pharmacological treatment of frontotemporal NCD?

Table 19.5 Variants of primary progressive aphasia, language and neuropathology characteristics [3, 12, 29, 51]

	Language	Predominant neuropathology
Primary progressive aphasia and its variants	*Nonfluent/agrammatic* Low fluency of word output Distorted syntax Good comprehension	Frontotemporal NCD-TAU
	Semantic High but aberrant fluency Poor comprehension Severe anomia	Frontotemporal NCD-TDP-43
	Logopenic Variable fluency Word-finding hesitation Impaired repetition Good comprehension	Alzheimer disease pathology Frontotemporal NCD-TDP-43

Case 2 Answers

Case 2 Answer 1 (Question 1—How would you differentiate language deficits due to nonfluent/agrammatical language variant from semantic-variant frontotemporal NCD?)

Table 19.5 lists the key elements of speech in primary progressive aphasia and its three variants [3, 12, 29, 51]. In contrast with the deficits of fluency of speech seen in nonfluent/agrammatical language-variant frontotemporal NCD (i.e., errors in language production; effortful, halting speech with speech sound errors; grammatical simplification; impaired syntactic comprehension; preserved content word comprehension; and preserved object knowledge), semantic-variant frontotemporal NCD involves early deficits of anomia and impaired single-word comprehension, poor object knowledge, and motor speech delineated by fluent aphasia with long strings of word production [3, 12, 29, 51]. Therefore, patients with semantic-variant frontotemporal NCD cannot name objects and are unable to say what the objects are. These patients often have *surface dyslexia* (or difficulty with whole word recognition and spelling, especially when the words have irregular spelling-sound correspondences, such as "pint" or "yacht"). In contrast with the nonfluent language variant, however, those with semantic variant repeat without difficulty. In semantic-variant frontotemporal NCD, the neuropathology can be variable, usually involving a frontotemporal pathology. Genetically, many patients with semantic-variant frontotemporal NCD have progranulin mutations, but a few have the Alzheimer disease pathology at autopsy [3].

Case 2 Answer 2 (Question 2—How can you tell if the language impairment is due to language variants of frontotemporal NCD versus Alzheimer disease-related NCD?)

The division into these variants is important because, for example, patients with nonfluent/agrammatic variant are typically characterized by tau pathology, while patients with logopenic variant generally have Alzheimer disease pathology, which can be one of the three atypical, nonamnestic, "focal" variants of Alzheimer disease, along with frontal Alzheimer disease and posterior cortical atrophy. (See ▶ Chap. 18.) Unlike patients with nonfluent language variant, those with logopenic variant generally have no dysarthria or motor speech abnormalities and no agrammatism. Unlike semantic-variant frontotemporal NCD, those with logopenic variant exhibit phonological paraphasias, impaired repetition and word retrieval, and preserved single-word comprehension and object knowledge.

Given the different underlying pathologies, nonlanguage clinical features may be helpful in distinguishing frontotemporal NCD from typical Alzheimer disease-related NCD. Personality changes, depression, apathy, and irritability appear in both frontotemporal NCD and Alzheimer disease-related NCD, but the actual behaviors that define these changes may help differentiate the underlying disorders. For example, a patient with Alzheimer disease-related NCD may present as withdrawn and irritable as a function of associated depression. The patient with frontotemporal NCD may have irritability and apathy manifested as part of a distinct personality change, such as a formerly proper gentleman choosing to sit around in underwear all day watching television and swearing at his spouse when she interrupts his viewing (as similarly presented in Case 1). Behavioral changes usually seen in frontotemporal NCD (as well as Alzheimer disease-related NCD) can resemble those in "subcortical" NCD (e.g., Parkinson disease-related NCD and subcortical ischemic vascular NCD), but specific motor features may help differentiate them (see ▶ section Case 2 Answers, Case 2 Answer 3). For example, patients with Alzheimer disease-related NCD do not develop parkinsonian features until very late in the disease. Patients with ischemic and parkinsonian-related NCD may develop motor rigidity and a shuffling gait, but subcortical NCD is more likely to present with a stooped posture rather than with axial rigidity as seen in progressive supranuclear palsy. Impaired downward and upward gaze represents pathognomonic features of progressive supranuclear palsy. As the subcortical NCD progresses, memory and judgment problems arise, and the end stages of illness result in the same total breakdown of brain functions as in the high-level functions of the cortical type (e.g., memory, language, reasoning, and problem solving), making the clinical distinction even more difficult.

Although language can be impaired in both frontotemporal and Alzheimer disease syndromes, some studies have shown that naming is more impaired in patients with Alzheimer disease, whereas letter-based fluency is more impaired in non-Alzheimer disease cases [3]. Nevertheless, impairment in learning and episodic memory (i.e., memory of an event which includes various details such as what happened, when it happened, and where it happened) is a key deficit in patients with typical Alzheimer disease, which is generally preserved in those with early frontotemporal NCD. The main domain differences of cognitive impairment between primary progressive aphasia and Alzheimer disease are summarized in Table 19.6 [3].

Table 19.6 Main domain differences among variants of frontotemporal neurocognitive disorder and Alzheimer disease [3]

	Behavioral variant	Primary progressive aphasia	Alzheimer disease
Hallmark of early impairment	Behavior/personality ++; motor function +	Language ++	Memory ++; social behavior –
Onset	Age 50s–60s	Age 50s–60s	Age 60s–70s
Working memory	++	+	+
Short-term memory	–	–	++
Syntactic and speech fluency	–	++	+
Attention (e.g., digit span)	++	++	+
Visuospatial	–	–	++
Executive dysfunction	++	++	+ (esp. focal syndromes)

Note: ++ impaired (early), + somewhat impaired, – preserved (early)

Teaching Point

Verbal episodic memory (i.e., the collection of past personal experiences that occurred at a particular time and place) can be tested by repeating a story or learning and recalling of word lists (the three-word list, as in MMSE, or the five-word list, as in MoCA). Copying a figure and then reproducing it at a later time can be used to assess visual episodic memory. Neuropsychological evaluation often can detect subtle deficits missed on screening tests like the MMSE or MoCA, and these subtle deficits may occur before changes in brain structure are seen on neuroanatomical imaging.

In order to differentiate patients with language-variant frontotemporal NCD from those with Alzheimer disease, several tests may have various clinical utilities [3, 44], but in 2017 they still remain largely experimental with uncertain predictive value, and are not part of routine diagnostic testing:

- Cerebrospinal fluid analysis for tau and beta-amyloid is promising; elevated spinal fluid tau and reduced spinal fluid beta-amyloid can support the diagnosis of Alzheimer disease.
- FDG-PET metabolism is not particularly useful; however, in primary progressive aphasia, cortical hypometabolism in the left temporal, and the left frontal lobe (in more advanced cases), is commonly detected. By comparison, in Alzheimer disease, the earliest detectable glucose hypometabolism is usually in the parietal lobes. This distinction can obviate the prescription of a cholinesterase inhibitor or memantine, which have not been shown to help with the symptoms of primary progressive aphasia.
- PET amyloid imaging is most informative if negative, by the exclusion of Alzheimer disease pathology. Patients with vascular cognitive impairment can also develop beta-amyloid deposits. However, the general cost and availability of performing both FDG-PET and PET amyloid studies create an impediment.
- Apolipoprotein E4 genotyping is not useful; apolipoprotein E4, which is associated with an increased risk for late-onset, sporadic Alzheimer disease, is infrequently increased in patients with primary progressive aphasia.

Teaching Point

For patients with nonfluent language variant, semantic variant, and logopenic variant of frontotemporal NCD, and those with frontal Alzheimer disease, clues to diagnosis for each of these syndromes may include findings from (1) cerebrospinal fluid analysis (e.g., marked increase in total tau or phosphorylated tau, decrease in beta-amyloid$_{1-42}$, and marked increase in tau/beta-amyloid$_{1-42}$ ratio in cases of Alzheimer disease) and (2) PET amyloid imaging, when available, which may suggest or exclude Alzheimer disease (with or without vascular cognitive impairment with variable development of beta-amyloid).

Case 2 Answer 3 (Question 3—What neurological characteristics differentiate frontotemporal NCD and its variants from Alzheimer disease?)

Frontal release signs (e.g., glabellar, grasp, snout, palmomental) often develop in major or mild frontotemporal NCD, particularly in the behavioral variant, as illustrated in the previous Case 1. Progressive supranuclear palsy, characterized by supranuclear gaze palsy and axial-predominant

parkinsonism, may develop in some patients with major or mild frontotemporal NCD, as was in the patient in Case 2. Unlike the stooped posture in Parkinson disease-related NCD, patients with progressive supranuclear palsy often walk hyper-erect. Corticobasal degeneration also can overlap clinically and pathologically with the variants of frontotemporal NCD and involves asymmetric rigidity and apraxia of the upper extremities, postural instability, myoclonus, alien limb phenomenon, and cortical sensory loss [3]. Some patients with behavioral-variant major or mild NCD show features of motor neuron disease, with muscle atrophy, weakness, fasciculations, and hyperreflexia [3]. The features of motor neuron disease tend to be mixed upper and lower motor neuron disease, and some patients may develop bulbar symptoms, including dysphagia and dysarthria [3], as also illustrated in both cases in this chapter. The patient in Case 2 clinically began with nonfluent language-variant frontotemporal NCD, but soon afterward exhibited findings of progressive supranuclear palsy including falls, inability to look up or down, and axial rigidity. The association of progressive supranuclear palsy and corticobasal degeneration with the nonfluent language variant is now well recognized, and the majority of the patients with this variant show progressive supranuclear palsy or corticobasal degeneration on postmortem examination [3]. By contrast, parkinsonian and extraocular signs and symptoms are not expected to occur in patients with Alzheimer disease until end-stage disease, and their occurrence may signal a non-Alzheimer disease pathology.

Case 2 Answer 4 (Question 4—What is the evidence-based pharmacological treatment of frontotemporal NCD?)

The options for pharmacological treatment are limited. Currently, there are no medications known to cure, prevent, or slow the decline in frontotemporal NCD. There are no treatments approved by the US Food and Drug Administration or Health Canada for any of the variants of frontotemporal NCD. The available pharmacological interventions are derived from the evidence based largely on small, open-label studies or case reports and used for the symptomatic treatment of specific behavioral and cognitive features of frontotemporal NCD [26]. Right from the outset, clinicians need to clearly state to the primary caregiver what the target symptom is and what the medication is intended to treat. This facilitates the caregiver's understanding of whether the clinician attempts to treat a symptom that is directly related to frontotemporal NCD (e.g., obsessive-compulsive, ritualistic behaviors) or that is a responsive behavior (e.g., seeking stimulation in response to boredom).

Most studies show abnormalities in the serotonergic system of patients with frontotemporal NCD, with a decrease in serotonin 5-HT_{1A} and 5-HT_{2A} receptors in frontotemporal regions and neuronal loss in the raphe nuclei, as well as a disrupted dopaminergic system, with reduced presynaptic dopamine transporters in putamen and caudate regions [16]. The following medications have been trialed, but none of these modalities have proven robust efficacy based on rigorous clinical trial data and, therefore, are currently used off-label or as investigational agents. (Also see ► Chap. 22.)

Antidepressants Clinical experience suggests that depression, apathy, disinhibition, anxiety, compulsive behaviors, and agitation may be controlled by serotonergic strategies, such as selective serotonin reuptake inhibitors (SSRIs) and trazodone [3, 26, 30]. SSRIs are the most widely used medications for the management of behavior symptoms in frontotemporal NCD; however, none of the antidepressants have demonstrated consistent evidence of response on the cognitive and behavioral aspects of frontotemporal NCD. In line with previously illustrated cases, studies have shown that SSRIs (such as sertraline, citalopram, and paroxetine) may be effective in reducing some affective and behavioral symptoms, with no observable impact on cognition [30]. In contrast, small double-blind, controlled trials have shown some modest improvement of behavioral symptoms with trazodone, but not paroxetine [26]. Trazodone may also help for sleep disturbances [3], which can be especially troublesome in the variants associated with progressive supranuclear palsy and corticobasal degeneration. SSRIs and trazodone also showed improvements in eating disturbances, reducing the cravings commonly associated with hyperorality [30, 34].

Anticholinesterase agents Studies suggest that cholinesterase inhibitors are prescribed in approximately 40% of patients with behavioral-variant frontotemporal NCD [16]. In contrast to Alzheimer disease, frontotemporal NCD is not a hypocholinergic NCD [30]. Given the lack of a specific cholinergic deficiency, cholinesterase inhibitors, approved for treatment of Alzheimer disease, have no clear utility in frontotemporal NCD [3]. Nevertheless, many clinicians prescribe these medications as a trial, as in Case 1, especially when the etiology of NCD is not clear. Moreover, there is anecdotal evidence that cholinesterase inhibitors may provisionally stabilize apathy and cognitive symptoms, including symptoms of language and executive dysfunction [3, 16]. On the other hand, these medications can have adverse responses in patients with frontotemporal NCD, including worsening impulsivity and disinhibition, so that extreme care should be taken in those with frontotemporal NCD, and some have recommended to avoid using these agents in patients with the behavioral variant [3, 16, 35]. If used, monitoring the effectiveness and tolerability of these medications is essential.

Memantine There have been anecdotal reports of efficacy of memantine in patients with frontotemporal NCD, but small randomized, double-blind, placebo-controlled clinical trials have not confirmed its efficacy [3, 26]. One study reported that memantine increased the metabolism in insula and orbitofrontal cortex, with no observable impact on behavioral changes [16].

Antipsychotics Agitated and aggressive behaviors are problematic for caregivers and can be difficult to treat. Florid psychotic features and other safety-related behaviors, such as agitation and aggression that do not respond to SSRIs or trazodone, may require the use of antipsychotic agents.

Antipsychotics are potentially associated with substantial risk of extrapyramidal and cognitive side effects, but adequate controlled studies to estimate the risk/benefit balance of these agents in frontotemporal NCD are lacking [26]. In this vein, second-generation antipsychotics should be considered for use at low doses when required for agitation that threatens the patient's safety and cannot be managed by other means [26]. Black box warnings regarding increased risk of mortality and cerebrovascular events with the use of antipsychotics in those with major NCDs have been issued over the past decade; subsequently, clinical guidelines to inform the use of antipsychotics were published in 2016 [48]. (See ▶ Chap. 22.)

Dopamine Agonists Dopaminergic agents in stroke-related transcortical motor aphasia have not shown convincing evidence for efficacy [3]. However, bromocriptine has been used for aphasia, with some reported improvement in verbal fluency, but a single, small randomized, placebo-controlled study did not demonstrate any benefit in patients with primary progressive aphasia [52]. Because dopamine may be lowered in frontotemporal NCD, an ongoing clinical trial (as of 2017) tests the effects of tolcapone (a drug that selectively increases prefrontal dopamine concentration) on the cognitive and behavioral symptoms of patients with frontotemporal NCD [53].

Other Medications A randomized-controlled trial suggests a transient benefit of intranasal oxytocin on emotion processing in those with behavioral variant [3, 26]. Oxytocin is an important mediator of social behavior, enhancing prosocial behaviors and some aspects of emotion recognition. Psychostimulants, such as modafinil and methylphenidate, may benefit some patients with apathy [3] and may be effective in reducing some affective and behavioral symptoms [30]. However, psychostimulant agents need to be used with extreme caution for behaviors related to frontotemporal NCD because the adverse outcomes are frequent, and these agents should not be used as first line [54].

Table 19.7 summarizes the multiple medications trialed for the symptomatic treatment of frontotemporal NCD [16, 52–56].

Table 19.7 Pharmacological treatment options for symptoms of frontotemporal NCD [16, 52–56]

Symptom	Medication	Evidence-based comments
Disinhibition	Fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram Trazodone Atypical antipsychotics: risperidone, olanzapine, quetiapine, aripiprazole	Open-label studies supporting the use of SSRIs. A double-blind, placebo-controlled study supporting the use of paroxetine Double-blind, placebo-controlled study supporting the use of trazodone Case reports supporting the use of antipsychotics
Apathy	Dopaminergic agents Cholinesterase inhibitors Psychostimulants: modafinil, methylphenidate	Ongoing clinical trial as of now with tolcapone (selectively increases prefrontal dopamine concentrations) Anecdotal evidence with cholinesterase inhibitors Anecdotal evidence with psychostimulants; not used as first line due to adverse outcomes
Loss of empathy/ social cognition	Oxytocin (intranasal)	Double-blind, placebo-controlled crossover study of single dose: potentially promising symptomatic treatment Randomized, parallel-group, double-blind, placebo-controlled study in behavioral variant or semantic variant: no significant changes in the overall neuropsychiatric inventory
Perseverative behavior	Fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram Trazodone	Open-label studies, supporting the use of SSRIs. A double-blind, placebo-controlled study supporting the use of paroxetine Double-blind, placebo-controlled study supporting the use of trazodone
Hyperorality	Fluoxetine, paroxetine, fluvoxamine, sertraline, citalopram Trazodone	Open-label studies supporting the use of SSRIs. A double-blind, placebo-controlled study supporting the use of paroxetine Double-blind, placebo-controlled study supporting the use of trazodone
Executive dysfunction	Dopaminergic agents: tolcapone Psychostimulants: methylphenidate	Ongoing clinical trial with tolcapone A study with a single dose of methylphenidate (40 mg) reported on eight subjects with behavioral variant; risk-taking behavior reduced to normal levels as measured by Cambridge Gamble Task, suggesting that decision-making and impulsivity may be affected
Agitation/ aggression	Atypical antipsychotics: risperidone, olanzapine, quetiapine, aripiprazole	Minimally studied in frontotemporal NCD A meta-analysis showed a small but significant effect in decreasing agitation, psychosis, and overall behavioral disturbances in NCDs (mostly Alzheimer disease type) Case reports supporting the use of small doses of risperidone and aripiprazole Open-label study for olanzapine over 24 months supporting decreased agitation and delusions in frontotemporal NCD cases

Case 2 Analysis In Case 2, Mrs. B. initially had a clinical presentation of nonfluent language-variant major frontotemporal NCD, characterized by an effortful and halting speech, agrammatic production, dysarthria (a motor speech abnormality), and letter-based fluency impairment (fewer words beginning with a given letter generated in 1 minute than the standard). Her comprehension of words and simple sentences, as well as recognition of nouns (object knowledge), was generally preserved. The Boston Naming Test is a measure of confrontation naming that helps in profiling access to language in patients with frontotemporal NCD. Mrs. B. performed relatively well on the Boston Naming Test, which ruled out logopenic and semantic-variant frontotemporal NCD. EMG was generally normal except for a reduced amplitude from the orbicularis oculi muscle suggesting possible visual signs of progressive supranuclear palsy. Mrs. B. had a tauopathy, as is the case with most patients with nonfluent language variant (see ◘ Table 19.3). On postmortem examination, a definite diagnosis of major frontotemporal-progressive supranuclear palsy was confirmed in this case.

19.3 Key Points: Major or Mild Frontotemporal Neurocognitive Disorder

- Major or mild frontotemporal NCD is a leading cause of NCDs in patients younger than age 65 and presents with sporadic and familial forms and variants associated with genetic mutations at different loci.
- Major or mild frontotemporal NCD can be distinguished from other types of NCDs based on good clinical reasoning and neuroimaging. The clinical syndromes correlate with regional patterns of atrophy on neuroimaging studies and with the genetic variants of the disease. However, in the absence of neuroimaging and genetic testing, diagnosis relies heavily on clinical reports of behavioral or language changes.
- Clinicians should consider a diagnosis of frontotemporal NCD when (i) patients present with disinhibition or indifference appearing in middle age; (ii) patients present with progressive unexplained aphasia, or patients who ask, e.g., "What is clock, pen?" etc.; and (iii) patients present with neurocognitive impairment and vertical gaze palsy, falls, or motor neuron disease, indicating the considerable clinical overlap among these entities.
- Major or mild frontotemporal NCDs are divided into the following two main subsyndromes: (1) behavioral-variant frontotemporal NCD and (2) primary progressive aphasia. The latter has three clinical variants: (a) nonfluent/agrammatical language-variant frontotemporal NCD, (b) semantic-variant frontotemporal NCD, and (c) logopenic-variant frontotemporal NCD.
- Objective evaluation emphasizes the neuropsychological evaluation, which shows significant impairment on frontal lobe tests in the absence of severe memory impairment or perceptuospatial deficits. The electroencephalogram is usually normal despite clinically evident major NCD. Neuroimaging (structural or functional) studies show predominant frontal and temporal lobe abnormality. Physical examination can reveal signs such as primitive reflexes, akinesia, rigidity, and tremor.
- Clinicians must be able to differentiate frontotemporal NCD from other types of NCDs as well as other neuropsychiatric disorders in order to identify patients as early as possible and provide optimal management. An early and accurate diagnosis of frontotemporal NCD is a key component in the care for these patients and their caregivers.
- There is currently no cure for frontotemporal NCD; the management includes a multifaceted, supportive approach, including symptomatic treatment with a trial of medication, environmental modification, and long-term care planning.
- Education and support are needed for both family members and professional caregivers as the patient's dramatic changes in behavior can be emotionally distressing.

19.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Diagnostic prediction of frontotemporal NCD is likely to require neuroimaging information in addition to clinical findings, which may suggest the underlying neuropathology. Which of the following statements is correct?

A. Atrophy of anteromedial temporal lobes in a patient presenting with behavioral variant may suggest progranulin mutations
B. Atrophy of lateral temporal and parietal lobes in sporadic forms may suggest either a progranulin or C9ORF72 mutation
C. Greater atrophy of the parietal lobe would be more suggestive of progranulin pathology, whereas greater atrophy of the sensorimotor cortices and occipital lobe would suggest C9ORF72 pathology
D. The absence of early frontal atrophy in a younger patient would suggest C9ORF72 pathology

Answer: C

All four frontotemporal variants have shown some involvement of the frontal lobes; therefore, it may be difficult to differentiate variant groups based only on this brain region. It is essential to assess the relative involvement of each region in comparison with other regions of the brain [25] (see ◘ Fig. 19.2).

Taking into consideration the pattern of MRI atrophy, in a patient presenting with behavioral variant, the easiest gene mutations to identify appear to be mutations in MAPT, not progranulin as in statement A, since it is the only group in which atrophy predominantly and focally affects the anteromedial temporal lobes [25]. Therefore, statement A is incorrect.

Early in the disease course, a patient with progranulin mutation may have the same amount of parietal involvement as a C9ORF72 patient later in the disease course but, importantly, progranulin patients would still have relatively greater involvement of the parietal lobe compared with other regions [25]. Atrophy of lateral temporal and parietal lobes would suggest either a progranulin or C9ORF72 mutation; however, atrophy in sporadic cases does not tend to predominantly involve these regions, which makes statement B incorrect. Moreover, in sporadic forms of frontotemporal NCD, the expected change would be a predominant dorsolateral frontal atrophy. Therefore, statement B is, once again, incorrect.

The absence of early frontal atrophy would suggest a MAPT mutation, not a C9ORF72 mutation as in statement D. A striking dorsolateral frontal atrophy would point toward sporadic form of frontotemporal NCD [25]. Unlike progranulin and C9ORF72, MAPT mutation would be particularly suggestive of a younger age at onset [25]. Therefore, statement D is incorrect.

The differentiation of progranulin and C9ORF72 pathology appears to be more challenging due to the overlap in atrophy observed in these groups; a predominant atrophy of the parietal lobe would be more suggestive of progranulin pathology, whereas a greater involvement of the sensorimotor cortices and occipital lobe would suggest C9ORF72 pathology [25]. Therefore, statement C is correct.

MCQ 2. Characteristic features of early frontotemporal NCD include which one of the following statements:

A. Memory decline and spatial impairment
B. Change in social behavior and preference for sweet foods
C. Delusions and visual hallucinations
D. Motor neuron disease and multiple sclerosis

Answer: B

Predominant memory impairment is a characteristic of typical Alzheimer disease-related NCD. Spatial disorientation is also characteristic of non-frontotemporal NCDs, and therefore statement A is incorrect.

Psychosis is not a common feature of frontotemporal NCD. Nevertheless, there are rare cases of patients who present with frank psychotic symptoms, which then evolve into the frontal lobe syndrome [3]. The presence of frontotemporal atrophy as demonstrated on neuroimaging studies, executive dysfunction demonstrated by neuropsychological evaluation, as well as the temporal evolution, can assist in differentiating frontotemporal NCD presenting with psychotic symptoms from a primary psychotic disorder mimicking a frontotemporal NCD. Moreover, visual hallucinations greatly increase odds of a Lewy body NCD; therefore, statement C is incorrect.

Patients with frontotemporal NCD are typically physically well early in the disease course. However, parkinsonian signs of bradykinesia and rigidity develop later. Moreover, a proportion of these patients (about 10%) develop motor neuron disease. However, there is no association with multiple sclerosis, and thus statement D is incorrect.

The typical symptoms of frontotemporal NCD include a number of symptoms such as an alteration in the patient's personality and social conduct, lack of sympathy, empathy or concern for others, and altered dietary habits including altered preference for sweet foods [1]. In the later stages, patients may put inanimate objects into their mouth. Therefore, statement B is correct.

MCQ 3. Patients with behavioral-variant frontotemporal NCD:

A. Conform to social rules of conduct
B. Occasionally violate social rules and these may lead to criminal convictions
C. Frequently violate social rules but criminal convictions are rare
D. Frequently violate social rules, which often lead to criminal convictions

Answer: C

Socially disruptive behavior is a core feature of behavioral-variant frontotemporal NCD, and thus the answer A is incorrect [1]. Patients are unmindful of the social rules of conduct and laws of the land, which may suggest that these patients would frequently come into contact with the police and forensic psychiatric services for the first time in their adult or middle-age life or even later in life [57]. However, contact with the law does occur, although it is less common than might be expected. For example, accusations of indecent exposure may occur in patients who have developed a habit of removing their clothes in public, in whom there is no sexual intent. Contact with the law occurring in the context of new-onset criminal behavior in an adult should elicit a search for frontal and anterior temporal brain disease, which often makes it evident that the patient is ill (e.g., lack of premeditation, lack of social awareness, apathy); therefore, no charges are brought, which renders both answers B and D as incorrect. Therefore, the correct answer is C. Patients living alone are most vulnerable to prosecution because of the absence of a knowledgeable informant or advocate who can explain, defuse, or prevent deviant behavior. Aggression can occur in the context of the patient's wishes and behavior being thwarted.

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Major or Mild Neurocognitive Disorders with Lewy Bodies

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20.1 Background

20.1.1 Definition

Major or mild neurocognitive disorder with Lewy bodies (formerly termed dementia with Lewy bodies) is a leading cause of non-Alzheimer-related major or mild neurocognitive disorders (NCDs) [1]. Clinically, it is characterized by cognitive impairment accompanied by additional neuropsychiatric features, motor dysfunction, sleep, and autonomic disorders. At autopsy, NCD with Lewy bodies is characterized by the presence of Lewy bodies which are neuronal inclusions or aggregates of the protein alpha-synuclein. Neuropathological studies have demonstrated differential localization of Lewy bodies in major or mild NCD with Lewy bodies compared to other Lewy body diseases or alpha-synucleinopathies, which include major or mild NCD due to Parkinson disease and multiple system atrophy [2]. With histopathological evidence and efforts to clarify clinical diagnostic criteria over the years, NCD with Lewy bodies has been recognized as a distinct diagnostic entity since 1996 [3]. Yet, diagnostic challenges remain, and these criteria continue to be revised by the Lewy body NCD Consortium [4, 5] based on new clinical and histopathological information and have been incorporated in the *Diagnostic and Statistics Manual of Mental Disorders*, 5th edition (DSM-5), used in psychiatry. Table 20.1 clarifies the terms used in the Consortium criteria and the DSM-5 with regard to Lewy body NCD [6–8].

According to the DSM-5 [6], diagnosis of major or mild NCD with Lewy bodies requires that diagnostic criteria are met for major or mild NCD, with symptoms having an insidious onset and gradual progression. Given that definitive findings of Lewy body pathology can only be ascertained on autopsy, criteria have been developed to differentiate between probable versus possible NCD with Lewy bodies based on the number of core and suggestive diagnostic features that patients present with.

Core diagnostic features include fluctuating cognition, visual hallucinations, and parkinsonism. One or more core features are required for a diagnosis of probable NCD with Lewy bodies. Per the DSM-5, suggestive features include the presence of rapid eye movement (REM) sleep behavior disorder and demonstrated sensitivity to antipsychotics. The criteria proposed by the Lewy body NCD Consortium allow for the diagnostic weight of SPECT or PET studies of dopamine transporter uptake activity as a suggestive feature as well, which theoretically increases the sensitivity of the Consortium criteria [9]. However, these studies may not be accessible or practical in most clinical settings.

One or more suggestive features in the presence of one or more core features point to a diagnosis of probable NCD with Lewy bodies. If only one core feature is present without suggestive features, or if suggestive features are present without core features, then only a diagnosis of possible NCD with Lewy bodies is appropriate. This is summarized in Table 20.2 [4]. Table 20.3 compares the current key DSM-5 diagnostic criteria and the criteria put forward by the Consortium on Lewy body NCD [3, 4, 6]. The latter includes supportive features which are noted to be commonly present in Lewy body NCD but do not carry diagnostic weight. For a complete review of the DSM-5 diagnostic criteria for major or mild NCD with Lewy bodies, the reader is referred to the DSM-5 manual [6].

Features of NCD with Lewy bodies may overlap with those of other NCDs, notably Alzheimer disease and Parkinson disease-related NCD, at different time points in the course of the disease [10]. Hence, the time course of symptom presentation and progression is crucial in distinguishing

Table 20.1 Terminology of Lewy body diseases and related neurocognitive disorders (dementia) [6–8]

Lewy body dementias	An umbrella term that includes clinically diagnosed dementia with Lewy bodies and Parkinson disease dementia
Dementia with Lewy bodies	Dementia that occurs before or concurrently with parkinsonism or within 1 year of onset of motor symptoms. Not all patients develop parkinsonism [7]
Parkinson disease dementia	Dementia starting 1 year or more after well-established Parkinson disease [8]
Mild cognitive impairment in Parkinson disease	Cognitive impairment in patients with Parkinson disease not sufficient to interfere greatly with functional independence [7]
Lewy body disease	Pathological diagnosis. The distribution of Lewy body-type pathology and additional pathologies is often specified
Major or mild neurocognitive disorder with Lewy bodies or due to Parkinson disease	New terms proposed by DSM-5 corresponding to dementia with Lewy bodies and Parkinson disease dementia, respectively

Table 20.2 Diagnostic criteria for probable and possible major or mild NCD with Lewy bodies [4]

	Probable	Probable	Possible	Possible
Core features Fluctuating cognition Visual hallucinations Parkinsonism	≥ 2	≥ 1	1	0
Additional features	+	+	+	+
Suggestive features REM sleep behavior disorder Antipsychotic sensitivity	0	≥ 1	0	≥ 1

Table 20.3 Summary of the diagnostic criteria for neurocognitive disorder (dementia) with Lewy bodies (DLB) [3, 4, 6]

DSM-5 criteria	DLB Consortium criteria
The criteria are met for major or mild neurocognitive disorder There is insidious onset and gradual progression	Central feature (essential for a diagnosis of possible or probable DLB) Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention, executive function, and visuospatial ability may be especially prominent
Core diagnostic features: (a) fluctuating cognition/variations in attention and alertness; (b) recurrent visual hallucinations, well-formed and detailed; (c) spontaneous parkinsonism (onset after development of cognitive decline) *Suggestive diagnostic features*: (a) meets criteria for REM sleep behavior disorder; (b) severe antipsychotic sensitivity *Probable*: 2 core features or 1 suggestive feature *with* 1 (or more) core feature *Possible*: 1 core feature or 1 (or more) suggestive feature	*Core features*: (a) fluctuating cognition/variations in attention and alertness; (b) recurrent visual hallucinations, well-formed and detailed; (c) spontaneous parkinsonism *Suggestive features*: (a) REM sleep behavior disorder; (b) severe antipsychotic sensitivity; (c) low dopamine transporter uptake in basal ganglia demonstrated by SPECT or PET *Probable*: 2 core features or 1 suggestive feature *with* 1 (or more) core feature *Possible*: 1 core feature or 1 (or more) suggestive feature
	Supportive features (commonly present but not proven to have diagnostic specificity): repeated falls and syncope; transient, unexplained loss of consciousness; severe autonomic dysfunction; hallucinations in other modalities; systematized delusions; depression; relative preservation of medial temporal lobe on CT/MRI; generalized low uptake on SPECT/PET with reduced occipital activity; low uptake MIBG myocardial scintigraphy; EEG slow wave activity with temporal lobe transient sharp waves
The disturbance is not better explained by cerebrovascular disease, another neurodegenerative disease, the effects of a substance, or another psychiatric, neurological, or systemic disorder	A diagnosis is less likely: (i) if cerebrovascular disease is evident as focal neurologic signs or on neuroimaging; (ii) if any other physical illness or brain disorder is sufficient to account for the clinical picture; (iii) if parkinsonism only appears for the first time at a stage of severe dementia

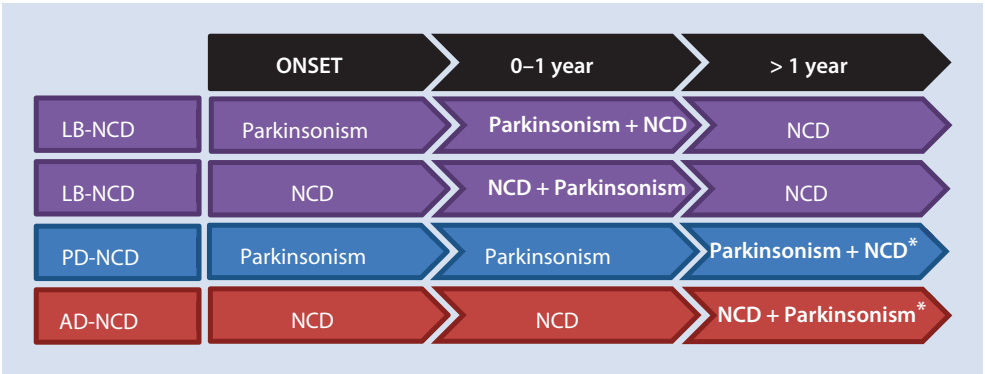

Fig. 20.1 Time course of LB-NCD versus PD-NCD versus AD-NCD [5]. *AD-NCD* neurocognitive disorder due to Alzheimer disease, *LB-NCD* neurocognitive disorder with Lewy bodies, *PD-NCD* neurocognitive disorder due to Parkinson disease. *Parkinsonism and NCD may co-occur in later stages of AD-NCD and PD-NCD due to generalization of the neuropathology to various brain regions but do not represent LB-NCD

among these entities. Predominance of parkinsonism during initial presentation may be a prelude to either Parkinson disease or NCD with Lewy bodies. Development of cognitive symptoms of major or mild NCD within the subsequent year would point to a diagnosis of NCD with Lewy bodies (see Fig. 20.1; purple arrows) [5]. If cognitive symptoms of NCD develop after the 1 year mark, the disease is defined as NCD due to Parkinson disease (see Fig. 20.1; blue arrow). Predominance of cognitive impairment early in the disease course may portend the development of Alzheimer disease (see Fig. 20.1; red arrow) (if parkinsonism does not occur or occurs very late (greater than 1 year) in the course of the disease) or NCD with Lewy bodies (see Fig. 20.1; purple arrows) (if parkinsonism develops within 1 year of presentation). Thus, in NCD with Lewy bodies, features of either cognitive impairment or parkinsonism may be initially present at disease onset and necessitate close observation and evaluation of other symptoms that may develop within the first year of disease for diagnostic clarity. Often times, these distinctions are difficult to parse out as they require meticulous gathering of history to determine the time course of specific symptoms, especially when patients present at a later stage of disease and are already experiencing concurrent symptoms of parkinsonism and cognitive impairment.

20.1.2 Epidemiology

Epidemiological studies of NCD with Lewy bodies are limited and have been confounded by overlapping diagnostic features with Parkinson disease-related NCD and other NCDs. The prevalence and incidence of NCD with Lewy bodies vary tremendously based on study type, age range, and location of the populations that are studied. Neuropathology at autopsy demonstrates NCD with Lewy bodies findings in 10–15% of autopsy cases [5]. In similar studies using the same clinical criteria, the prevalence of NCD with Lewy bodies ranged from 2.6% in rural Japan [11] to 10.9% outside London, England [12], whereas population studies of those aged 65 and older range show a population prevalence ranging from 0.1% in Sri Lanka [13] to 2% in London, England [12]. Prevalence of NCD with Lewy bodies is reported to be higher in studies conducted in Europe which parallels a higher reported rate of overall major NCD.

Since the most recent revision of the Lewy body NCD Consortium criteria in 2005 [5], which added diagnostic weight to suggestive features, the proportion of cases of probable major NCD has increased by 24% [14] with a 15.8% rate of probable major NCD with Lewy bodies and 4.1% of possible major NCD with Lewy bodies of all NCD cases. Studies incorporating dopamine transporter imaging [15] and screening for REM sleep behavior disorder [12] into the diagnostic criteria suggest a prevalence of 10–15% of NCD with Lewy bodies in those with major NCDs. Two studies looking at the incidence of NCD with Lewy bodies estimated an incidence rate of 0.1% of patients with Lewy body NCD older than 65 years of age in Cache County, UT [16], and an incidence of 3.5 per 100,000 person-years in Olmsted County, MN [17]. There is a slight male predominance [18, 19], although not as pronounced as in Parkinson disease-related NCD. The mean age at initial diagnosis is 75 years (range, 50–80 years of age) [20]. In a study on the projected prevalence of major NCDs, it is estimated that the prevalence of Lewy body NCD will increase by 131% by 2050 [21]. A recent study in Sweden suggests a 16–20% prevalence of major NCD with Lewy bodies in the nursing home population [22].

20.1.3 Etiology

NCD with Lewy bodies is characterized by the accumulation of alpha-synuclein inclusion bodies, also known as Lewy bodies, within neurons. Lewy neurites are also composed of alpha-synuclein aggregates but have a distinctive curvilinear shape or dot-like process [23]. Alpha-synuclein is a member of a family of presynaptic proteins thought to be involved in neurotransmitter release at the presynaptic terminals. It is coded by the alpha-synuclein gene (SNCA) on chromosome 4. Duplications [24] and point and missense mutations in the SNCA gene have been implicated in the pathogenesis of NCD with Lewy bodies [25] and are speculated to be involved in the regulation of dopamine transmission [26].

Other genes that have been implicated in NCD with Lewy bodies include the leucine-rich repeat kinase 2 (LRRK2) on chromosome 12 [27] and the glucocerebrosidase (GBA) gene on chromosome 1 [28]. A study of familial NCD with Lewy bodies in a Belgian family recently mapped Lewy body pathology to chromosome 2q35–36 [29], although a specific mutation of a gene or regulatory region at this locus has not yet been described. The mechanism of accumulation of alpha-synuclein inclusion bodies is not known. It is speculated that oxidative stress may upregulate both SNCA and LRRK2 [27]. Both mitochondrial dysfunction [30, 31] in the oxidative stress pathway and lysosomal dysfunction [32, 33] in the autophagy pathway have been implicated in the accumulation of alpha-synuclein inclusion bodies in Lewy body disease in general and NCD with Lewy bodies specifically [30, 31].

Lewy bodies occur in Lewy body disease broadly, encompassing neuropathology in NCD with Lewy bodies, Parkinson disease, Parkinson disease-related NCD, and multiple system atrophy [34]. The distinguishing factor that leads to the variable manifestations of Lewy body pathology in these different alpha-synucleinopathies lies in the primary location of these aggregates. In Parkinson disease, Lewy bodies primarily affect the midbrain substantia nigra and other brainstem nuclei leading to primary manifestations of a movement disorder [35]. Alpha-synuclein pathology may spread to other areas in the brain (e.g., neocortical areas) later in the course of Parkinson disease leading to Parkinson disease-related NCD, but the initial insult in Parkinson disease lies in the basal ganglia.

In NCD with Lewy bodies, Lewy bodies are seen additionally in the limbic (hippocampus, amygdala), paralimbic (anterior cingulate), and cortical areas (frontal, inferior temporal) and the peripheral nervous system [10, 36, 37]. Lewy neurites can also be seen in high densities in the limbic cortex, amygdala, and CA2/3 sectors of the hippocampus [28]. These explain the additional manifestations such as cognitive dysfunction, visual hallucinations, REM sleep behavior disorder, and autonomic dysfunction that are seen earlier in the course of the disease along with parkinsonism (by definition, within 1 year). The differential localization of Lewy body pathology has also been detected in SPECT studies in probable and possible cases of NCD with Lewy bodies [38].

20.1.4 Clinical Description

The early course of NCD with Lewy bodies is marked by complex and heterogeneous cognitive, other neuropsychiatric, motor, sleep, and autonomic symptoms. Initial manifestation of NCD with Lewy bodies may involve a combination of cognitive and/or motor symptoms and/or a core feature with or without parkinsonism or cognitive impairment [39]. For example, there are case reports of isolated initial symptoms such as autonomic dysfunction [40, 41], REM sleep behavior disorder [42, 43], or other symptoms without accompanying parkinsonism or cognitive impairment. On the other

hand, autopsies have revealed the presence of Lewy bodies in asymptomatic patients [44].

Cognitive Impairment

Cognitive impairment is a frequent initial symptom of NCD with Lewy bodies [45]. Around 15% of patients with major NCD are found to have Lewy body type [5]. As an initial symptom alone, cognitive impairment in NCD with Lewy bodies is most commonly misdiagnosed as Alzheimer disease [37]. However, while the hallmark of cognitive dysfunction in Alzheimer disease centers on anterograde memory loss and language loss, cognitive impairment in NCD with Lewy bodies more consistently involves the domains of attention and concentration, executive functioning, and visuospatial functioning [46]. Patients will have difficulty with sequential tasks, for example, using a microwave oven and finding their way in familiar surroundings. On cognitive screening test of Mini Mental State Examination (MMSE), patients will show difficulty with attention (serial 7s, spelling WORLD backward), following the three-step command, and difficulty with intersecting pentagons and/or clock drawing.

Some patients with initial NCDs that later overlap with developing psychotic and extrapyramidal symptoms may simultaneously meet criteria for both frontotemporal NCD and NCD with Lewy bodies [47]. However, the cognitive features of frontotemporal NCD are more prominent for behavior and personality changes than those of NCD with Lewy bodies. Patients presenting with major or mild NCDs need comprehensive initial evaluations to determine specific domains of cognitive dysfunction and co-occurring symptoms that may help categorize their NCD in order to direct appropriate treatment. Often serial assessments are necessary in 6–12 month intervals to follow the trajectories of various symptoms in order to make the most reliable clinical diagnosis. There, the initial finding of mild or major NCD alone warrants close follow-up to detect symptoms that may point to the development of a specific type of NCD.

Fluctuating Cognition

Fluctuating cognition refers to changes in cognition and arousal from baseline and reflects interruption in the flow of awareness and/or attention [39, 48]. It is a core diagnostic feature of NCD with Lewy bodies but remains ill-defined and circumscribed in clinical practice. The use of structured scales to more clearly describe this feature has been encouraged. More recent neuroimaging techniques suggest a link with thalamic damage and cholinergic imbalance as the etiology of this feature [49], while others propose that it is more likely a feature of an underlying sleep disorder [50]. Of note, fluctuating cognition may affect performance on cognitive testing and lead to higher variability in formal results.

Neuropsychiatric Features

Delusions and hallucinations are present in 50–75% of patients with NCD with Lewy bodies with visual hallucinations occurring in up to 60% of patients. The visual hallucinations are usually complex, recurrent, well-defined three-dimensional images of people or animals [39]. Auditory and tactile hallucinations are less frequently reported. Patients' responses vary from fear to amusement to anger if others do not believe their report of symptoms. These symptoms are presumably related to the involvement of the limbic system in the neuropathology of Lewy bodies. There may also be a link with the occipital (visual) cortex with studies showing increased excitability [51] and GABAergic involvement [52] associated with recurrent complex visual hallucinations in NCD with Lewy bodies. Delusions also occur in high frequency and can be complex. Themes vary widely and may be non-bizarre, bizarre, or, more commonly, paranoid (e.g., theft, conspiracy, infidelity). Patients may report the Capgras syndrome (i.e., that their loved ones have been replaced by impostors) [53, 54]. Depression is also common in NCD with Lewy bodies, as it is in other Lewy body disease, and is proposed to represent a pure psychiatric presentation of NCD with Lewy bodies [55].

Motor Dysfunction

The spontaneous development of parkinsonism is a hallmark of NCD with Lewy bodies. The word "spontaneous" clarifies the involvement of Lewy bodies in the basal ganglia in the etiology of these symptoms rather than secondary causation via exposure to dopamine antagonists. Patients may present with parkinsonism as an initial syndrome, with masked facies, stooped posture, shuffling gait, tremors (intention more commonly than resting), symmetrical rigidity, and bradykinesia, or these symptoms may develop soon after the onset of cognitive impairment. Patients presenting with initial parkinsonian symptoms need to be followed closely with serial cognitive testing as the timeline of the development of cognitive dysfunction (◘ Fig. 20.1) distinguishes between a diagnosis of NCD with Lewy bodies (within 1 year) or Parkinson disease-related NCD (greater than 1 year).

Sleep Dysfunction

REM sleep behavior disorder is the sleep disorder most closely linked with NCD with Lewy bodies. It is characterized by loss of atonia during REM sleep, and patients appear to "act out" their dreams. A patient may not be aware of the REM sleep behavior disorder unless he or she has a sleep partner who is able to witness and report this behavior. REM sleep behavior disorder may present as the sentinel symptom (without accompanying core or suggestive features) [39, 43], and there is momentum building to promote it to a core feature to increase the sensitivity of the Consortium criteria for Lewy body NCD [39, 56]. NCD with Lewy bodies is also associated, less commonly, with other sleep disorders such as obstructive sleep apnea, central sleep apnea, restless legs syndrome, and periodic limb movement disorder [57]. As a point of differentiation, daytime sleepiness occurs more commonly in NCD with Lewy bodies than in Alzheimer disease [50].

Autonomic Dysfunction

Lewy bodies and Lewy neurites have been found in the peripheral nervous system, more specifically, the autonomic plexus, and are thought to explain the autonomic dysfunction seen in NCD with Lewy bodies. These alpha-synuclein inclusions have been detected in the intermediolateral column of the spinal cord, thoracic sympathetic nerves (including those that surround the heart), and Auerbach's and Meissner's plexus in the abdomen. As a result, pathology involving these nerve groups can lead to significant autonomic dysfunction, causing orthostatic hypotension (50%), constipation (30%), urinary incontinence (30%), and impotence [58, 59]. The presence of persistent orthostatic hypotension with or without constipation and/or urinary incontinence is linked with a shorter survival period [58]. As mentioned before, autonomic dysfunction may be the only presenting symptom of NCD with Lewy bodies and may represent a prodrome to the full-spectrum disease [60].

20.1.5 Diagnostic Evaluation

Accurate diagnosis of NCD with Lewy bodies is challenging and may require multiple visits over time given the importance of the time course of progressing symptoms. The initial evaluation may only warrant a rule out of the diagnosis or possible NCD with Lewy bodies. Patients and their caregivers need education to remain vigilant on reporting the development of relevant symptoms as well as the time course associated with new symptoms. Identification of a prodromal period of NCD with Lewy bodies has been suggested [9, 61, 62], although a consensus on what symptoms the prodrome may include has not been reached.

Clinical History

A thorough personal history and review of systems should be obtained and can be very informative in the diagnostic process. This should include a history obtained from a partner or caregiver who may report symptoms unacknowledged by the patient. This is especially useful in the domains of cognitive dysfunction, REM sleep behavior disorder, delusions, and visual hallucinations where patients may not be aware of minor cognitive deficits, or that they are acting out their dreams, or if they believe that their delusions or visual hallucinations are real.

Family history is equally important. While NCD with Lewy bodies is a relatively newer diagnostic entity, it would be important to determine if there were family members with formal clinical diagnoses of major NCDs and/or a movement disorder or uncharacterized motor and/or cognitive symptoms without any formal diagnoses. It is also important to rule out other etiologies of major NCDs, previous exposure to antipsychotics (including antiemetics with antidopaminergic activity), and other secondary causes of major NCDs or parkinsonism (see ▶ Sect. 20.1.6). With regard to antipsychotics, it is noted that a test of sensitivity to antipsychotics should never be a part of a diagnostic workup for NCD with Lewy bodies given the increased risk of mortality associated with antipsychotic treatment. Given the heterogeneity of symptoms in Lewy body disease, a thorough review of all systems is important to detect the broad-ranging symptoms that will need to be addressed clinically (especially autonomic and neuropsychiatric symptoms).

Cognitive Assessment

Formal cognitive testing should be a routine part of the initial and follow-up evaluations. In the early stages of cognitive impairment, whenever possible, it is helpful to characterize specific domains of cognitive deficiencies that may help differentiate between cognitive domains seen more in NCD with Lewy bodies (e.g., diminished attention, visuospatial deficits, executive dysfunction) from those seen in Alzheimer disease (e.g., anterograde amnesia, language impairment). The Montreal Cognitive Assessment (MoCA) and Mini Mental State Examination (MMSE) are good starting points to screen for domains of dysfunction. More comprehensive testing may be pursued, as clinically indicated and if tolerated by the patient (see ◘ Table 20.4 for recommended formal cognitive

◘ **Table 20.4** Recommended cognitive tests in Lewy body disorders [5, 9]

Cognitive domain	Subcategory	Examples
Brief screening tools		Montreal Cognitive Assessment, Parkinson's Disease Cognitive Rating Scale, Parkinson Neuropsychometric Dementia Assessment Instrument, Scales for Outcomes in Parkinson's Disease—cognition
Visuospatial	Figure copy tests	Cube, clock, interlocking pentagons, or complex figures
	Spatial judgment tests that do not rely on motor functions	Visual Object and Space Perception Battery, Benton Judgement of Line Orientation
Executive or attention	Measures of working memory, selective attention, set shifting, planning, and verbal fluency	Wisconsin Card Sorting Test, NIH EXAMINER test battery, Trail-Making Test, Stroop Test
Memory	Word list, figure, or associative learning with delayed recall and recognition	Rey Auditory Verbal Learning Test, California Verbal Learning Test, Free and Cued Selective Reminding Test, Brief Visuospatial Memory Test-Revised (Note: visual memory might be poor for reasons of visual perceptual or memory deficit)

Table 20.5 Structured scales used in measuring fluctuating cognition [5]

Scales	Comments
Clinician Assessment of Fluctuation Scale	Structured; requires experienced clinician to administer and interpret
One Day Fluctuation Assessment Scale	Semistructured; can be administered by less experienced raters
Mayo Fluctuations Composite Scale	Uses caregiver answers to structured questions
Other	Recording variations in attentional performance using a computer-based test system

tests in Lewy body disorders) [5, 9]. The utility of formal testing at a given time point may be limited. However, repeat administrations over time help clinicians determine disease progression, development of new symptoms, and patient response to symptomatic treatment.

The core feature of fluctuating cognition may confound a patient's performance in cognitive testing over time. Specifically quantitating cognitive fluctuation remains a vague and somewhat arbitrary construct. Subjective caregiver- and observer-rated scales may be useful [63], although it has been found that caregiver ratings of fluctuations are less reliable predictors of NCD with Lewy bodies and less able to differentiate between Lewy body type and Alzheimer disease-related NCD compared to more formal questions [63]. Some formal psychometric measures exist that attempt to quantify the severity of this feature but have not been tested for their reliability or validity [64]. The Lewy body NCD Consortium, however, recommends the use of at least one formal measure of cognitive fluctuation in applying the diagnostic criteria [5] though their use is dependent on the clinical setting and availability of expert clinicians in administering and interpreting these scales. The names of the suggested scales and administration are summarized in Table 20.5 [5].

Physical Exam

A thorough physical exam including a complete neurological examination is required at each encounter. A detailed motor exam including specific attention to laterality can help differentiate between typical (resting tremor, limb rigidity, bradykinesia) and atypical (intention tremor, axial rigidity, bulbar or balance disturbances, vertical gaze paresis, myoclonus) parkinsonian symptoms. While motor dysfunction in Parkinson disease more distinctively presents with typical and asymmetrical motor signs, those of NCD with Lewy bodies can present with either typical or atypical parkinsonism and can be symmetrical or asymmetrical, reflecting the heterogeneity of the disease pathology [65].

Laboratory Studies and Electroencephalogram (EEG)

There are no specific blood or cerebrospinal fluid laboratory studies diagnostic of NCD with Lewy bodies. Patients should have routine laboratory tests and any abnormal results followed up, if only to rule out other etiologies of their symptoms (e.g., nutritional deficiencies and hypothyroidism presenting with neuropsychiatric and cognitive dysfunction). Cerebrospinal fluid studies of tau protein and alpha-synuclein levels may help differentiate between Alzheimer and Lewy body disease [66], although neither plasma nor cerebrospinal fluid studies have yielded a reliable biomarker for the diagnosis of NCD with Lewy bodies. Similarly, while slow wave activity on EEG is prominent in NCD with Lewy bodies [67], there has yet to be a distinctive pattern of neuroelectrical activity that is specific to NCD with Lewy bodies; hence EEG is not routinely recommended.

Neuroimaging

Structural neuroimaging such as routine CT and MRI studies should be part of an initial neuropsychiatric workup for patients presenting with signs and symptoms of NCD and Parkinson disease. MRI is preferred unless clinically unobtainable. MRI findings in NCD with Lewy bodies may show a more diffuse pattern of atrophy compared to other types of NCD and less medial temporal lobe atrophy compared to Alzheimer disease. Diffusion tensor imaging may show loss of parieto-occipital white matter [9]. Depending on the time course, and especially early in disease progression, routine neuroimaging results are often nonspecific or normal, yet it may remain useful in ruling out other secondary etiologies (e.g., vascular NCD, normal pressure hydrocephalus, corticobasal degeneration).

Functional neuroimaging can more precisely differentiate between Lewy body disease and other NCDs but may not be able to differentiate Lewy body NCD from Parkinson disease-related NCD and other parkinsonian syndromes. However, some studies have been determined to be specific enough to be given diagnostic weight as a suggestive feature of NCD with Lewy bodies. Hypometabolism of dopamine transporter markers or overall hypoperfusion of the occipital lobe may be seen on SPECT. The [123-I]-FP-CIT SPECT marker shows a 78% sensitivity and 90% specificity in differentiating between NCD with Lewy bodies and other NCDs [68]. Decreased glucose metabolism in the occipital lobe may also be detected on PET studies [69]. In addition, metaiodobenzylguanidine (MIBG) myocardial scintigraphy showing reduced activity at post-ganglionic sympathetic terminals as part of the manifestation of autonomic dysfunction in the disease has a sensitivity of 94% and specificity of 96% in predicting a diagnosis of NCD with Lewy bodies in subjects with mild cognitive impairment [70].

Polysomnography

The use of polysomnography can help clarify sleep disturbances in NCD with Lewy bodies. It can help differentiate between moderate-to-severe obstructive sleep apnea which may have dream enactment behavior similar to REM sleep behavior disorder, restless legs syndrome, periodic limb movement in sleep, and central sleep apnea, all of which require different approaches in treatment.

20.1.6 Differential Diagnosis

As mentioned earlier, given the core features of NCD and parkinsonism, the major differential diagnoses for NCD with Lewy bodies include Parkinson disease-related NCD and Alzheimer disease. The timeline of the development of cognitive and motor symptoms and functional neuroimaging can help to differentiate between Lewy body disease (Lewy body NCD and Parkinson disease-related NCD) and Alzheimer disease. The distinction between Parkinson disease-related NCD and Lewy body-related NCD is usually less clear cut particularly if the timeline of symptoms is unclear, leading to the diagnostic approach of classifying probable or possible diagnoses. Similarly, NCD with Lewy bodies may also be misdiagnosed as other forms of NCDs (e.g., frontotemporal NCD [47]).

On a broader scale, the differential diagnosis includes other sporadic degenerative parkinsonian syndromes such as multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration. Similarly, other forms of secondary parkinsonian syndromes with cognitive deficits including drug-induced parkinsonism, vascular parkinsonism, normal pressure hydrocephalus, Whipple disease, and dementia pugilistica are also on the differential diagnosis and can more easily be distinguished with routine evaluation, laboratory studies, and neuroimaging.

20.1.7 Treatment

Thus far, no disease-modifying therapy has been found for Lewy body disease or other alpha-synucleinopathies. Therefore, treatment remains symptomatic, targeting the various clinical manifestations of the disease. Treatments may improve symptoms but only rarely will eliminate them. A general approach is to determine, together with the patient, the degree of symptomatology that is acceptable or tolerable to ascertain whether it should be treated. Of note, aside from the evidence supporting the safety and efficacy of cholinesterase inhibitors in improving cognition in Lewy body disease [56], there is generally mixed or insufficient evidence (namely, lack of randomized controlled trials) for the use of pharmaceuticals in addressing other symptoms associated with NCD with Lewy bodies. Hence, prudent and cautious use of medications is advised, with low initial doses and slow and small increments of dose titration with close follow-up. There is great variability in treatment response from patient to patient and from none to minimal to robust. Hence, during the course of treatment, clinicians should discuss the risks and benefits of continuing with treatments that may not yield significant clinical improvement, more so if they carry significant risks of morbidity and/or mortality.

Treatment of Cognitive Impairment with Cholinesterase Inhibitors and Other Agents

Autopsy studies have found a greater degree of cholinergic deficit and less neuronal loss in Lewy body disease than in Alzheimer disease [71]. Thus, it is thought that patients with Lewy body pathology may be more responsive to cholinesterase inhibitor therapy. In a placebo-controlled, double-blind, multicentered study, patients with Lewy body NCD taking 6–12 mg of rivastigmine daily for 20 weeks showed significantly less apathy and anxiety and had fewer delusions and hallucinations than controls [72]. More recently, a randomized, double-blind, placebo-controlled phase 2 trial of donepezil in Japan yielded similar findings with Lewy body NCD patients showing significant improvement in cognitive, behavioral, and global domains at doses of 5 mg or 10 mg daily [73]. The NMDA-receptor antagonist, memantine, has recently been shown in a randomized double-blind, placebo-controlled multicenter trial to improve cognitive tests of attention and episodic recognition in subjects with either Lewy body NCD or Parkinson disease-related NCD at a dose of 20 mg daily [74]. Some uncontrolled trials, as well as clinical experience, report the efficacy (although unpredictable) of galantamine and wakefulness promoters (armodafinil and modafinil) in improving cognition or preventing cognitive deterioration in NCD with Lewy bodies, but there has yet to be efficacy or safety studies with these agents [39, 75].

Treatment of Visual Hallucinations with Antipsychotic Agents

The use of antipsychotics in treatment of visual hallucinations associated with NCD with Lewy bodies should be approached cautiously and judiciously, not least due to the hallmark of antipsychotic sensitivity which partially defines the disease. Visual hallucinations may improve with the use of cholinesterase inhibitors alone so these agents should be tried first [72]. A trial of lower-potency atypical antipsychotics (e.g., quetiapine) may be initiated if the hallucinations continue to be significantly distressing and impairing after the trial of a cholinesterase inhibitor. There is some evidence for the efficacy of quetiapine, olanzapine, and clozapine, as well as risperidone (which is of higher D_2 potency), in the treatment of visual hallucinations in patients with NCD with Lewy bodies [76–80]. However, a meta-analysis of various medications for NCD with Lewy bodies indicated that many patients are unable to tolerate the antipsychotic quetiapine (33% withdrew from small retrospective study of 9 patients), risperidone (65% withdrew in randomized

controlled study of 31 participants), and olanzapine (38% did not tolerate even small doses of 2.5 mg daily in retrospective study) [75]. As noted earlier, an adverse reaction or worsening of motor symptoms after antipsychotics is often used as a diagnostic feature for NCD with Lewy bodies. In our clinical experience, low-dose quetiapine does appear to be helpful for some patients and is a reasonable first-line antipsychotic if the sedation and other side effects are tolerated. Clozapine has the strongest evidence supporting its use [75]; however, due to monitoring of blood neutrophil count requirements and risk for seizure and delirium, clozapine is infrequently used. A newer agent, pimavanserin (a serotonin-2A receptor inverse agonist), has recently been approved by the FDA to treat hallucinations and delusions associated with psychosis in patients with Parkinson disease. This medication was studied in a 6-week clinical study with 199 participants [81]. It was found to be effective in reducing frequency and severity of psychosis without worsening the motor symptoms of Parkinson disease. Its application in NCD with Lewy bodies would be off-label. While this medication holds promise in NCD with Lewy bodies, given the similarities between Lewy body NCD and Parkinson disease, further prospective studies and post-marketing monitoring are needed to better understand the benefits versus risks in real-world settings.

It should be noted that somnolence, dizziness, and orthostatic hypotension are potential side effects of some atypical (second generation) antipsychotics and extra caution should be employed in their use in Lewy body patients with manifestations of autonomic dysfunction. Similarly, further caution is advised as these agents carry a "black box" warning due to the risk of increasing mortality in patients with major NCD [82]. Typical (first generation) antipsychotics should not be used as they have a higher relative risk of inducing antipsychotic sensitivity in this high-risk population.

Dopaminergic Therapy to Target Motor Dysfunction

There are some uncontrolled studies but overall insufficient evidence for broad use of L-dopa in the treatment of motor dysfunction in NCD with Lewy bodies [9, 75]. A small study of 14 patients with Lewy body NCD showed that low doses of L-dopa were generally well tolerated but produced a significant motor response in only 1/3 of patients, who tended to be of younger age [83]. In general, motor dysfunction in NCD with Lewy bodies appears to be less responsive to L-dopa than in Parkinson disease, although this might be an artifact of insufficient dosing due to the amount of caution exercised given the risks of worsening neuropsychiatric symptoms in NCD with Lewy bodies. These risks should be balanced against the benefits of improved functioning in patients who respond well to a trial of L-dopa therapy. There has yet to be any evidence for the use of other dopaminergic agents such as selegiline, pramipexole, bromocriptine, and ropinirole. Anticholinergic medications should be avoided in NCD with Lewy bodies due to the increased risk of further cognitive impairment and/or delirium with their use. Other treatment modalities for parkinsonism such as deep brain stimulation or pallidotomies are contraindicated in patients with NCDs, thus excluding Lewy body patients.

Treatment of Autonomic Dysfunction

Orthostatic hypotension, constipation, and urinary incontinence are common manifestations of autonomic dysfunction in NCD with Lewy bodies. Many non-pharmacologic strategies can be used to address these symptoms. Orthostatic hypotension can be addressed with increasing fluid and salt intake, use of compression stockings, and elevating the head of the bed during sleep to avoid "pressure natriuresis" [39]. Should these strategies fail, clinicians may start a trial of fludrocortisone and/or midodrine to address orthostatic dysfunction. Constipation may be minimized with increased fiber and water intake. Symptomatic over-the-counter treatments for constipation are generally safe on an as-needed basis. Patients with urinary incontinence may attempt behavioral modification with scheduled urination. Oxybutynin, a potent anticholinergic agent, should be avoided. An alternative treatment for urinary incontinence is trospium chloride, which was shown to be noninferior to oxybutynin in addressing urinary incontinence with fewer reports of dry mouth [84], although there have not been any specific studies in patients with NCD with Lewy bodies.

Treatment of Sleep Dysfunction

Treatment of sleep disorders associated with NCD with Lewy bodies can be complicated. Accurate diagnosis is essential for appropriate treatment, and clinicians should not hesitate to obtain formal polysomnography to delineate the etiology of sleep dysfunction in NCD with Lewy bodies which can be due to one or more primary sleep disorders, depressive disorders, medication, or circadian rhythm dysfunction. Clonazepam is considered the most effective treatment for REM sleep behavior disorder, but it should be avoided in obstructive sleep apnea due to risk of further depressing respiratory drive. There is increasing evidence for the use of melatonin in improving sleep and reducing dream enactment in REM sleep behavior disorder [85], although it has not been specifically studied in NCD with Lewy bodies. Patients with comorbid obstructive sleep apnea may benefit from a trial of continuous positive airway pressure. If already used to target neuropsychiatric symptoms, atypical antipsychotics with more sedating effects such as quetiapine (at a dose of 25 to 100 mg at nighttime) [57] may be used to target insomnia. Other classes of medications (e.g., trazodone, mirtazapine, zolpidem, zaleplon, chloral hydrate) may also be tried [39]. If depressive disorder is associated with the insomnia, antidepressants may be added to treat both. Gamma-hydroxybutyrate and eszopiclone are being considered in NCD with Lewy bodies and related insomnia. Modafinil and methylphenidate have shown some efficacy in addressing excessive daytime somnolence [57].

20.2 Case Studies

The following cases are intended to illustrate the variable initial presentation and disease course of major or mild NCD with Lewy bodies, as well as the diagnostic approach and treatment options for the disease.

20.2.1 Case 1

Case 1 History

Mr. A. was a 75-year-old man who presented to a geriatric psychiatric clinic with a chief complaint of "depression" and "thinking problems" for the previous 3 months. He reported increasing symptoms of insomnia, poor concentration, and anhedonia. He also reported a low appetite associated with abdominal pain from constipation. He used to look forward to watching the Wheel of Fortune program every day but had lost interest due to difficulty paying attention to the program. His wife reported that he started to fall asleep in the middle of the show which aired at 11:00 AM. He denied any items on review of systems. He was otherwise healthy and denied any medical problems, except dizziness. On mental status exam, he was an older male sitting hunched over on the chair. His gait was normal and no tremor was noted. His speech was soft, slow, and monotone. His mood was described as "depressed" and he had a flat affect. He scored 24 out of 30 points on the MoCA due to difficulty with serial 7 subtraction starting at 100 and being unable to copy the cube. He did not show impairment in anterograde memory.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What is the differential diagnosis at this point in time?

Question 2. What further workup should be pursued?

Case 1 Answers

Case 1 Answer 1 (Question 1—What is the differential diagnosis at this point in time?)

The patient presents with a combination of depressive (depressed mood, flat affect, poor appetite, poor concentration, and insomnia) and cognitive symptoms (MoCA score less than 25, with poor attention and visuospatial functioning). The differential diagnosis will therefore include major depressive disorder or unspecified depression and mild NCD. Certainly Alzheimer disease is on the differential as well. However, the presence of symptoms of autonomic dysfunction (constipation, urinary incontinence, and dizziness) should alert the clinician to think about Lewy body disease as a category that needs to be ruled out.

As major or mild NCD with Lewy bodies is not a widely known entity, patients may report symptoms as fitting into specific categories they are more familiar with. In the case above, a low appetite may be seen as fitting into the paradigm of major depressive disorder. However, the source of the low appetite appears to be due to constipation, which points toward an element of autonomic dysfunction. At the same time, the loss of interest in his television program may represent anhedonia or, in this case, with the reasoning given by the patient, was due more to issues of attention and daytime somnolence, which may represent fluctuating cognition or effects from a sleep dysfunction which is common in Lewy body disease. In addition, a depressed mood and flat affect could herald development of parkinsonism (masked facies or hypomimia), and clinicians will need to be vigilant in monitoring for further development of other symptoms of Parkinson disease. In analyzing the results of the MoCA, an experienced clinician may be able to note the specific domains of dysfunction—in this case inattention and poor visuospatial functioning—which can help differentiate from the anterograde memory loss which is typically more prominent in Alzheimer disease.

Teaching Point

Symptoms of depression, cognitive decline, and/or autonomic dysfunction can be initial presenting symptoms of Lewy body disease.

Case 1 Answer 2 (Question 2—What further workup should be pursued?)

Before the patient leaves the office, the psychiatrist can perform orthostatic vital signs to determine if there is orthostatic hypotension. The psychiatrist should perform a preliminary neurological exam. In either case, the patient should be encouraged to follow up with their primary care physician for a full medical workup including routine laboratory tests and, if indicated, referral for a full neurological workup. To facilitate continuity of care, the patient should be provided with a summary of the initial psychiatric visit, noting the suspicion for Lewy body disease, so that it can be provided to the primary care physician.

Teaching Point

A simple intervention psychiatrists can do in their office when suspecting Lewy body disease is to obtain orthostatic vital signs.

Teaching Point

Communication and collaboration with the patient's primary care physician and/or neurologist are key to accurate diagnosis when Lewy body disease is suspected.

Case 1 Analysis Patients with early stage of NCD with Lewy bodies may initially present for evaluation in a psychiatric setting. Major or mild NCD with Lewy bodies should be

considered in the differential when older patients present with new-onset depression and cognitive impairment. The initial interview should include careful exploration of the sources of reported symptoms that may be attributed to a depressive disorder. A full review of systems and formal cognitive testing is also essential. While a full physical examination is not feasible in a psychiatric clinic, a psychiatrist can obtain orthostatic vital signs to rule out autonomic dysfunction, and, if not already done, patients should be referred for a full medical workup with their primary care physician. Coordination of care among general medical, psychiatric, and neurology clinicians is essential to facilitate accurate diagnosis and treatment of major or mild NCD with Lewy bodies.

20.2.2 Case 2

Case 2 History

Mr. B., a 70-year-old man, was diagnosed with major depression and started on citalopram 20 mg daily. Six months later, he presented to the emergency department for distressing visual hallucinations and paranoia. He told his wife that he saw zoo animals in their living room, including tigers, zebras, and monkeys. He became angry when his wife did not believe him. He was evaluated by a psychiatrist in the emergency department and treated for a diagnosis of major depressive disorder with psychotic features. The psychiatrist increased citalopram to 40 mg daily and added risperidone 1 mg daily. Three months after that, Mr. A. moved into a residential home, and his risperidone dose was discontinued, and paliperidone 6 mg daily was started. After a single dose, the patient became more confused, rigid, and ataxic. He was taken back to the emergency department for further evaluation.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What may explain the patient's extreme response to paliperidone?

Question 2. What is the patient's diagnosis? What should be done next?

Question 3. What is a reasonable treatment approach for this patient?

Case 2 Answers

Case 2 Answer 1 (Question 1—What may explain the patient's extreme response to paliperidone?)

Mr. B. appeared to have suffered a side effect from paliperidone, the principal active metabolite of risperidone, which is roughly equipotent to risperidone. It appears that he was given a dose that is about six times the risperidone equivalent by mistake. Although it is possible that his rigidity likely reflected extrapyramidal side effects from a potent atypical antipsychotic, the symptoms could in fact have been secondary to antipsychotic sensitivity.

Teaching Point
In older adult patients with extrapyramidal symptoms after antipsychotic administration, consider that the patient may be exhibiting the suggestive feature of antipsychotic sensitivity related to NCD with Lewy bodies.

Case 2 Answer 2 (Question 2—What is the patient's diagnosis? What should be done next?)

By definition, patients with major or mild NCD with Lewy bodies develop cognitive symptoms around the same time or within 1 year of the onset of parkinsonism. Cognitive symptoms that occur 1 year or more after the diagnosis of Parkinson disease had been called Parkinson disease with dementia or, now in the DSM-5, NCD due to Parkinson disease (see Fig. 20.1). In this case, mild or major NCD due with Lewy bodies should be considered. This patient meets criteria for probable NCD with Lewy bodies as he has at least one core feature (visual hallucinations) and at least one suggestive feature (antipsychotic sensitivity) (see Table 20.2). A full neurological and cognitive workup should be performed. Examination of this patient may reveal Parkinson disease symptoms such as bradykinesia, asymmetric rigidity, shuffling gait, hypomimia or masked facies (reduced facial expression), and/or hypophonia. Patients with NCD with Lewy bodies and Parkinson disease are highly sensitive to antipsychotic side effects because of the neurodegeneration of the nigrostriatal pathway. Antipsychotics may precipitate or worsen confusion and may paradoxically even increase hallucinations. Catatonia and mutism in patients with major NCD with Lewy bodies have also been reported. The patient's previously undiagnosed NCD with Lewy bodies predisposed him to acute extrapyramidal symptoms when an antipsychotic medication with a relatively high extrapyramidal side effect profile was increased by up to sixfold.

Teaching Point
Symptoms of cognitive impairment and parkinsonism occurring within 1 year of each other are suggestive of major or mild NCD with Lewy bodies, and further workup should be pursued.

Teaching Point
Antipsychotic sensitivity can occur in patients with NCD with Lewy bodies at lower doses during initial administration. It can also be unmasked when there is a large increase in the dosing of antipsychotics. It is a suggestive feature of major or mild NCD with Lewy bodies.

Case 2 Answer 3 (Question 3—What is a reasonable treatment approach for this patient?)

First, the highly potent antipsychotic paliperidone should be discontinued. Next, a cholinesterase inhibitor should be considered as this class of medication appears to have the strongest evidence base and may be helpful for cognition and possibly even for hallucinations [72, 74]. Sleep should be monitored carefully, and melatonin and other medications may be considered to help with insomnia, if present. Finally, quetiapine with gradual dose titration or pimavanserin may be considered.

Teaching Point

Visual hallucinations in patients with major or mild NCD due to Lewy bodies can be addressed with low-potency atypical antipsychotics. Typical antipsychotics should be avoided. Cognitive symptoms and possibly hallucinations can improve with treatment with a cholinesterase inhibitor. Pimavanserin may be considered in patients with NCD with Lewy bodies given its efficacy in treating psychosis in Parkinson disease.

Case 2 Analysis In this case, a patient with NCD with Lewy bodies was initially misdiagnosed with major depressive disorder with psychotic features. Thus, NCD with Lewy bodies should be on the differential when older adults present with symptoms of depression and psychosis. If the patient indeed meets criteria for NCD with Lewy bodies, cholinesterase inhibitors should be considered and treatment with antipsychotics reconsidered. Patients vary in terms of sensitivities to antipsychotics. Some patients with NCD with Lewy bodies may not exhibit sensitivity to antipsychotics at lower doses but may experience severe extrapyramidal symptoms at higher doses or during dose titrations. Antipsychotics should be used judiciously in the older adults given the increased risk for mortality and morbidity. Risks and benefits should be discussed with the patient. (See ▶ Chap. 22.) In this case, the visual hallucinations appeared to be impairing Mr. B.'s functioning and relationships. Low-potency atypical antipsychotics should be considered first to avoid extrapyramidal symptoms.

20.3 Key Points: Major or Mild Neurocognitive Disorder with Lewy Bodies

- Major or mild NCD with Lewy bodies is a leading cause of non-Alzheimer-related NCDs and should be considered in the differential of new-onset cognitive impairment or parkinsonian symptoms in the older adults.
- Time course of symptoms is important for diagnosis of NCD with Lewy bodies. The development of cognitive impairment and parkinsonian symptoms within 1 year of each other strongly suggests a diagnosis of NCD with Lewy bodies.
- Core (fluctuating cognition, visual hallucinations, parkinsonism) and suggestive (REM sleep behavior disorder, antipsychotic sensitivity) features are used in the diagnosis of NCD with Lewy bodies.
- The early course of the disease is marked by heterogeneity, and patients may present with a range of symptoms at onset including autonomic, sleep, and motor dysfunctions and neurocognitive and neuropsychiatric symptoms (e.g., depression, hallucinations, delusions).
- Unlike NCD due to Alzheimer disease with early impairment in language and memory, cognitive symptoms in NCD with Lewy bodies are marked by impairment in executive function.
- When NCD with Lewy bodies is suspected, complete psychiatric, medical, and neurological examinations should be performed. Coordination of care among clinicians helps with the diagnosis and treatment of NCD with Lewy bodies.
- Treatment with cholinesterase inhibitors may help slow the progression of cognitive symptoms.
- Antipsychotics should be used judiciously and cautiously in patients with NCD with Lewy bodies. Carefully weigh the risks and benefits to the patient. Consider low-potency antipsychotics to begin with slow titration if needed.

20.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. A 72-year-old man has mild cognitive impairment and presents with parkinsonism and orthostatic hypotension. What is his diagnosis?

A. Probable major NCD with Lewy bodies
B. Probable mild NCD with Lewy bodies
C. Possible major NCD with Lewy bodies
D. Possible mild NCD with Lewy bodies

Answer: D

Diagnosis of NCD with Lewy bodies requires that patient meet criteria for major or mild NCD. Diagnosis of probably NCD with Lewy bodies requires two or more core features (fluctuating cognition, visual hallucinations, parkinsonism) or one or more core features plus one or more suggestive features (REM sleep behavior disorder, antipsychotic sensitivity). If only one core feature or one suggestive feature is present, criteria are only met for possible NCD with Lewy bodies. In addition, given his mild cognitive impairment, the patient likely has mild NCD. Therefore this patient's diagnosis is possible mild NCD with Lewy bodies. Therefore the correct answer is D.

MCQ 2. A 78-year-old patient presents with complaints of forgetfulness. What is his likely diagnosis if he were to develop Parkinson-like symptoms in (1) 8 months versus (2) 3 years?[1]

A. (1) AD-NCD, (2) LB-NCD
B. (1) LB-NCD, (2) PD-NCD
C. (1) LB-NCD, (2) AD-NCD
D. (1) LB-NCD, (2) LB-NCD

Answer: C

Occurrence of cognitive impairment and parkinsonism within 1 year of each other warrants a diagnosis of probable or possible major or mild NCD with Lewy bodies. If these symptoms are not linked temporally within 1 year of each other, another diagnosis should be considered. In this case, if the patient with cognitive impairments develops parkinsonism in 8 months, it is likely that he has LB-NCD. If the patient developed parkinsonism greater than 1 year after cognitive impairment, one would consider a diagnosis of AD-NCD as symptoms of parkinsonism may develop late in the evolution of Alzheimer tauopathy as the pathology generalizes to various neurological domains. Therefore, the correct answer is C.

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1 AD-NCD, neurocognitive disorder due to Alzheimer disease; LB-NCD, neurocognitive disorder with Lewy bodies; PD-NCD, neurocognitive disorder due to Parkinson disease.

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Major or Mild Vascular Neurocognitive Disorder

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21.1 Background

21.1.1 Definition

According to the 5th edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [1], those cases that meet the criteria for major or mild neurocognitive disorder (NCD) (formerly dementia), but with suggestion of a link to cerebrovascular pathology, are referred to as "probable" or "possible" major or mild vascular NCD. The "probable" designation is given when at least one of the following criteria is met:

- Clinical criteria are supported by neuroimaging evidence of parenchymal injury attributed to cerebrovascular disease.
- There is a temporal relationship between the neurocognitive syndrome and one or more documented cerebrovascular events.
- Both clinical and genetic evidence of cerebrovascular disease is evident; this is relevant to cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).

The "possible" designation is used for a suggestion of vascular contribution to NCD without meeting any of the above criteria [1].

The *International Classification of Diseases*, 10th revision (ICD-10), published by the World Health Organization [2] uses "vascular dementia" as the main terminology for this illness, with subtypes including:

- Vascular dementia of acute onset
- Multi-infarct dementia
- Subcortical vascular dementia
- Mixed cortical and subcortical vascular dementia

The terminology of this illness has evolved over time. Early terminology included multi-infarct dementia, which referred to dementia in the context of a diagnosed stroke (single or multiple) [3]. The Hachinski Ischemic Index Score was developed in the mid-1970s to differentiate between Alzheimer disease and multi-infarct dementia; it is composed of 13 features, each assigned 1 or 2 points. This tool has reasonable sensitivity (89%) and specificity (89.3%) to distinguish multi-infarct dementia from Alzheimer disease using a cutoff of 4 or below for Alzheimer dementia and 7 or above for multi-infarct dementia. Using the same cutoff scores, this tool is not as specific when it comes to distinguishing Alzheimer disease from mixed dementia (specificity of 29.4%) or multi-infarct dementia from mixed dementia (specificity of 17.2%) [4]. The scale was modified subsequently reducing the items to five composite or seven single-item scales that fare as well or better than the original index score [5]. Eventually, the term vascular dementia was used to refer to cognitive disorders stemming from a variety of cerebrovascular lesions, including overt strokes involving major vascular distribution, small but strategic strokes, and/or significant subcortical white matter hyperintensities [6]. This was summarized in the diagnostic criteria published by the National Institute of Neurological Disorders and Stroke and Association Internationale Pour La Recherché et L'Enseignement en Neurosciences (NINDS-AIREN) that identifies vascular dementia based on establishing the presence of dementia whereby two or more cognitive domains (including memory) are significantly impaired compared to previous baseline on objective examination, establishing the presence of cerebrovascular disease, and establishing a relationship between the two. This results in the following designations:

- Definite vascular dementia (requires probable vascular dementia confirmed by neuropathology with absence of tangles and plaques beyond normal or other pathology)
- Probable vascular dementia (evidence of NCD, cerebrovascular disease, and relationship between the two)
- Possible vascular dementia (evidence of NCD and cerebrovascular disease but the relationship between the two is not clear)
- Alzheimer disease with cerebrovascular disease (evidence for both Alzheimer disease and cerebrovascular disease)

Other published criteria for vascular NCD are the State of California Alzheimer Disease Diagnostic and Treatment Centers (ADDTC) criteria for probable and possible ischemic vascular dementia [7]. These criteria include cognitive impairment, though not specific to memory impairment of specific domains, and a focus on acute and chronic ischemic cerebrovascular disease (not hemorrhagic). These criteria do not specify associated neurological findings on physical exam, but, instead, require brain imaging finding of relevant cerebrovascular disease for probable ischemic vascular dementia to be diagnosed.

The inter-rater reliability for different criteria, including the DSM-IV (previous version of DSM-5) [8], the Hachinski Ischemic Index Score (original and modified), NINDS-AIREN, and ADDTC, was assessed using 25 standardized case vignettes rated by seven ADDTC centers using an established checklist from the criteria. This study demonstrated significant variability in frequency of the diagnosis of vascular dementia (highest for modified Hachinski Ischemic Index Score or DSM-IV, intermediate for original Hachinski Ischemic Index Score and ADDTC, and lowest for NINDS-AIREN). Inter-ratter reliability was the lowest for ADDTC and highest for the original Hachinski Ischemic Index Score [9]. This study identified the need for prospective clinico-pathological studies to establish better validity for diagnostic criteria.

As the field of NCD moved to detecting earlier stages of dementia such as mild cognitive impairment (MCI), a risk state/prodrome for Alzheimer disease, so did the field of cognitive disorder due to cerebrovascular disease. This led to the proposal of using more inclusive terms, like vascular cognitive impairment, as a preferred terminology, which is more inclusive to the full range of cognitive difficulties stemming from a wide range of cerebrovascular lesions [10]. The term "dementia" was somewhat problematic from

the beginning, as it was associated with neurodegenerative illnesses such as Alzheimer disease, while "pure" vascular NCD can range in the level of impairment from single cognitive domain impairment with otherwise relatively preserved function (vascular MCI) to impairment in multiple cognitive domains with impaired daily function reaching the threshold of "dementia" or major NCD. In 2011, a consensus scientific paper was published by the American Heart Association and American Stroke Association that covered the contribution of cerebrovascular disease to cognitive impairment and dementia [11]. In this paper it was proposed that vascular cognitive impairment refers to the range of cognitive changes from MCI to full spectrum dementia (i.e., major NCD) of vascular origin. The diagnosis would then range from vascular MCI to vascular dementia. Vascular MCI is diagnosed when there is an objective decline from baseline of at least one cognitive domain with normal or only mildly affected instrumental activities of daily living independent from motor or sensory deficit. Vascular dementia is diagnosed when there is an objective decline from baseline of two or more cognitive domains (amnesia is necessary to make the diagnosis) resulting in significant impairment in daily functioning, independent from deficits caused by motor or sensory deficits. Like DSM-5, a designation of "probable" versus "possible" vascular MCI or vascular dementia depends on the certainty of the association between vascular pathology and the cognitive impairment. Table 21.1 summarizes the clinical criteria for vascular NCD in the DSM-5 [1], ICD-10 [2], and criteria proposed in the American Heart Association/American Stroke Association (AHA/ASA) consensus scientific paper [11]. Other criteria can be accessed from the references listed (see Table 21.1 [1, 2, 6, 11]).

Teaching Point

Published clinical criteria for vascular NCD require first establishing the presence of a NCD, specify if it is major (significant impact on function) or mild (minimum impact on function), and establish the link between vascular factors and the NCD (this can be "definite" as determined at autopsy or "probable" or "possible" depending on the strength of the association). Coding for behavioral symptoms is added similar to other NCDs.

21.1.2 Epidemiology

It is difficult to estimate the prevalence and incidence of NCDs due to cerebrovascular disease because of the overlap with Alzheimer disease and the differences in the threshold for detection of cerebrovascular lesions depending on the clinical and neuroimaging tools used. There is a range of disorders that span from "pure" Alzheimer disease, mixed Alzheimer and vascular NCD, and "pure" vascular NCD [12]. In clinical samples, vascular NCD is the second most common case of "dementia" [13]. Age-adjusted rate of 14.6/1000 per person-year for vascular NCD compares to 19.2/1000 per person-year for Alzheimer disease [14].

About two thirds of stroke survivors suffer some degree of cognitive impairment [15], and one third will have frank dementia (or major NCD) [16–18]. Also, there is a significant overlap between vascular and neurodegenerative neuropathology in autopsy studies [19–24]. Despite significant contribution of vascular disease to cognitive impairment, stroke scales do not assess cognitive function, with the exception of the Toronto Stroke Scale, which is not commonly used in clinical trials.

This has resulted in difficulty in getting better understanding of the true epidemiology of vascular NCDs. To counter some of these challenges, a joint workshop of the NINDS and Canadian Stroke Network was assembled from experts in the field of vascular cognitive impairment. A paper was published by Hachinski et al. in 2006 which summarized this important effort to harmonize the standards for screening and diagnosis of vascular cognitive impairment, which may help generate better epidemiological data [25].

Teaching Point

There is significant overlap between Alzheimer disease and vascular NCD; on one extreme there is pure Alzheimer's disease and the other extreme there is pure vascular NCD, while mixed cases are in between, where both pathologies are present. Epidemiological data are affected by this overlap making it difficult to establish accurate prevalence data for vascular NCD. Better definition and diagnostic tools may improve this.

21.1.3 Etiology

It is assumed that the underlying etiology of vascular NCD is related to vascular lesion(s) directly resulting in cognitive impairment by disrupting cognitive brain networks. On the other hand, this relationship is complex because of the overlap and coexistence of vascular and neurodegenerative processes in NCDs. In this section we will outline some of the factors that have been associated with a higher risk for cerebrovascular changes and associated cognitive impairment, underlying neuropathological features, and the possible underlying mechanisms involved.

Risk Factors

Several risk factors have been investigated in terms of association with cognitive impairment. In general, these associations are difficult to study given the variety of confounds that affect the interpretation of positive and negative results. Some of these factors are non-modifiable:

- *Demographics:* There is an exponential increase in risk of vascular NCD with age that follows the stroke risk. Some ethnic groups are at a higher risk of developing major vascular NCD ((also referred to as vascular dementia) after stroke than others (e.g., black compared to white

Table 21.1 Summary of main clinical criteria for vascular neurocognitive disorders [1, 2, 6, 11]

Source	Designation	Criteria
DSM-5 [1]	Probable or possible: Major NCD due to VD Mild NCD due to VD Code: With/without behavioral disturbance Specify: Mild, moderate, or severe	Meet criteria for major or mild NCD At least one of the following for probable: Neuroimaging evidence of VD Temporal relationship between VD and NCD Both clinical and genetic evidence of VD (e.g., CADASIL)
ICD-10 [2]	Vascular dementia of acute onset	Usually develops rapidly after a succession of strokes from cerebrovascular thrombosis, embolism, or hemorrhage. In rare cases, a single large infarction may be the cause
	Multi-infarct dementia	Gradual in onset, following a number of transient ischemic episodes, which produce an accumulation of infarcts in the cerebral parenchyma. Predominantly cortical dementia
	Subcortical vascular dementia	Includes cases with a history of hypertension and foci of ischemic destruction in the deep white matter of the cerebral hemispheres. The cerebral cortex is usually preserved, and this contrasts with the clinical picture, which may closely resemble that of dementia of Alzheimer disease
	Mixed cortical/subcortical, other VaD, and unspecified	Other forms of vascular cognitive disorders
AHA/ASA scientific consensus paper [11]	VCI	Inclusive of the full spectrum of cognitive changes attributed to CVD. It cannot be used for those with active drug/alcohol abuse/dependency (3 months substance-free required). It cannot be used for those with delirium
	Probable VaD	Criteria for dementia are met: Objective decline from baseline of two or more cognitive domains Testing should include executive, attention, memory, language, and visuospatial functions, but amnesia is not necessary for the diagnosis Significant functional impairment independent of motor/sensory deficit There is clear temporal relationship between CVD and onset of CI or clear relationship in the severity and pattern of CI and the presence of diffuse, subcortical CVD
	Possible VaD	Criteria of dementia are met as per above and imaging findings of CVD but: There is insufficient information to confirm the relationship between dementia and CVD Difficulty testing due to severe aphasia (can be diagnosed with other evidence) There is evidence to suggest neurodegenerative process in addition to CVD
	Probable or possible VaMCI	Evidence of objective deficit in at least one cognitive domain (listed above) with IADLs normal or only mildly impaired independent of motor/sensory deficit Evidence of CVD Probable and possible designation is based on establishing the relationship between CVD and CI similar to VaD
	Unstable VaMCI	Those designated as VaMCI that revert to normal
NINDS-AIREN [6]	Probable, possible, or definite VaD	Probable VaD requires all of the following: Evidence of dementia (impairment of two or more cognitive domains including memory from baseline affecting function) not due to other causes Clinical and imaging evidence of CVD Evidence of a relationship between the above two as inferred by: Temporal relationship (within 3 month) Clinical features (abrupt cognitive deterioration, fluctuating or stepwise course) Clinical features consistent with probable VaD include: Early gait changes not explained on other basis Unsteadiness, unexplained falls Urinary symptoms not explained on other basis Pseudobulbar palsy Personality changes, abulia, depression, emotional incontinence, and other subcortical features like psychomotor retardation and executive dysfunction Definite VaD: requires probable VaD confirmed by neuropathology with absence of tangles and plaques beyond normal or other pathology Possible VaD: when criteria for probable VaD are not met despite meeting criteria for dementia and suggestion of CVD or when there are course features suggestive of other etiology AD with CVD is reserved for those with possible AD plus clinical or imaging evidence of relevant CVD

AD Alzheimer disease, *AHA/ASA* American Heart Association/American Stroke Association, *CADASIL* cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, *CI* cognitive impairment, *CVD* cerebrovascular disease, *DSM Diagnostic and Statistical Manual of Mental Disorders*, *NCD* neurocognitive disorder, *VaD* vascular dementia, *VaMCI* vascular mild cognitive impairment, *VD* vascular disease

and Hispanic Americans). Differences in risk between females and males have not been confirmed.
- *Genetics:* CADASIL that is causative of vascular NCD is discussed below. Other genetic markers are more along the line of susceptibility genes. One such gene is apolipoprotein E4, a risk gene for Alzheimer disease but which seems to increase risk for vascular NCD as well. The relationship is complex due to the overlap in diagnosis and comorbidity between the two illnesses.
- *Education:* Education is difficult to separate from sociodemographic factors and difficult to modify as it mainly refers to early education. Cognitive rehabilitation has limited evidence in vascular NCD at this time.
- *Diet:* Several nutrients have been considered including antioxidants (vitamin E, vitamin C, beta-carotene), vitamin D, as well as vitamin B_6 and B_{12}, which are both part of the homocysteine pathway; high homocysteine results in cerebrovascular disease. The Mediterranean diet is reasonable as an early prevention strategy. All these factors have suggestive rather than confirmed evidence.
- *Physical activity:* This may enhance cognitive and cerebrovascular well-being.
- *Alcohol intake:* Moderate intake is advised that might be protective.
- *Smoking:* This increases risk for cerebrovascular disease and therefore increases risk for vascular NCD.
- *Obesity:* This has an increased risk for vascular NCD.

Details around modifiability and recommendations regarding risk factors are available in the treatment section of this chapter.

Teaching Point

Risk factors for vascular NCD include non-modifiable (demographics, ethnicity, genetics) and potentially modifiable factors (lifestyle, physiological and concomitant vascular diseases). The section on treatment will detail recommendations regarding modification of risk factors.

Neuropathology Lesions

There are several neuropathological lesions identified in vascular NCD. Below we briefly summarize the most clearly substantiated causative lesions. In the subsequent section we will discuss some of the known and proposed mechanisms underlying these neuropathological lesions. This section is based on a review of a few key publications that the reader is referred to for more details [11, 25, 26].

A. Cerebral infarcts. These are the most common lesions associated with vascular neurocognitive impairment. These usually refer to discrete lesions of brain tissue loss that can be "macroscopic" or "microscopic." The designation of "macro" or "micro" infarct is somewhat arbitrary. Some authors suggested a cutoff of 4 millimeters (lesion diameter) [27], while others used 2 millimeters [28]. The National Institute of Neurological Disorders and Stroke-Canadian Stroke Network (NINDS-CSN) vascular cognitive impairment harmonization standards suggest reserving microinfarcts to lesions that are not visible to the naked eye, but detected on histological examination [25].
- *Macroscopic infarcts:* In general, the larger the volume and number of these lesions and the more "strategic" the location they affect, the more likely that they will contribute to cognitive impairment. But, again, the correlation between these variables and cognitive impairment is weak and inconsistent. Some strategic locations that have been reported include the thalamus, basal ganglia, and angular gyrus, but several other cortical and subcortical areas have been suggested as well. Multi-infarct dementia is usually caused by atherosclerosis and thrombosis affecting cranial blood vessels, but can also be due to emboli from atrial fibrillation and other distant sources [29].
- *Microscopic infarcts:* These tend to be even more prevalent than macroscopic infarcts, and it was suggested that they are more likely to cause vascular NCD [30].

B. Non-necrotic white matter hyperintensities. This refers to white matter lesions that do not involve microinfarcts but rather other changes in the integrity of white matter. These lesions can be focal, patchy, or confluent and are common in the periventricular area (periventricular hyperintensities). They are usually attributed to partial ischemia [31, 32], but they do have pathological features such as myelin membrane changes (pallor), astrocytosis (change in morphology, ballooning), decline in oligodendrocytes, and clasmatodendrosis (loss of astrocyte processes) [33] in addition to spongiosis [34] that suggests other mechanisms [26].

C. Microhemorrhages. This refers to hemorrhages that typically happen spontaneously in cortical or cortical-subcortical (lobar) areas. They are caused by several factors, but apart from direct trauma and excess anticoagulation, they all involve a structural defect in arterioles and capillaries. Structural abnormalities in vessel walls can be the result of inborn error in vascular genesis, aging, hypertension, and atherosclerosis but can also be due to abnormal protein accumulation such as cerebral amyloid angiopathy, which involves infiltration of cerebral arterioles and capillaries with amyloid-beta peptide, which result in structural deficits in vessel walls and several lesions such as microaneurysms, perivascular leakage, and fibrinoid necrosis [35–37]. This pathology can happen sporadically in the population (10–30%) but more commonly coexists in brains with Alzheimer disease pathology [38], although it has also been independently associated with cognitive changes in old age [39].

The basic mechanism underlying cerebrovascular changes is complex. Full discussion of these mechanisms is beyond the scope of this chapter. Below is a brief discussion of some of the key mechanisms being investigated in the field of vascular NCD:
- Arteriosclerosis/lipohyalinosis: This refers to stiffening of arteries that commonly happens with age and involves loss of elastin and an increase in collagen fibers in the arterial wall [40]. This can be examined noninvasively by

measuring carotid-femoral pulse wave velocity [41] and, in addition to aging, is associated with hypertension [42] and structural and genetic factors [43]. Arterial stiffening has been associated with cognitive decline with and without major NCD in old age [44–48]. Thickness of the arteries negatively correlates with cognitive performance level [49].

- Atherosclerosis: Artery intima-media thickening due to atheroma formation is common with increased age and can be measured by Doppler studies in arteries like the carotid artery. This process can affect any artery, but carotid and cerebral arteries are particularly relevant in vascular neurocognitive impairment. There is an association between atherosclerosis and cognitive impairment in old age, the mechanism of which is multifactorial but likely involves thrombosis of large arteries and secondary hypoxia, emboli from ruptured atheroma, oxidative stress, inflammatory response, dysregulation of blood pressure control, and change in blood-brain barrier regulation. All of these factors are likely in play in other pathological changes related to vascular neurocognitive impairment.
- Neurovascular unit regulation: This mechanism assures consistency in cerebral blood flow despite variation in systemic blood pressure [50], and there is evidence of dysfunction in this mechanism in vascular and Alzheimer-related NCDs and disruption in the integrity of the blood-brain barrier [51–55]. Neurovascular unit dysfunction can be the result of structural changes affecting large and small cerebral vessels due to vascular risk factors and aging.
- Partial ischemia: As a consequence of several structural changes outlined above in large and small vessels, partial ischemia can result in local hypoxia in vulnerable areas such as the periventricular white matter and results in a cascade of neuroinflammatory and oxidative stress responses [34].
- Role of inflammation: Another possible aspect of vascular NCD pathophysiology is the role of inflammation [56]. Inflammatory mediators potentially contribute to further neuronal dysfunction and eventually result in cellular death.
- Genetic factors: Genetic factors have also been linked to vascular NCD. Cerebral Autosomal Dominant Arteriopathy with Subcortical Infarcts and Leukoencephalopathy (CADASIL) is a condition of heritable small-vessel disease caused by mutations in NOTCH3 gene, which is normally expressed in vascular smooth muscle cells and pericytes (including those of the cerebral vasculature). The gene encodes a cell-surface receptor which has a role in arterial development. It appears to be involved in directing smooth muscle cell proliferation and differentiation. About 95% of patients with the CADASIL condition have missense mutations of NOTCH3 gene (which is linked to cysteine metabolism), but the pathogenic mechanism is still unknown [57].
- Hyperhomocysteinemia: Homocysteine is a nonessential amino acid that contains sulfur. Vitamin B_{12}, B_6, and folic acid are cofactors involved in the formation and turnover of homocysteine, which is why hyperhomocysteinemia reflects deficiencies in these nutrients. Homocysteine is a product of methionine metabolism and can be remethylated to methionine with B_{12} as a cofactor or transsulfurated to cystathionine and then to cysteine, which then leads to the production of glutathione, an important antioxidant. The conversion to glutathione through the intermediates cystathionine and cysteine uses B_6 as a cofactor and is clearly delineated in the liver but remains to be confirmed in the brain. There is evidence of neurotoxicity and vasculotoxicity with high level of homocysteine [58]; the association of homocysteine to cognitive disorders is not specific to vascular cognitive impairment but rather affects the brain through a mechanism related to oxidative stress and glutamate-mediated toxicity [59].
- Choline acetyltransferase activity: There has been a link to choline acetyltransferase activity, which is reduced in patients with vascular NCD [60]. Recent studies have shown that loss of cholinergic function is greater if vascular NCD coexists with Alzheimer disease [61].

There are several challenges when it comes to confirming the contribution for cerebrovascular lesions to cognitive impairment:

- These lesions are common in older adults with and without cognitive disorders occurring in a third to one half of this population [62–64] and even higher if microscopic infarcts are included [20].
- They tend to vary in volume and location, and there are no specific neuropathological criteria to help confirm a diagnosis of vascular NCD.
- They are common in neurodegenerative illnesses like Alzheimer disease, likely interact with underlying Alzheimer pathology [63, 65], and have an additive negative effect [66–68].

Teaching Point

Several pathological lesions have been identified in vascular NCD including cerebral infarcts (macroscopic and microscopic), white matter lesions, and microhemorrhages. These lesions stem from different pathological processes including arterial stiffening, atherosclerosis, partial ischemia, neurovascular unit impairment, and blood-brain barrier abnormalities. Causes of these processes come from multiple sources including aging, genetics, physiological factors, metabolic factors, oxidative stress injury, and inflammatory factors.

21.1.4 Clinical Description

Vascular NCD symptoms vary, depending on brain regions and networks affected. Symptoms often overlap with those of other NCDs, especially Alzheimer disease, and can vary depending on the subtype of vascular NCD [69]. Clinical cri-

teria described previously include features that increase the likelihood of vascular NCD (possible or probable) as the clinical designation used after certain criteria are met. Although a cognitive concern by the patient or family/caregiver is usually the main reason for assessment, it is important for clinicians to identify those at risk for vascular NCD. This may help in prevention of further cognitive, functional, and behavioral changes by controlling vascular risk factors and lifestyle modification.

The presence of significant vascular risk factors and history of clinical stroke or stroke-like event, like transient ischemic attacks temporarily affecting aspects of neurological function, should raise suspicion of vascular NCD. Sudden onset, stepwise worsening, although not always present, would also raise suspicion of vascular contribution to the cognitive presentation. Quality of cognitive and behavioral symptoms can be helpful as well. Below we will outline key components of the diagnostic evaluation for vascular NCD and key features that the clinician should look for.

21.1.5 Diagnostic Evaluation

The clinical diagnosis is made based on diagnostic criteria in DSM-5 for major or mild NCD plus specific criteria for vascular NCD. The ICD-10 criteria are used in many jurisdictions especially for coding purposes, and therefore it is advisable of the clinician to be familiar with them.

The NINDS-AIREN criteria or the proposed AHA/ASA criteria described above are likely to be used in specialized memory clinics and in research settings, but clinicians should be familiar with these criteria given their higher specificity. This set of criteria is based mainly on three core features [6, 11, 70]:

1. Acute onset of NCD
2. Neuroimaging of cerebrovascular lesions
3. Evidence of a relation between stroke and cognitive loss

Diagnostic evaluation aims to verify and rule in and out criteria to support or dispute the diagnosis of vascular NCD and consider alternative diagnoses. Core elements of the workup for vascular NCD typically include several domains, which will be described below.

Clinical History

Like other NCDs, it is not usually sufficient to obtain history solely from the patient alone due to cognitive impairment and limited insight in some cases. Therefore, history from a reliable informant who interacts with the patient frequently is essential.

Elements from the clinical history that need to be elicited and verified that suggest vascular neurocognitive impairment include:

- Cognitive change from baseline with or without major impact on function (to establish the presence of major or mild NCD).
- The presence of vascular risk factors especially if there is indication of poor control (e.g., uncontrolled high blood pressure, untreated atrial fibrillation).
- History of possible or confirmed cerebrovascular events (stroke or stroke-like event). This could be recent or remote, single or multiple.
- Temporal relationship between the cerebrovascular event and cognitive change. This requires careful inquiry around the recovery from strokes and residual symptoms.
- The course of change in cognitive function might be suggestive of vascular origin especially when it follows a stepwise course with episodes of acute decline and periods of plateau as related to the cerebrovascular events. On the other hand, it is important to note that subcortical white matter hyperintensity-related vascular NCD can have a course that is difficult to distinguish from that of Alzheimer disease. A clinical cohort study of 970 patients comparing baseline and course characteristics among pathologically confirmed pure vascular NCD (n = 141), pure Alzheimer NCD (n = 663), and mixed vascular and Alzheimer NCD (n = 166) reported better baseline cognitive function and slower rate of decline in the pure vascular group followed by the mixed group and the fastest for the pure Alzheimer group [71].
- The pattern of cognitive impairment tends to be more patchy and involves more prominent executive dysfunction (discussed in cognitive and functional assessment section below).
- There are often prominent features of mood, anxiety, and apathy. This is usually the result of disruption of frontal-limbic networks especially due to subcortical vascular lesions but can be a feature of other NCDs (see ► section Neuropsychiatric Symptoms of Vascular Neurocognitive Disorder for discussion).
- There are frequently features of gait impairment including unsteadiness, fear of falling, and actual falls. This is usually the result of disruption of frontal-subcortical gait regulation networks, although the mechanism might involve other elements (see ► section Gait Issues in Vascular Neurocognitive Disorder for discussion).

The above elements are suggestive of vascular neurocognitive impairment, although they are not very specific as they can be present in other forms of NCDs like in Alzheimer disease.

Neuropsychiatric Symptoms of Vascular Neurocognitive Disorder

Neuropsychiatric symptoms of NCDs are covered in more details in another chapter of this text. (See ► Chap. 22). Here we highlight some of the clinical findings relevant to neuropsychiatric illness in the context of vascular NCDs. Depressive disorders [72] and apathy [73] have been reported as being particularly common in vascular NCD. In a study comparing neuropsychiatric symptoms in vascular versus Alzheimer-related NCDs, anxiety and depression were found to be higher in vascular NCD [74]. Euphoria, in contrast, has been shown to be the least common symptom [73], whereas other studies demonstrated that sleep disturbances and depressive disor-

ders are very common [75]. Sleep disturbance seems to be particularly common in cortical vascular NCD [76]. Apathy is known to be common in subcortical ischemic vascular disease because of the occurrence of white matter lesions and/or lacunar infarcts in the basal ganglia and thalami, which lead to interruption of the cortico-subcortical circuit. Patients with multi-infarct dementia tend to have wider range of neuropsychiatric symptoms including hallucinations, agitation, aggression, irritability, and/or euphoria [73].

These symptoms cause significant distress to patients and their families and caregivers, so appropriate identification and management of these problems is in the core of managing patients with vascular NCD. The NINDS-Canadian Stroke Council vascular cognitive impairment harmonization standards [25] recommended the use of the Neuropsychiatric Inventory Questionnaire version (NPI-Q) as a screening tool [77]. Several tools have been used to detect depression related to cerebrovascular disorders, e.g., the Center for Epidemiological Studies Depression Scale (CES-D) [78]. The Geriatric Depression Scale (GDS); the Zung Self-Rating Depression Scale (SDS), both self-rated; and the Comprehensive Psychopathological Rating Scale-Depression (CPRS) were shown to have good sensitivity and predictive value in poststroke depression [79].

Gait Issues in Vascular Neurocognitive Disorder

Patients with vascular NCD (pure or mixed with Alzheimer disease) have more gait impairment compared to those with pure Alzheimer disease. Changes in gait due to motor impairment as a result of strokes (e.g., in multi-infarct dementia) are usually obvious. On the other hand, there are a set of changes in gait resulting from disruption of frontal-subcortical networks that require further clarification. Clinically, gait changes can be confused with Parkinson disease features. Reports of slowing down, shuffling gait, smaller strides, falls, or fear of falling are elements that can be elicited from clinical history. It has been long known that subcortical white matter changes can cause "parkinsonism" [80] especially in illnesses like Binswanger disease, whereby extensive periventricular white matter abnormality is found and seen on brain imaging as hyperintensities. This illness has been linked to chronic hypertension and is associated with cognitive, functional, behavioral, and gait changes simulating Parkinson disease [81]. More studies have confirmed this association and described it as "parkinsonism" [82, 83] or apraxia of gait [84]. Using perfusion scanning such as single photon emission computed tomography (SPECT), a study showed that impairment in higher processing of gait in 12 older patients with significant cerebrovascular changes (multi-infarct, single infarct, and leukoaraiosis) with gait apraxia was associated with lower activation in medial frontal gyrus (including supplementary motor area) and anterior lobes of the cerebellum bilaterally, supporting the role of higher cortical centers in processing gait control information [85].

Functional Changes in Vascular Neurocognitive Disorder

Functional inquiry is part of the clinical history and is usually obtained from the patient and from a reliable informant. This is covered in more detail in other chapters of this text. (See ▶ Chap. 18). Using questionnaires to assess basic and instrumental activities of daily living is very helpful especially when obtained from the patient and an informant to counter some of the confounds related to the patient's cognitive and insight deficits. There are several useful validated tools to use in the clinic that were found to be helpful in supporting the diagnosis of major NCDs (dementia) including the Index for Activities of Daily Living, the Modified Blessed Dementia Scale, the Instrumental Activities of Daily Living, and the Functional Assessment Questionnaire [86]. The Functional Assessment Questionnaire was studied specifically in vascular NCD and found to be useful [87].

Cognitive Profile

The cognitive profile of patients with vascular NCD includes a wide range of cognitive deficits, but typically shows impairment in executive functioning (including elements of slowed processing speed), difficulty with working memory (e.g., holding and manipulating information online), difficulty in shifting attention, and deficits in multitasking. Therefore, when testing cognitive function in this context, we need to use tools that are broad enough, but also need to be sensitive to deficits in executive functioning. The NINDS-Canadian Stroke Council vascular cognitive impairment harmonization standards recommend comprehensive cognitive profiling to cover executive (frontal-subcortical) function and to use operational definitions for cognitive decline (e.g., 1–1.5 standard deviation below norm for vascular MCI and two or more standard deviations for "vascular dementia") [25]. This group's neuropsychology section recommended three levels of testing, 60-minute, 30-minute, and 5-minute protocols taking into account several factors including psychometric properties, feasibility for the clinical setting, domain specificity, repeatability (to avoid practice effect), cross-cultural generalizability, ceiling and flooring effect of the tests, and previous use in this population. The 60-minute protocol is comprehensive, usually applied in subspecialty and research clinics, and includes coverage of executive/activation, visuospatial, language/lexical retrieval, memory/learning, neuropsychiatric/depressive symptoms, and premorbid status. Tests selected are standardized and validated and testing will result in giving patient performance statistical reference compared to age and education normative data. The 30-minute protocol is an abbreviation of the 60-minute protocol including semantic and phonemic fluency, digit symbol-coding, and the revised Hopkins Verbal Learning Test in addition to CES-D and NPI-Q. Supplemental tests include trail making test, parts A and B, and the Mini Mental State Examination (MMSE). For the 5-minute protocol, the decision was to not use the MMSE due to its limited testing of executive function and limited sensitivity of the 3-item delayed recall for memory impairment. Instead,

a subset of the Montreal Cognitive Assessment (MoCA) test [88] was proposed including 5-word immediate and delayed recall, letter "F" 1-minute phonemic fluency test, and 6-item orientation task. Most clinics would do the full MoCA test or supplement with other tests like the MMSE. (See ► Chap. 4).

The quality of memory impairment in vascular NCD is usually different from that in Alzheimer disease. While difficulty in episodic memory *encoding* is the core early deficit (related to early hippocampal complex involvement) [89] in Alzheimer disease resulting in anterograde episodic memory impairment [90], deficits in memory *retrieval* are usually more prominent in vascular NCD resulting in consistently better recognition memory compared to Alzheimer disease [76].

Mental Status and Physical Examination

Mental status examination includes the following elements:

- General appearance of the patient: elements of executive functioning and ability to care for him or herself, signs of cardiovascular impairment.
- Attitude: cooperativeness.
- Language/speech: from direct examination, the examiner should attend to aspects of speech and language, including, but not limited to, comprehension, fluency, grammar, paraphasic errors (substituting one word for another that could be conceptually or phonetically related), repetition, reading, and writing.
- Movements: gait changes observed as the patient walks to the exam room, any evidence of abnormal movements, as psychomotor slowness is common in vascular NCD.
- Mood: as reported by patient such as irritability, depression, and anxiety.
- Affect: emotional status as observed during the interview; apathy (with flattening of affect) can be seen in these cases quite commonly.
- Cognitive function: from the interview and from testing (as previously described).
- Thoughts: assessment of thought content for any delusional material like paranoia or mood-congruent delusions related to depression. Thought process is also important and can show slowness but usually no disorganization such as is seen in primary psychotic disorder.
- Perception: any hallucinations in any modality. These symptoms are usually suggestive of other processes like delirium or Lewy body disease but can also occur in vascular NCD.
- Suicidal and homicidal ideations: particularly in the context of depression or psychosis.
- Insight: usually relatively preserved regarding cognitive deficits as compared to other illnesses like Alzheimer disease or frontotemporal lobar degeneration, but issues like neglect can result in impaired insight into having deficits (anosognosia).
- Judgment: impairment in judgment is not uncommon given the impairment in executive function, and this affects safety and management of vascular risk factors.
- General physical examination is important because of the need to assess general health, to look for other causes of neurocognitive changes, and to identify and assess vascular risk factors such as high blood pressure and evidence of complications from chronic and poorly controlled diabetes mellitus and high lipids.
- Careful attention to gross and subtle neurological findings is essential; e.g., focal neurological signs due to underlying stroke and features related to frontal-subcortical disconnection syndromes can be seen.

Laboratory Examination

The investigation of any NCD requires ruling out reversible factors. Laboratory tests should be performed including a complete blood count, chemistry, thyroid function, vitamin B_{12} level, and urinalysis, in addition to other tests when there is suspicion of specific medical processes like infection (e.g., serology for syphilis and human immunodeficiency virus), autoimmune disease (e.g., systemic lupus erythematosus), and neoplasm (e.g., paraneoplastic syndrome). When it comes to vascular NCD, brain imaging holds the most value in the diagnostic process as it identifies cerebrovascular lesions that likely contribute to the clinical presentation. Neuroimaging modalities are discussed in a separate chapter in this volume. (See ► Chap. 3). In the following section we will highlight the role of clinical neuroimaging tools in identifying cerebrovascular lesions.

Structural Brain Imaging

Given the wide range of cerebrovascular pathology that can be identified by structural brain imaging, it is important to interpret imaging findings in the clinical context and take into account their nature, severity, and location.

Computed tomography (CT) and magnetic resonance imaging (MRI) findings that are suggestive of vascular neurocognitive impairment include:

- Multiple and/or large infarcts involving the dominant hemisphere or bilaterally
- Single or few infarcts involving strategic areas involved in cognitive processing
- Multiple lacunar strokes
- Periventricular white matter lesions (also known as leukoaraiosis) extending into the deep white matter

Patients with vascular MCI (which can be a prodromal stage for subcortical vascular neurocognitive impairment) have MRI features that differ from patients with amnestic MCI (which can be a prodromal stage for Alzheimer disease). The former tends to show more extensive white matter abnormality, lacunar infarcts, and leukoaraiosis, with minimal hippocampal and cortical atrophies [91].

When considering the significance of cerebrovascular lesions identified by structural imaging in relation to neurocognitive impairment, one needs to take into account the size, count, location, and distribution of the lesions. Despite neuroimaging-neuropathological validation studies, it is still not possible to ascertain the pathological nature of lesions seen on routine structural imaging. The following are neuroimaging findings that suggest different subtypes of vascular NCD.

A. Multiple infarcts. Multiple infarcts found on brain imaging that are likely to disrupt cognitive networks can support vascular contribution to neurocognitive impairment and are consistent with the definition of multi-infarct dementia coined by Hachinski et al. in the 1970s [3].

B. Lacunar infarcts. The number and location of lacunae required to make the diagnosis of vascular NCD is nonspecific, but it is generally accepted that multiple lacunae and the ones that involve strategic cognitive structures are more likely to contribute to vascular NCD. The appearance of a lacuna on brain imaging can be due to lacunar infarct, lacunar hemorrhages, or dilated perivascular space, the latter being a benign finding [91]. Lacunar infarcts generally refer to the occlusion of small penetrating vessels and are of two main pathological types: (i) lipohyalinosis (which mainly results from chronic hypertension) and (ii) microatheromatosis (which usually results in a single clinically significant lacuna) [92]. Subtyping of lacunae to these two entities was supported by a large study in which lacunae associated with leukoaraiosis, which was thought to share the same pathology as lipohyalinosis subtype of lacunae, had stronger association with hypertension and was found to have higher mortality and worse overall outcome (higher re-stroke and lower functional recovery) [93]. Lacunae are seen on T1-weighted MRI but are best visualized on proton density/T2-weighted MRI or fluid-attenuated inversion recovery (FLAIR) MRI scan. It appears as a small hypointense area surrounded by a rim of hyperintensity [94]. What is termed "silent" lacunae (without overt neurological findings on exam) measuring 3 or more millimeters in diameter are 10–20 times higher in prevalence than overt strokes in older adults, occurring in about 25% in those 60 years and older [95]. These lesions contribute to a higher risk of developing a major NCD (dementia) [96].

C. White matter hyperintensities (leukoaraiosis). The other type of cerebrovascular lesion that can be seen on structural brain imaging is white matter hyperintensity (or leukoaraiosis) [97], which can be focal or multiple and can become confluent to involve much or all of the white matter [98]. Studies have shown that white matter hyperintensities are common in old age [95]. It is difficult to estimate the exact amount of these lesions to be considered clinically significant [99]. Some rating scales have been developed to estimate the extent of white matter hyperintensities and to correlate them with cognitive function [100]. These scales are not normally used in clinical practice as they require further validation to assess their diagnostic merits, but they are useful in research setting. Some of these scales depend on visual inspection of brain images (usually T2-weighted MRI) and rating of the white matter lesions in terms of size, number, location, and distribution. Visual rating scales include scales like Manolio, Fazekas, and Schmidt [100]. A study that examined the validity and inter-rater reliability of these scales demonstrated reasonable validity and reliability but gave Fazekas and Schmidt scales the edge over the Manolio scale, which is more global and less detailed [100]. Other methods have been developed that include automated and semiautomated segmentation of brain tissue to gray and white matter and delineation of white matter hyperintensities with a relatively high level of accuracy, but these methods tend to be applied in research settings [101].

White matter hyperintensities are seen in patients with Alzheimer disease, Lewy body disease, and frontotemporal lobar degeneration [26]. Hippocampal atrophy is associated with vascular cognitive impairment [102]. This adds to the challenge to the specificity of these lesions in diagnosing vascular NCD. The exact nature of white matter hyperintensities is still not clear but includes necrotic and non-necrotic lesions, as previously described in the neuropathology lesions section (see ▶ section Neuropathology Lesions).

D. Microhemorrhages. Fresh blood from large vessel rupture can be seen on CT scan, but asymptomatic microhemorrhages are not visible [103]. The best diagnostic tests to detect microhemorrhages are iron-sensitive MRI sequences, including gradient-echo T2 and susceptibility weighted image (SWI) [104]. What is being imaged are actually hemosiderin deposits around the affected vessels. SWI is the standard test in visualizing these lesions because it is the most sensitive tool detecting as small as 1 mm size lesions [105]. Causes for microhemorrhages include cerebral amyloid angiopathy and hypertension-induced changes [106]. ◘ Table 21.2 summarizes brain imaging correlates of vascular cognitive impairment lesions.

Teaching Point

Pathological lesions can be detected in vivo via brain imaging. There have been several imaging-pathological validation studies. Structural imaging (CT and MRI) both can detect clinical stroke (macroinfarct), but MRI (especially T2 FLAIR sequence) can detect smaller infarcts and infarcts adjacent to bone or cerebrospinal fluid. For microhemorrhages, imaging hemosiderin is important and two MRI sequences have been used: gradient-echo T2 and susceptibility weighted image (SWI), the latter having higher resolution.

Genetic Testing

Genetics plays a role in vascular neurocognitive disorders. Genetic testing is usually considered when there is suspicion of CADASIL, which is characterized by vascular smooth muscle defects and is caused by a mutation in the NOTCH 3 gene (previously discussed) [107]. Another cause of vascular lesions in the brain that can present with cognitive disorder after set of strokes and stroke-like events is a rare syndrome called mitochondrial myopathy encephalopathy, lactic acidosis, and stroke-like episodes (MELAS). This syndrome is usually caused by a mutation in mitochondrial DNA and can be diagnosed through clinical course, metabolic changes, and muscle biopsy in addition to genotype analysis [108].

Table 21.2 Summary of cerebrovascular lesions implicated in vascular neurocognitive impairment and their brain imaging correlates

Lesion	Imaging finding	Comment
Multi-infarct (macro)	Several strokes involving cortical areas	This is visualized on T1 and T2 MRI
Lacunar infarcts (macro)	Multiple and/or strategic lacunae in subcortical structures (gray and white matter). Strategic location: Frontal and parietal cognitive areas including angular gyrus Basal ganglia Thalamus Hippocampus	Can be seen on both T1 and T2 MRI T2 fluid-attenuated inversion recovery (FLAIR) is useful for lacunae adjacent to ventricles as it attenuates cerebrospinal fluid signal to make the lacunae more visible
White matter hyperintensities	Focal, multiple, or confluent opacities in periventricular, subcortical, or deep white matter areas	Can be necrotic due to microinfarcts or non-necrotic due to other pathologies (myelin changes, glial cell change, spongiosis). Amount and location can be rated for significance. Best visualized on T2 FLAIR
Microhemorrhages	Multiple small amount of blood or hemosiderin deposits in cortical or lobar locations (cortical-subcortical)	Due to hypertensive vessel changes or cerebral amyloid angiopathy, best visualized on susceptibility weighted image (SWI) or as a second choice gradient-echo MRI; both visualize hemosiderin deposits

21.1.6 Differential Diagnosis

Like other NCDs, one needs to consider cognitive impairment as a result of:

- Other major or mild NCDs: Alzheimer disease, frontotemporal lobar degeneration, and Parkinson-related NCD all have clinical overlap with vascular NCD.
- Medication- and substance-induced cognitive changes (e.g., alcohol, anticholinergic drugs).
- Cognitive changes due to general medical conditions, including metabolic disease (e.g., hypothyroidism, B_{12} deficiency), cardiac disease (e.g., heart failure with low cardiac output), respiratory disorders (e.g., uncorrected sleep apnea, chronic obstructive pulmonary disease), and infections (e.g., urinary, pulmonary, tertiary syphilis, Lyme disease, human immunodeficiency virus dementia complex). Abrupt onset of cognitive and behavioral changes from baseline in a patient with marked inattention and fluctuating course over the day are suggestive features of delirium.
- Normal pressure hydrocephalus can present similarly to periventricular white matter disease, with impaired gait, cognitive changes, and urinary incontinence. This triad will prompt brain imaging and a finding of out of proportion enlargement of the ventricles, however, with no significant white matter changes.
- Depression can be associated with stroke. It is very important to diagnose depression early as it is treatable, and treatment may improve cognitive function.
- Cerebral vasculitis may cause a progressive major NCD. Its course is usually faster than vascular NCD. It usually manifests with focal neurological signs and white matter changes.
- Multiple sclerosis can present with very similar picture to subcortical white matter vascular NCD. There are different subtypes of multiple sclerosis including relapsing-remitting course—with/without residual deficit—and primary and secondary progressive course, with/without superimposed acute episodes [109]. Clinical history and findings of neurological deficits may help in differentiating multiple sclerosis from vascular NCD, but in some cases further investigations are needed, including brain imaging and immune markers from cerebrospinal fluid. On brain imaging there are certain criteria that suggest multiple sclerosis. Those cases should meet three out of the following criteria [110]:
  1. One gadolinium-enhanced lesion or nine hyperintensity lesions on T2 if there is no gadolinium-enhancing lesion
  2. At least one infratentorial lesion
  3. At least one juxtacortical lesion
  4. At least three periventricular lesions

Teaching Point

Like other NCDs, vascular NCD needs to be differentiated from other causes of cognitive impairment (e.g., other major or mild NCDs, NCD due to another medical condition or substance use, delirium, and other psychiatric illnesses).

21.1.7 Treatment

The mainstay for the treatment of vascular NCD is prevention of further vascular lesions by controlling modifiable vascular risk factors. Other treatments target improvement of symptoms in areas of cognition, behavior, and function. This section will summarize recommendations from the AHA/ASA scientific statement [11]. The recommendations vary in

strength based on current evidence from clear recommendation, reasonable recommendation, to no recommendation. They classified the evidence as *Class I* where there is established benefit outweighing the risk, *Class IIa* where there is indication of benefit exceeding the risk but more studies are needed, *Class IIb* where benefit might outweigh or equals the risk and more studies are needed to clarify, and *Class III* where there is either no benefit or clear harm. Certainty was rated as Level A, B, or C based on the quality of the studies.

Lifestyle Modification

The AHA/ASA scientific statement considers reasonable to recommend smoking cessation (*Class IIa; Level A*), moderation in alcohol intake, weight control, and physical activities (*Class IIb; Level B*). Consideration of the use of antioxidants and vitamin B is not beneficial (*Class III; Level A*).

Physiological Risk Factor Modification

The AHA/ASA scientific statement definitively recommends treatment of hypertension (*Class I; Level A*) and considers it reasonable to recommend treatment of hyperglycemia (*Class IIb; Level C*) and hypercholesterolemia (*Class IIb; Level B*). There is a stated uncertainty around treatment of inflammation (*Class IIb; Level C).*

Treatment of Concomitant Clinical Vascular Disease

This includes coronary artery disease, stroke, chronic kidney disease (resulting in uremia and hypertension, both of which increase risk of cognitive decline), atrial fibrillation, peripheral arterial disease, and low cardiac output. Optimizing the treatment of these factors is recommended.

Modifying Symptoms with Pharmacological Interventions

Modest cognitive improvement has been shown with donepezil, galantamine, and memantine, although a positive impact on function is less clear, except in some cases of mixed Alzheimer and vascular NCD. The AHA/ASA stated that donepezil can be useful for cognitive enhancement in patients with vascular dementia (i.e., vascular major NCD) (*Class IIa; Level A*). Galantamine can be beneficial for patients with mixed Alzheimer and vascular NCD (*Class IIa; Level A*). The benefit of rivastigmine and memantine is not well established (*Class IIb; Level A*).

Some agents used in Europe and elsewhere but not in North America include pentoxifylline and, to a more limited extent, ergoloid mesylates (Hydergine). These agents may be useful for increasing cerebral blood flow. In the European Pentoxifylline Multi-Infarct Dementia Study, a double-blinded, placebo-controlled, multicenter study treatment with pentoxifylline was found to be beneficial for patients with multi-infarct NCD. Significant improvement was observed with pentoxifylline in the scales used for assessing cognitive function [111].

The potential for calcium channel blockers as neuroprotective agents due to controlling excessive calcium influx-related excitotoxicity has been studied. A small study using nimodipine showed a nonsignificant trend of benefit in subcortical white matter disease but not in multi-infarct dementia [112]. More recently, a Chinese group studied the combination of nimodipine with acupuncture in poststroke patients for cognitive improvement and found that the combination was significantly better than each treatment alone in improving MoCA scores and that acupuncture alone fared better than nimodipine alone [113].

It is important to note that with the high level of depression in the context of vascular neurocognitive impairment, the use of antidepressant is common. The use of antipsychotic medications for aggressive agitation is confounded by risk of mortality and morbidity including increased risk of stroke. The use of psychotropic medications in treating neuropsychiatric symptoms of NCDs is discussed in ► Chap. 22 in this textbook.

Non-pharmacological Interventions

There is a paucity of literature on the role of non-pharmacological interventions in vascular NCD. Most of the studies targeted Alzheimer disease with and without a vascular component. Evidence for cognitive rehabilitation remains inconclusive and needs to be studied further. The rule of acupuncture in enhancing cognition in animal models of vascular cognitive disorder is not yet confirmed in humans. Non-pharmacological interventions for psychological and behavioral symptoms arising in the context of vascular NCD are discussed in ► Chap. 22.

Primary Prevention

The AHA/ASA scientific statement addressed question related to preventing NCDs (including Alzheimer and vascular type) through lifestyle and risk factor treatment. The recommendations include lowering blood pressure in patients with stroke (*Class I; Level B*) and lowering blood pressure in middle-aged and younger-old-aged as being useful in preventing late-life dementia (*Class IIa; Level B*), but not for lowering blood pressure in older adults above age 80 (*Class IIb; Level B*). The usefulness of treating hyperglycemia and hyperlipidemia for prevention of dementia (major NCD) was uncertain (*Class IIb; Level C*). There was no evidence to support the benefit of antiplatelet therapy in the prevention of major NCDs, and therefore it is not recommended (*Class IIb; Level B*).

When it comes to lifestyle modification, a Mediterranean-type diet has been associated with less cognitive decline in several studies and is reasonable to recommend (*Class IIb; Level B*); vitamin supplements had no clear benefit on cognition even if they lowered homocysteine levels (*Class IIb; Level B*). It is reasonable to recommend physical activity as potentially useful in prevention of major NCD (*Class IIb; Level B*). ◘ Table 21.3 lists the risk factors, evidence-based recommendations regarding these factors, and potential for modifiability.

Table 21.3 List of risk factors for vascular neurocognitive disorders, recommendations from AHA/ASA scientific statement and modifiability

Risk factor	Recommendation	Comment
Demographics, ethnicity	Be aware of the risk, no recommendations	Unmodifiable
Education	Be aware of the risk, no recommendations	Unmodifiable, confounded by socioeconomic status
Lifestyle		
Diet		
Mediterranean diet	Reasonable to recommend for primary prevention (Class IIb; Level B)	Mainly from epidemiological data (fish, green leaves, nuts, olive oil, etc.)
Vitamins (including B_6, B_{12}, D, E, other antioxidants)	No evidence of benefit for primary or secondary prevention (both Class IIb; Level B)	Modifiable and relatively safe (except for cost) but no evidence of benefit
Smoking	Recommend smoking cessation for secondary prevention (Class IIa; Level A), likely the same for primary prevention, although not specifically done	Modifiable, challenging, and need significant support to implement
Alcohol intake	Reasonable to recommend moderation in intake for secondary prevention (Class IIb; Level B)	Modifiable, challenging, and need significant support to implement
Weight control	Reasonable to recommend for secondary prevention (Class IIb; Level B) likely the same for primary prevention, although not specifically done	Modifiable, challenging, and need significant support to implement
Physical activity	Reasonable to recommend for primary and secondary prevention (Class IIb; Level B)	Modifiable, challenging, and need significant support to implement
Physiological markers		
Hypertension	Definite recommendation to treat for secondary prevention (Class I; Level A), secondary prevention after stoke (Class I; Level B), reasonable as primary prevention in middle age and younger seniors (Class IIa; Level B) but not in age > 80 seniors (Class IIb; Level B)	Modifiable, definite adherence can be a challenge
Hyperglycemia	Reasonable to treat hyperglycemia for secondary prevention (Class IIb; Level C), uncertain benefit for primary prevention (Class IIb; Level C)	Modifiable, secondary prevention is reasonable, adherence can be a challenge
Hyperlipidemia	Reasonable to treat hyperglycemia for secondary prevention (Class IIb; Level B), uncertain benefit for primary prevention (Class IIb; Level C)	Modifiable, secondary prevention is reasonable, not clear if specific to cholesterol or include triglycerides, adherence can be a challenge
Anti-inflammatory	Uncertain	
Antiplatelets	Not recommended for primary prevention (Class IIb; Level B), but can be a treatment of concomitant clinical vascular disease	
Concomitant clinical vascular disease	Recommend optimizing treatment, no specific evidence recommendation	Includes coronary artery disease, stroke, chronic kidney disease, atrial fibrillation, peripheral vascular disease, and low cardiac output

Teaching Point

Treatment of vascular NCD follows the same principles of other NCDs: supporting the patient and family/caregivers, maintaining safety, and addressing any unmet needs of the patient. Prevention of further vascular lesions is a core component of treating this illness, and the evidence-based recommendations regarding modifying risk factors are discussed previously. Specific symptomatic treatment of vascular NCD is limited where some studies addressed cognition and some addressed behavioral symptoms.

21.2 Case Studies

The following case-based studies are reflective of the symptomatology of the clinical variants of major or mild vascular NCD and the intricate neuropathology and comorbidity that may present in such cases. For further review, other illustrative case examples are presented in ► Chap. 3.

21.2.1 Case 1

Case 1 History

Mrs. A., a 75-year-old woman, was referred by her primary care physician for a cognitive assessment. She was previously seen by geriatric medicine team along with her son one and a half year ago for mild cognitive changes. Since then, her family noticed further subtle cognitive changes over the previous year, which they reported as being mild and slowly progressive. The patient had become more repetitive, and she was relying more on notes to remember things. Her planning and problem-solving skills had changed requiring more help from her family, although she was still relatively independent in most of her tasks, including taking care of her household and basic financial affairs, and she continued to drive safely. She recognized that she had some cognitive challenges but thought that they were "normal for age." Her son reported that she had also developed increased anxiety around events and showed signs of depression and irritability. She now called her children more for help when faced with new instrumental tasks like preparing her tax returns.

Mrs. A. had no previous psychiatric or substance use history. There was no family history of diagnosed major NCDs.

Medical history included:

- Hypertension for many years, on antihypertensive medications.
- Osteoarthritis of right hip, with previous joint cortisone injection.
- Vaginal sanguineous discharge.
- Gastroesophageal reflux disease.
- Hypothyroidism.
- There was no history of traumatic brain injury or stroke.

Surgical history included:

- Childhood appendectomy
- Left breast carcinoma resected with total mastectomy 8 years previously, without chemotherapy, radiotherapy, or tamoxifen treatment
- Partial thyroidectomy for a benign goiter over 10 years previously

Mrs. A. lived a relatively healthy lifestyle, used wine occasionally, and never smoked tobacco, although her late husband was a smoker. Mrs. A. was a former schoolteacher with a teacher's college degree.

Her current medications were set up in a dosette box by her family and included rabeprazole, levothyroxine, metoprolol, hydrochlorothiazide, perindopril (started recently), enteric-coated small-dose aspirin, estrogen vaginal cream, and over-the-counter probiotics, lutein, vitamin D, and magnesium powder for bowel function. She had allergies to penicillin and celecoxib.

Functionally, Mrs. A. was independent in all her basic activities of daily living. Her family visited every 1–2 days. Regarding instrumental activities, Mrs. A. was managing her finances independently up until 1 year previously. Her friend helped setting her up with online banking. She was able to do online banking independently. She made no financial errors. She was still driving. One year prior, she hit a low post in a parking lot.

On examination, her weight was 137 pounds, and height was 5 foot 3 inches. She had an adequate hearing and corrected vision. Neurological exam was largely non-focal except for slight bradykinesia (right more than on the left side) and a subtle resting tremor on the right side, which was uncovered with distraction when she performed motor task with her left hand. She was unable to perform the Luria Hand Test with either hand. She could arise independently from a chair without the use of her arms. Romberg test was negative. She could perform tandem stance bilaterally. Her Timed Up and Go test (getting up from sitting, walk for 3 meters, turn around, walk back, and sit again) was 9 seconds (normal 10 seconds or below) [114].

Her blood pressure supine with rest was 198/80 mm Hg; heart rate was 47–50 beats per minute. At 2 minutes of standing, her blood pressure was 170/84 mm Hg, with a heart rate of 51 beats per minute. She had pitting edema to mid shin. She had a loud S1-S2 with no added sounds. She had a small vaginal prolapse with small amount of sanguineous discharge. Cognitive scores showed that MMSE was 26/30 while MoCA was 16/30.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. At this stage, what would be the differential diagnosis?

? Question 2. What is the most appropriate next step to clarify the diagnosis?

? Question 3. What is the differential diagnosis now, and what are the changes from initial impression?

? Question 4. What would be the most appropriate management plan?

Case 1 Answers

Case 1 Answer 1 (Question 1—At this stage, what would be the differential diagnosis?)

This is a case of insidious onset, slowly progressive NCD in an older adult female. As such, Alzheimer disease needs to be on top of the differential diagnostic list. On the other hand, having subtle neurological signs, history of hypertension that was in suboptimal control, and history of cancer required further workup to rule out other central nervous system pathology such as cerebrovascular disease and brain metastasis. Other differential diagnosis items could be

general medical conditions like infections (e.g., urinary tract infection), hypothyroidism (if not adequately corrected), electrolyte imbalance, and medication and substance effect, but all were lower on the list given that the patient was alert with no indication of delirium.

Case 1 Answer 2 (Question 2—What is the most appropriate next step to clarify the diagnosis?)

In addition to a general screening with chemistry, renal, liver, and thyroid function tests and other more targeted tests based on the patient's medical history, review of medication intake adherence, and assessment for inappropriate consumption of substances (like excessive alcohol or over-the-counter medications), the next step is brain imaging to rule out cerebrovascular disease and/or brain metastasis. In Mrs. A.'s case, an order for a clinical MRI was appropriate including using contrast to rule out metastasis but also use of susceptibility weighted image (SWI) sequence, which will allow for the detection of microbleeding.

Case 1 (Continued)

Six months later, Mrs. A. was seen again by the geriatrician because of changes in her mood and behavior. Family members had noticed that Mrs. A. was needing more cueing, often called her son about medication clarification (although she used a dosette system), and did not know what to do sometimes. She had also developed more anxiety.

MRI of brain scan obtained after the first assessment was reviewed and, although it did not show any evidence of metastatic disease, it did show punctate lesions on SWI indicating microhemorrhages with mild white matter hyperintensity. Mrs. A. was referred to geriatric psychiatry for increasing difficulty with anxiety, irritability, and agitation. (See Fig. 21.1 for MRI images in this case.)

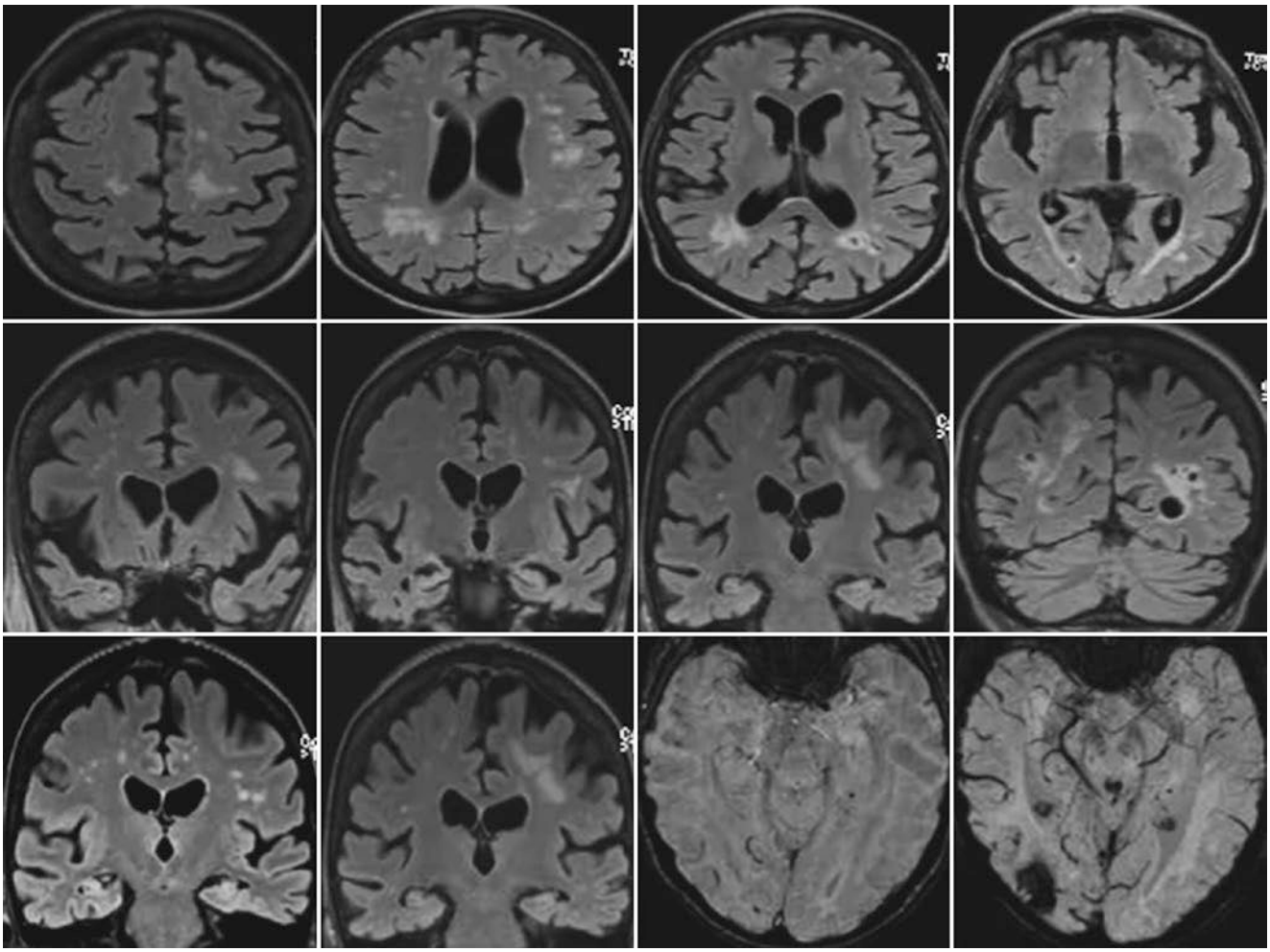

Fig. 21.1 MRI images from Case 1, upper panel: selected T2 FLAIR MRI images in transverse sections showing significant white matter hyperintensities in subcortical and deep white matter areas. Middle panel: selected T2 FLAIR MRI images in coronal sections also showing significant white matter hyperintensities in subcortical and deep white matter areas; some hippocampal volume loss is seen but difficult to confirm with visual examination alone. Lower panel: from left to right, two MRI T2 FLAIR images taken 1 year apart showing progression of white matter hyperintensities (the sections are approximately at the same level); the last two images show susceptibility weighted images (SWI) also 1 year apart showing new cortical bleeding in the latter image. The location of the bleeding suggests hypertensive microbleeding, although clinically the patient has been normotensive raising the possibility of amyloid angiopathy. Transverse and coronal images are displaced in radiological convention (left side of the image is right side of the patient)

A month later, she was seen in the geriatric psychiatry clinic. She had difficulty with her semantic memory, she had expressive aphasia and anxiety, and she expressed frustration. She was unable to drive any longer. Her MMSE at this visit (7 months after the initial assessment) was difficult to perform due to her anxiety and irritability, but with encouragement she eventually completed it and was scored at 17/30.

Case 1 Answer 3 (Question 3—What is the differential diagnosis now, and what are the changes from initial impression?)

At this stage, this case represents a rapidly progressive NCD. In general, illnesses like Alzheimer disease tend to be slowly progressive (approximately 3–4 points decline on MMSE annually). (See ▶ Chap. 18). In this case, MMSE score went down by 9 points in 7 months. Factors to consider in this case include a superimposed condition that could be a psychiatric, substance-related, or systemic medical illness. Details of the workup of a rapidly progressing NCD are beyond the scope of this chapter. The reader is referred to publications that provide guidance on how to work up a patient with this rapid course [115]. In this case, basic investigations including chemistry, metabolic screening (such as thyroid function and B_{12}), screening for infections, and screening for substance use including over-the-counter and herbal therapies were all negative. There was no indication of a seizure activity or delirium per se in this case. Due to the rapid decline, another MRI of the brain was ordered (8 months after her initial MRI). Findings now included new cortical bleeding that was most likely driven by high blood pressure, but with the possibility of amyloid angiopathy. In this case, vascular changes in the form of increasing white matter hyperintensity and spontaneous hemorrhages (exacerbated by hypertension) likely caused the rapid decline in her cognition. In this case, it is difficult to ascertain if there was any Alzheimer disease pathology at this point in time when significant vascular changes were prominent, but the course and the pattern of hippocampal atrophy now evidenced on her repeat MRI scan suggested a combined Alzheimer disease and vascular pathology.

Case 1 Answer 4 (Question 4—What would be the most appropriate management plan?)

General principles include supporting the patient, family, and caregivers and utilize non-pharmacological interventions to reduce anxiety and distress (e.g., reorientation, added functional support, safe activation, protection from harm, psychological support). Of great importance is psychoeducation and support to family and caregivers about the nature of the illness and prognosis and addressing issues with informed consent, substitute decision makers, placement, finances, and personal care decisions.

To modify the underlying illness, the clinicians should aim to control vascular risk factors but more urgently, as in this case, by controlling blood pressure, avoiding antiplatelet agents and other agents that may increase bleeding risk (e.g., aspirin, selective serotonin reuptake inhibitors), monitoring progression, and adding support as needed.

Case 1 Analysis In Mrs. A.'s case, the initial presentation was that of a typical neurodegenerative illness, such as Alzheimer disease, but because of vascular risk factors (hypertension with high blood pressure on examination), history of breast cancer, and subtle neurological findings, it was essential to rule out other brain processes, mainly cerebrovascular disease and brain metastasis. Initial brain imaging did show microbleeding suggesting an etiology of hypertensive and/or cerebral amyloid angiopathy. The patient's course became rapidly progressive with significant cognitive, functional, and behavioral deterioration within 6–8 months. A repeat MRI showed further bleeding likely from hypertension and/or amyloid angiopathy. The patient was diagnosed with rapidly progressive major NCD due to amyloid angiopathy. Susceptibility weighted image (SWI) would be helpful to show the bleeding. Finding evidence of atrophy involving hippocampal formation raised the possibility of Alzheimer disease pathology making this case a combined Alzheimer-related and vascular NCD with strong suggestion of a combination of hypertensive and cerebral amyloid angiopathy.

21.2.2 Case 2

Case 2 History

Mr. B., a 76-year-old man who lived with his wife of almost 50 years, was referred to you in the geriatric psychiatry clinic for clarification of his cognitive disorder and comment on prognosis. He was initially admitted to the hospital 6 months prior with an acute stroke. His stroke presented with word-finding difficulty, confusion, slurred speech, agitation, and aggressive behavior for a few days. The patient was known to have end-stage renal failure due to hypertension requiring hemodialysis. He had a 25-pound weight loss because of interruptions due to dialysis. When he was seen 1 month after his stroke by nephrology for his dialysis, he was becoming anxious, and his wife reported that he was becoming aggressive toward her and expressing thoughts that she was trying to kill him. Also, he made statements indicating wishing to die, but no suicidal behavior was noted otherwise. He had recently missed out on one of his dialysis appointments because of feeling confused about the dialysis dates; his confusion worsened and then improved after his next dialysis treatment. You learned that, as a result of his stroke, he was unable to drive any longer and his activity level had declined significantly. His medical and surgical history included:

- End-stage renal disease secondary to hypertension currently on hemodialysis
- Previous episodes of transient ischemic attacks, at least two over the previous 3 years
- Ischemic stroke 6 months prior, reportedly involving right occipital and temporal areas
- Neuropathic pain
- Restless leg syndrome
- Prostate cancer treated with transurethral resection of the prostate; no recurrence reported

He had no previous psychiatric history including no active substance use disorder. He did not use much alcohol but he had smoked many years ago. His father had multiple strokes and related memory impairment, but there was no history of other NCDs in the family. He was a former machinist, having worked for different companies, and had 10 years of formal education.

His current medications included small-dose enteric-coated aspirin, amitriptyline (25 mg for sleep), amlodipine, atorvastatin, furosemide, hydroxyzine, pantoprazole, tamsulosin, acetaminophen, diclofenac topical, docusate, lorazepam as needed for agitation (recently prescribed and used a few times with some sedating effect), levodopa-carbidopa (one tablet for restless legs at night), polyethylene glycol, and over-the-counter vitamins and natural health supplements. His medications on dialysis were dalteparin and Aranesp. He has no known drug allergies.

On a recent examination in the primary care physician office, Mr. B. had left homonymous hemianopsia with no other neurological symptoms. Vital signs included blood pressure 145/90 millimeter mercury and heart rate of 95 beats per minute. There were no respiratory abnormalities and heart sounds (S1, S2) were normal with no murmur. His MRI was reported as positive for white matter hyperintensity and a stroke in right occipital and temporoparietal lobe involving the angular gyrus, with some atrophy and white matter changes (see Fig. 21.2 for selected MRI images for this patient).

Mr. B. was scheduled to be seen by a geriatric psychiatry specialist based on a referral from his primary care physician for clarification of his cognitive disorder and prognosis, because the nephrology team and his wife were questioning the utility of continuing dialysis given that the patient had "advanced and progressive dementia." His current status was

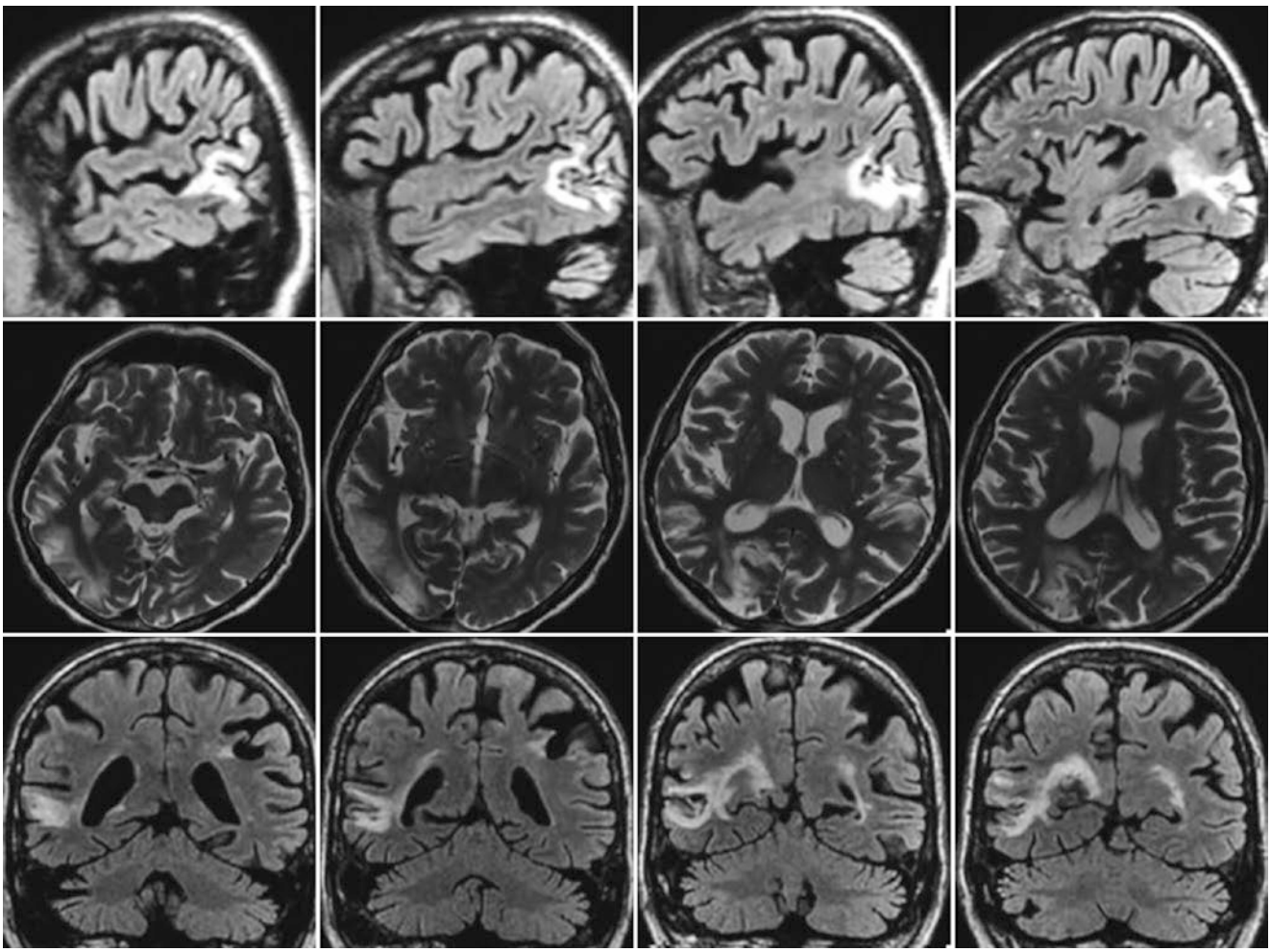

Fig. 21.2 MRI images from Case 2, upper panel: a set of T2 FLAIR images in sagittal sections showing the stroke involving posterior-inferior aspect of parietal lobe above the calcarine fissure, posterior aspect of superior and middle temporal lobe, and part of the occipital lobe; the angular gyrus is part of the inferior parietal lobule temporo-parietal junction and is affected in this case. Middle panel: same stroke demonstrated in T2 propeller images; notice the difficulty seeing the lesion adjacent to the ventricles due to cerebrospinal fluid white signal, which is removed in the FLAIR sequences in the top and lower panel. Lower panel: the same stroke demonstrated in T2 FLAIR coronal sections. The relationship to the calcarine sulcus is clearer in this section. Transverse and coronal images are displaced in radiological convention (left side of the image is the right side of the patient)

that he was more forgetful and wandered around the house without a clear purpose. His wife had noticed that he had been acting "very strange" since his stroke 6 months prior, repeating questions, and asking her to help him with things that were normally easy to perform for him. When you examined him in your office, his MoCA test now scored at 21/30. On executive functioning, he scored 1/5, and on spontaneous delayed recall, he scored 0/5, but he was able to recall all five words with a cue. All the other parameters such as naming, memory, attention, and language were normal. Geriatric Depression Scale (short version) was 6/15 indicative of some symptoms of depression, but Mr. B. did not think he was depressed. He had just noticed that he cried more easily.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What is the preferred diagnosis?

Question 2. What other diagnoses need to be considered?

Question 3. What would be the most appropriate management suggestion regarding the vascular NCD?

Question 4. What is the significance of stroke location in the major NCD in this case?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is the preferred diagnosis?)

Mr. B.'s likely diagnosis is probable major vascular NCD. This diagnosis is supported by evidence of cognitive change from the baseline that impacted function (making the diagnosis of a major NCD), evidence of cerebrovascular disease involving strategic cognitive area (angular gyrus), and a temporal relationship between the cerebrovascular disease and cognitive changes (according to DSM-5 diagnostic criteria).

Case 2 Answer 2 (Question 2—What other diagnoses need to be considered?)

A. Major NCD due to Alzheimer disease and mixed with cerebrovascular disease: this is an important consideration because we do not have a clear understanding of this patient's baseline. It is not uncommon for Alzheimer disease to have an insidious and slowly progressive course, and it is not usually detected in very early stages unless the patient has thorough cognitive testing. Furthermore, comorbidity between Alzheimer disease and cerebrovascular disease is common. This has important implication on prognosis, as it is more likely to see a steady decline in cognition and function with the Alzheimer disease component, whereas vascular NCD can stay stable if vascular risk factors are controlled. This is relevant in this case because the assumption of the patient having a neurodegenerative dementia (major NCD due to Alzheimer disease) led the nephrology team to suggest discontinuing dialysis.

B. Delirium: this is a possibility especially at the time when the patient had missed dialysis (e.g., uremia, electrolyte, and acid-base balance disturbance), medications (e.g., anticholinergic drugs like amitriptyline), any infections that he was vulnerable to develop, and acute brain process after stroke (e.g., edema, neuroinflammation).

C. Depression-induced cognitive changes: at this point this is unlikely given his depressive symptoms were relatively mild.

Case 2 Answer 3 (Question 3—What would be the most appropriate management suggestion regarding the vascular NCD?)

It is important to clarify the patient's diagnosis and the level of cognitive impairment to the primary care and nephrology teams. At this stage, this patient is in a relatively mild-to-moderate stage of neurocognitive disorder (he scored 21/30 on MoCA test), and he is functionally independent in his basic activities of daily living. He would likely score 4 (out of seven stages) on the Global Deterioration Scale [116]. Furthermore, at this stage his diagnosis is probable major vascular NCD. As such, he should continue to be offered options to treat his illnesses including dialysis. This is part of educating other medical professionals on the nature of the illness and its prognosis and advocating for the patient to get optimum level of care. It would be essential to control his vascular risk factors and follow optimum stroke prevention strategy according to clinical guidelines. Also, reducing the burden of medications, like amitriptyline and other centrally acting drugs with anticholinergic and depressant mechanisms, is essential. Based on the evidence to date, it is not clear whether cholinesterase inhibitors are indicated. Some guidelines do not recommend these agents in pure vascular major NCD, but if there is concurrent with Alzheimer disease component, these agents may be beneficial. For this case, reassessment of cognitive scores in 6 months to 1 year will allow us to rule in or out an Alzheimer disease process. There are differences in the choice of agents when it comes to decreased renal clearance, so that galantamine would likely be safer. However, for patients on dialysis, the use of cholinesterase inhibitors that are renal clearance dependent like rivastigmine and donepezil can be considered.

Case 2 Answer 4 (Question 4—What is the significance of stroke location in the major NCD in this case?)

The angular gyrus is involved in this case. This is an area of heteromodal association cortex with role in executive functioning. Left-sided lesions would have affected language, calculation, finger identification, and left-right orientation (Gerstmann syndrome) [117]. Right-sided (non-dominant) angular gyrus lesions also affect executive functioning but would not affect language and calculation. Other strategic areas for stroke include thalamus, basal ganglia, and medial frontal areas. A small stroke in these areas can result in major vascular NCD.

Case 2 Analysis This case involves an infarct in right posterior circulation affecting posterior temporal, inferior parietal, and occipital cortex. One of the areas involved is the angular gyrus which is important for cognitive processing. The patient had a complex medical comorbidity including renal failure needing dialysis, which was likely a complication from hypertension, but which also resulted in difficulty with blood pressure control. His presentation with confusion after his stroke and after missing dialysis was almost certainly due to delirium induced by brain injury, uremia, and electrolyte imbalance. This was interpreted as advanced dementia by his spouse and medical practitioners caring for him, with the suggestion to move him to a palliative care level by stopping his dialysis. Geriatric psychiatry assessment pointed out that the picture is suggestive of vascular cognitive impairment due to a "strategically located" stroke and that patient's cognitive course can be stable if further cerebrovascular lesions are prevented. There was a possibility that this patient was experiencing a combined Alzheimer and vascular NCD; this assumption would be appropriate if his cognitive course continued to decline progressively, independent from vascular and general medical events. The hippocampal areas were not particularly atrophic, which argued against the possibility of Alzheimer pathology. His cognitive profile with intact cued recall on the MoCA test also supported a vascular process.

21.3 Key Points: Major or Mild Vascular Neurocognitive Disorder

- Vascular neurocognitive disorders are common and can cause cognitive disorder independently or in combination with other pathology like Alzheimer disease.
- Reaching the diagnosis of vascular neurocognitive disorder requires the presence of neurocognitive disorder (major or mild) and cerebrovascular disease that is deemed causative to the cognitive disorder based on established clinical criteria.
- There are several subtypes of vascular neurocognitive disorders including multi-infarct, strategic infarcts, subcortical white matter disease, microhemorrhages, or a combination of the above.
- There are several risk factors that increase the risk for this illness; some are modifiable like vascular risk factors, but these risk factors also increase the risk of Alzheimer disease.
- Diagnosis is established through clinical data, but brain imaging is essential in confirming cerebrovascular lesions relevant to the cognitive disorder.
- The course of this illness tends to be slower than that of Alzheimer disease and can be modified by preventing further cerebrovascular events.
- Apart from modifying risk factors, there are relatively few studies that examined therapies to modify this illness directly, although some of the therapies used in Alzheimer disease may have a role in vascular neurocognitive disorder especially when there is a comorbidity of Alzheimer disease pathology.

21.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which one of the following areas is *not* considered strategic when it comes to vascular neurocognitive disorder?

A. Thalamus
B. Amygdala
C. Hippocampus
D. Anterior cingulate
E. Angular gyrus

Answer: B

Although the amygdala is part of the limbic system and is in close proximity to the hippocampus, it has not specifically been identified as a strategic cognitive structure; instead it is involved in emotional tagging of information and emotional processing.

MCQ 2. Gait abnormality can be a feature of all of the following neurocognitive disorders, *except*:

A. Normal pressure hydrocephalus
B. Corticobasal degeneration
C. Lewy body disease
D. Subcortical vascular neurocognitive disorder
E. Angular gyrus stroke-related neurocognitive disorder

Answer: E

The angular gyrus is not significantly involved in gait control.

MCQ 3. Current recommendations for treatment of vascular neurocognitive disorder include:

A. The use of an antiplatelet agent
B. The use of a selective serotonin reuptake inhibitor to prevent depression
C. The use of memantine to improve function
D. Treating hypertension

Answer: D

Treating hypertension is a firm recommendation in the context of vascular neurocognitive disorder. The use of antiplatelet agents is not routinely recommended and can be harmful in the context of cerebral amyloid angiopathy and uncontrolled hypertension. Although selective serotonin reuptake inhibitors can be used to treat depression in the context of vascular neurocognitive disorders, they are not indicated as prevention of depression in this context. There has been some evidence to support the use of these antidepressants in the prevention of depression after acute stroke and evidence of improved mortality, cognitive, and functional outcomes [118–120]. The evidence for memantine is limited, and at this time it is not recommended for the symptomatic treatment of vascular neurocognitive disorders.

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Neuropsychiatric Symptoms of Major or Mild Neurocognitive Disorders

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22.1 Background

22.1.1 Introduction

By 2050, it is estimated that more than 100 million people worldwide will have major neurocognitive disorders (NCDs) (formerly dementia) [1]. The management of these progressive diseases is often complicated by non-cognitive symptoms of major or mild NCDs such as neuropsychiatric symptoms (NPS).

According to the 5th edition of the *Diagnostic and Statistical Manual for Mental Disorders* (DSM-5) [2], diagnostic criteria for major or mild NCD (formerly dementia or mild cognitive disorder) include NPS [2]. The NPS are almost universally present during the course of NCD. The DSM-5 criteria limit NPS as "specifiers" such as psychotic features, agitation, disinhibition, hoarding, or mood disturbances [3]. In addition, they are used as "associated features supporting the diagnosis" [2].

Undetected, unmonitored, and untreated NPS have detrimental consequences on the disease course, management, and quality of life for people with NCDs and for caregivers and clinicians. Those with NCDs and untreated NPS have a poor quality of life and a more rapid progression of their disease and may be placed in structured living environments or institutionalized at an earlier time in the disease course [4–7]. Behavioral symptoms seen in NCD cases also cause dissatisfaction, burnout, and depression in informal and formal care providers [8, 9]. One reason for this is that patients with NCDs engage in more physical aggression if they suffer from delusions [10]. Delusional patients are also more restless, prone to wandering, and are often noisier than non-delusional patients [11]. NCD patients with delusions also require a significant amount of supervision, which leads to caregiver burnout and increases health-care costs [12, 13]. (See also ► Chap. 34.)

Teaching Point

Neuropsychiatric symptoms (NPS) occur during the course of nearly all NCDs, can cause the patient and caregiver substantial distress if untreated, and can lead to earlier institutionalization.

22.1.2 Definitions

Originally called behavioral and psychological symptoms of dementia (BPSD) [14], they are now more commonly referred to as neuropsychiatric symptoms (NPS) [15, 16]. Depending on the scales used to profile and measure NPS, there are several ways of clustering these symptoms. For example, they can be clustered into five major domains [17–19]:

- Depression: including neurovegetative signs/symptoms
- Agitation/aggression: excessive motor behavior and verbal or physical aggressive behavior, causing significant disability and not attributed solely to other psychiatric, medical, or substance-related illness [20]
- Apathy: lack of reactivity and initiative and blunted affect (as opposed to distressed/tearful affect as seen in depression) [21]
- Psychosis: delusions and/or hallucinations
- Sleep disturbances

The neuropsychiatric inventory (NPI) (described later in more detail) has items that can be clustered under:

- Psychotic symptoms (delusions, hallucinations)
- Affective symptoms (depression, irritability, anxiety, apathy)
- Hyperactivity symptoms (agitation, euphoria, disinhibition)

Using the Cohen-Mansfield Agitation Inventory (CMAI) (described later in more detail), agitation can be clustered into:

- Physical aggressive agitation
- Physical nonaggressive agitation
- Verbal aggressive agitation
- Verbal nonaggressive agitation

Most of the challenging behaviors in the context of NCD can fit within the above clusters although clinical presentations can involve a wide range of symptom combinations.

There are several validated scales that can screen for the various symptoms and behaviors of NPS and give account of the severity and related distress:

1. *The Neuropsychiatric Inventory (NPI).* The NPI was developed to screen for 12 common non-cognitive symptoms related to NCD. When a symptom is identified, it is rated on severity, frequency, and distress to the caregiver. The symptoms are delusions, hallucinations, agitation/aggression, depression/dysphoria, anxiety, apathy/indifference, euphoria/elation, disinhibition, irritability/lability, aberrant motor behavior, sleep/nighttime behaviors, and appetite/eating disturbances. There are several forms of this scale, including the NPI-questionnaire that is completed by a reliable informant (like a family member or care provider), which is commonly used in clinical studies [22, 23]. Scoring the NPI can be done in several ways depending on the forms used, but it is common to use the interaction of severity by frequency and distress to come up with a meaningful score on each item scored as positive. There are several versions of these scales including NPI-12 items, NPI-10 items, NPI-Nursing Home, NPI-Questionnaire, and NPI-Clinician Form. Some versions of this copyrighted test, originally developed in the English language, have been translated to several other languages. For access to more details about this scale, the reader is referred to the test website: ► http://npitest.net/index.html.
2. *The Cohen-Mansfield Agitation Inventory (CMAI).* The CMAI was developed to systematically profile "agitation" by screening for and rating the frequency of 29 items related to verbal and physical agitated behaviors [24].

Table 22.1 List of behaviors that can be reported under "agitation" according the Cohen-Mansfield Agitation Inventory (CMAI) [24]

Category of agitation	Behaviors
Physical aggressive behavior	Hitting Biting Kicking Pushing Grabbing onto people Scratching Spitting Making physical sexual advances Hurting self or others Throwing things Tearing things or destroying property
Physical nonaggressive behavior	Paces, aimless wondering Inappropriate dress or disrobing Trying to get to different places Hiding things Hoarding things Intentional falling Eating/drinking inappropriate substances Handling things inappropriately Performing repetitious mannerisms General restlessness
Verbal aggressive behavior	Screaming Making verbal sexual advances Cursing or verbal aggression
Verbal nonaggressive behavior	Repetitive sentences or questions Strange noises (like weird laughter or crying) Complaining Negativism Constant unwarranted request for attention or help

Note: Practitioners need to be specific on what behavior is being targeted with intervention and level of distress/harm that the behavior is causing

Items include 11 physically aggressive behaviors (e.g., hitting self or others, kicking, grabbing, pushing, throwing things, biting, spitting, scratching, hurting self or others, destroying things, physical sexual advances), three verbal aggressive behaviors (e.g., screaming at others, making inappropriate sexual advances, cursing), ten physical nonaggressive behaviors (e.g., pacing/aimless wondering, intentional falling, general restlessness, exit seeking/trying to leave, eating or drinking inappropriate items, handling things inappropriately, hiding things, hoarding things, repetitive mannerisms, inappropriate dressing or disrobing), and five verbal nonaggressive behaviors (e.g., repetitive questions or sentences, complaining, negative statements, strange noises/vocalization, constant unwarranted requests for attention) (see Table 22.1). These behaviors are usually rated by care providers based on the frequency of occurrence from 1 (never) to 7 (several times per hour). The CMAI was validated in long-term care (nursing home) settings and was found to have good internal consistency and reliability. Inter-rater reliability was modest, which is a limitation for most rating scales [25].

3. *The Behavioral Pathology in Alzheimer's Disease (BEHAVE-AD).* This scale in its original form is based on information obtained from the caregiver and other informants and covers several areas including paranoid and delusional ideation, hallucinations, activity disturbance, aggressiveness, diurnal rhythm disturbance, affective disturbance, anxiety, and phobias [26]. The empirical BEHAVE-AD (E-BEHAVE-AD) is a validated clinician interview that includes 12 items rated from 0 to 3 yielding a total score between 0 and 36 [27].
4. *The Neurobehavioral Rating Scale (NBRS).* The NBRS is a multidimensional 27-item scale, rated by the observer with each item given a score of 0–7. This scale measures behavioral challenges encountered in neurobehavioral disorders like traumatic brain injuries and NCD due to Alzheimer disease and vascular disease [28–30].
5. *Scales that assess depression and apathy in NCDs.* It is often difficult to distinguish between depression and apathy in NCD. Both of these symptoms are common, but also can be overlapping [31]. The Cornell Scale for Depression in Dementia (CSDD) is based on information obtained from both patient and informant and rates 19 items from 0 to 2. It includes items that cover mood, behavioral, and physical changes that can indicate depression in addition to diurnal variation and negative statements [32]. The Apathy Evaluation Scale has been developed to facilitate distinguishing apathy states, with a lack of concern and reactivity from depressive disorders, where there is dysphoric/tearful affect and obsessive rumination on depressive themes [21]. Several versions of the scale have been developed including those completed by the patient, informant, and clinician. A shorter version was developed and validated for the long-term care setting for patients with NCD [33].

All the scales mentioned previously cover a wide range of NPS commonly presenting in NCDs, and the choice among different scales depends on the specific goal of the examiner and the feasibility of scale application. A study by Ismail et al. compared the performance of E-BEHAVE-AD, NBRS, and NPI in quantifying improvement of agitation and psychosis associated with NCD [34]. They reported that these scales have significant similarity in performance, but some differences in sensitivity and specificity related to cutoff scores on target symptoms in clinical trials. For example, the E-BEHAVE-AD performed best at a cutoff point of 30% reduction in target behavioral symptoms from baseline (sensitivity 0.79, specificity 0.73), while both the NBRS and NPI performed best at cutoff point of 50% reduction in target behavioral symptoms (sensitivity 0.89, specificity 0.85 for NBRS, and 0.86 and 0.76 for NPI, respectively). Furthermore,

the NPI was the most likely to classify improvement in agitation followed by the NBRS then the E-BEHAVE-AD. All three scales were equally likely to classify improvement in psychosis [34]. Another scale that measures behavioral disturbances in NCD is the Behavioral Syndromes Scale for Dementia (BSSD) [35].

One approach that is quite feasible and provides thorough information to aid in identifying target symptoms is to combine complementary scales; e.g., the NPI initially, and when agitation is identified, follows with the CMAI. The specific items identified on CMAI can then be monitored using tools like the Dementia Observation System (DOS) tool, which will allow individualizing symptoms and identify behavioral frequency prospectively. The DOS can be accessed from: ► https://www.interiorhealth.ca/sites/Partners/SeniorsCare/DementiaPathway/MiddleDementiaPhase/Documents/DementiaObservntlSysmDOSTool.pdf.

Teaching Point

Health-care personnel widely use the term "agitation" when referring to a distressing behavior in a patient with a NCD, and it is not uncommon for an on-call psychiatrist, geriatrician, or primary care physician to receive calls from hospital nurses, assisted living facilities, and nursing homes requesting a medication to treat "agitation." Regardless of the screening instrument used, it is critical for the clinician to ask the caregiver to specifically describe the behavior. It is important to bear in mind that what is considered "agitation" varies with the caregiver, the circumstance, and how the behavior is interpreted.

22.1.3 Epidemiology

Most of the studies on the epidemiology of NPS in NCD have focused on NCD due to Alzheimer disease, although some studies addressed differential prevalence among types of NCDs. In this section we will summarize key findings of the literature on the epidemiology of NPS in both Alzheimer- and non-Alzheimer-related NCD.

Prevalence of NPS in NCD Due to Alzheimer Disease

Up to 80–97% of patients with NCD due to Alzheimer disease suffer from NPS at some point during the progression of the disease [36]. Most of the studies used rating scales completed with caregivers such as the NPI and BEHAVE-AD (see full description of these scales in ► Sect. 22.1.2). Published data on the prevalence of NPS in NCD due to Alzheimer disease are conflicting, but a 2015 meta-analysis found that NPS prevalence was influenced by the disease duration, stage, age, educational level, country of origin, and severity of cognitive impairment [37]. By analyzing high-quality studies, the pooled prevalence of aggression was 40%, disinhibition 17%, irritability 36%, euphoria 7%, delusions 31%, hallucination 16%, sleep disorders 39%, depression 42%, anxiety 39%, apathy 49%, and appetite disorders 34% (see Table 22.2) [37]. It was noted that the prevalence of NPS varied widely across studies, though the most frequent NPS in Alzheimer disease-related NCD were apathy, depression, aggression, anxiety, and sleep disturbances and the least frequently reported NPS was euphoria.

Table 22.2 Prevalence of neuropsychiatric symptoms in neurocognitive disorder due to Alzheimer disease [37]

Neuropsychiatric symptoms	Prevalence (%)
Apathy	49
Depression	42
Aggression	40
Sleep disturbances	39
Anxiety	39
Irritability	36
Appetite disturbances	34
Delusions	31
Disinhibition	17
Hallucinations	16
Euphoria	7

Prevalence of NPS in NCD Due to Alzheimer Disease Across the Types of NPS and Severity Spectrum

Aalten et al. categorized subtypes of NPS in almost 200 patients living in the community with NCDs. Of the three most common subtypes, mood/apathy was the most common NPS, occurring in almost 80% of the patients; next was hyperactivity at 60%, followed by psychosis at 37% [38].

Steinberg et al. looked at the 5-year period prevalence of NPS in a sample of 408 participants diagnosed with incident NCD and provided a longitudinal perspective on NPS in this community-based sample [39]. Five-year period prevalence was greatest for depression (77%), apathy (71%), and anxiety (62%) and lowest for disinhibition (31%) and elation (6%).

In patients with mild NCD (formerly mild cognitive impairment, MCI), which is considered a risk state for Alzheimer disease, 43% exhibited NPS in a 30-day period, with depression (20%), apathy (15%), and irritability (15%) being the most prevalent [40]. In the same study, patients meeting diagnostic criteria for major NCD (formerly dementia) had apathy (36%), depression (32%), and agitation/aggression (30%) as the most prevalent NPS, with 75% of the individuals in the study having at least one NPS in a 30-day period [40].

A study by Chen et al. investigated the prevalence of different NPS using the BEHAVE-AD scale (see description in

▶ Sect. 22.1.2) across the spectrum of severity of NCD (mainly due to Alzheimer disease) as classified based on the Clinical Dementia Rating (CDR) Scale. This study reported a higher prevalence of affective symptoms in very mild/mild (CDR = 0.5–1) and moderate (CDR = 2) NCD due to Alzheimer disease (62% and 60%, respectively), compared to severe (CDR = 3) and terminal (CDR = 4–5) stages of NCD due to Alzheimer disease (37% and 13%, respectively). Anxiety symptoms were also more common in the CDR very mild/mild and moderate NCD due to Alzheimer disease (69 and 66%, respectively) relative to CDR severe and terminal stages of NCD due to Alzheimer disease (58 and 13%, respectively). Aggression was common across the spectrum but with a nonsignificant trend to be higher later in the illness (a peak in terminal stages of NCD at 75%). A similar trend was found for delusions, which peaked in the severe stage of NCD (82%). Sleep disturbance was more common in moderate to severe stages of the illness (55 and 40%, respectively). A similar pattern was seen with hallucinations, which was also more common in moderate and severe stages of the illness (36 and 47%, respectively). Disturbances in activities (wandering or purposeless and inappropriate activities) were common across the spectrum but peaked in moderate and severe stages of NCD (94 and 95%, respectively) [41].

Prevalence of NPS in NCD Due to Alzheimer Disease in Different Settings

Differences in prevalence of NPS across settings could be driven by several factors, including the stage of NCD (severity of cognitive impairment), environmental factors (e.g., crowding, noise), caregiver factors (e.g., staffing ratio, staff training), as well as the differential willingness of facilities to accept patients with NPS. In community samples, reported prevalences have ranged from 61% to 88% [8]. The median prevalence of any NPS in long-term care settings (i.e., nursing homes) is 78% [42] although some studies reported a prevalence of any BEHAVE-AD symptoms to be as high as 92%, with aggression having the highest prevalence at 77% [43].

Prevalence of NPS in Non-Alzheimer Disease-Related NCD

In a large study involving 329 community residents with major NCDs (214 had NCD due to Alzheimer disease, 62 had vascular NCD, and 53 had other forms of NCD), only modest differences were observed in the prevalence of psychological or behavioral disturbances across different types of NCDs or at different stages of illness: participants with NCD due to Alzheimer disease were more likely to have delusions and less likely to have depression. Agitation/aggression and aberrant motor behavior were more common in participants with advanced major NCD [44].

Differences in NPS prevalence among different types of NCDs tend to become less significant when comparing patients at comparable levels of severity. In one study, the prevalence of behaviors like delusions, hallucinations, euphoria, and disinhibition varied among NCD due to Alzheimer disease, frontotemporal NCD, and vascular NCD, whereas agitation, apathy, and irritability had comparable, high prevalences across NCD types (> 90%) [45]. Kazui and colleagues collected NPI data on 2447 patients with NCD in Japan and stratified frequency, severity, and caregiver burden by stage and NCD type (NCD due to Alzheimer disease, frontotemporal NCD, vascular NCD, and NCD with Lewy bodies). They showed that within each level of severity, measured by the CDR scale, the prevalence of individual NPS varied by type of NCD [46]. Based on their data, the frequency of agitation, hallucination, and depression at early and late stages is illustrated for the four types of NCDs (◘ Fig. 22.1a–c).

Prevalence of NPS in Vascular NCD

Patients with different subtypes of vascular NCD were evaluated using the NPI to assess neuropsychiatric symptoms [47]. Neuropsychiatric symptoms were common in patients with vascular NCD across the cognitive deficit spectrum from mild to major NCD. Sleep disturbance was the most common symptom in all patient groups. Apathy was significantly lower in mild vascular NCD compared with major vascular NCD. Patients with major vascular NCD had the highest mean NPI scores [47]. Others have investigated the prevalence of NPS in vascular NCD comparing severity and relative frequency of symptoms between small-vessel vascular NCD and large-vessel vascular NCD [48]. NPS were reported in 92% of the vascular NCD patients, with a median number of 3 symptoms per patient. Apathy (65%) was the most prevalent, followed by depressive symptoms (45%), irritability (42%), and agitation/aggression (40%). Patients with small-vessel and large-vessel vascular NCD demonstrate different profiles of symptoms, with relatively more apathy in small-vessel vascular NCD and relatively more agitation/aggression in large-vessel vascular NCD [48].

Studies comparing vascular NCD to Alzheimer disease-related NCD have yielded variable results. Some studies reported that patients with vascular NCD had more severe behavioral retardation, depression, and anxiety than those with NCD due to Alzheimer disease with similar severity of cognitive impairment [29]. Other studies made a distinction between cortical vs. subcortical vascular NCD when it comes to prevalence of NPS compared to Alzheimer disease. Fuh et al. reported that patients with cortical vascular NCD had the highest composite score on the NPI compared to both Alzheimer disease and subcortical vascular NCD. Patients with Alzheimer disease-related NCD and subcortical vascular NCD were comparable in NPS profile, while those with cortical vascular NCD had more apathy and sleep disturbance [49].

In the nursing home setting, individuals with vascular NCD had a higher prevalence of depression, irritability, and appetite changes than those with NCD due to Alzheimer disease. The individuals with NCD due to Alzheimer disease had more euphoria and nighttime behavior disturbance than those with vascular NCD [50].

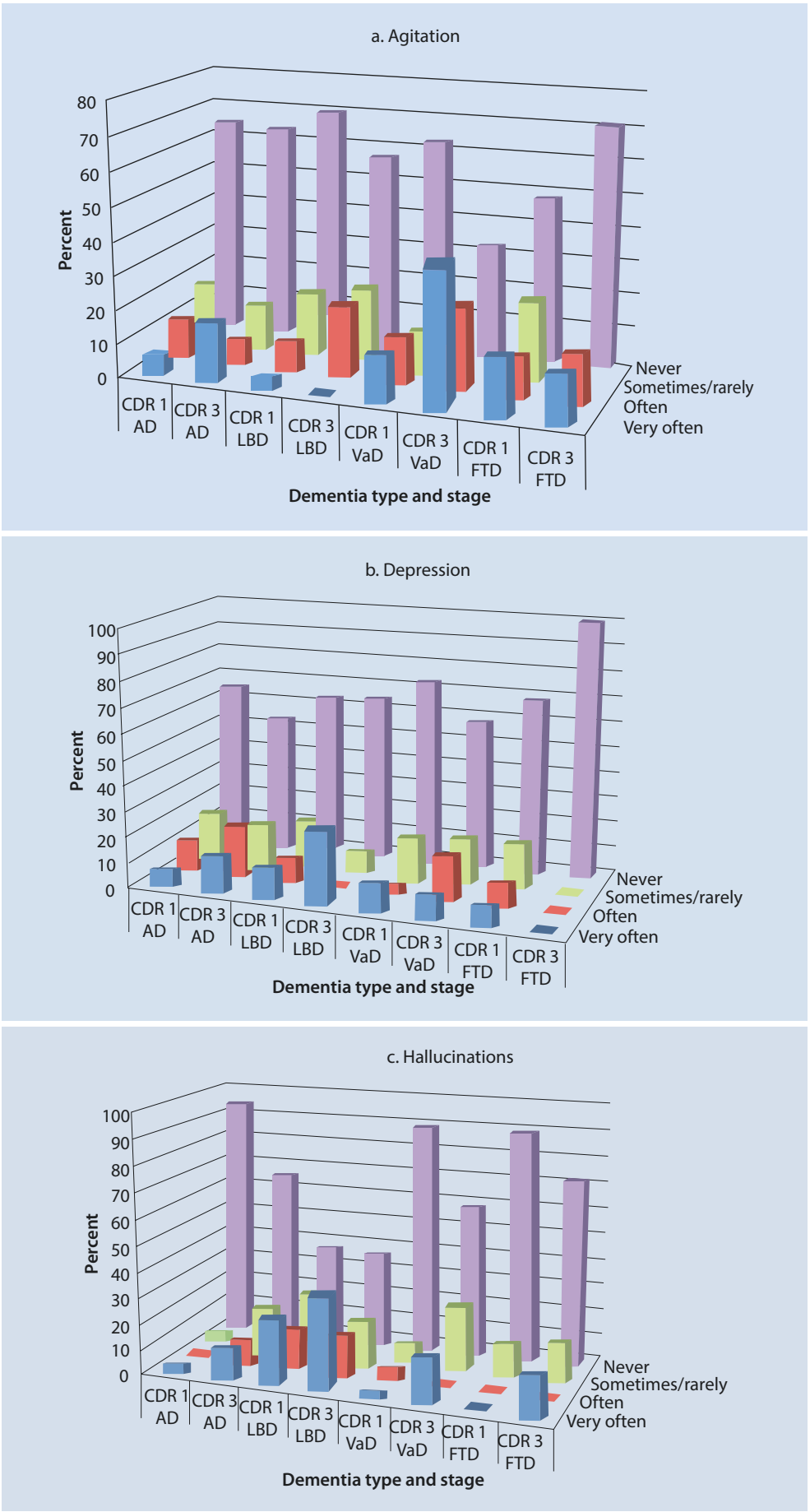

Fig. 22.1 Frequency of selected neuropsychiatric behaviors by type and stage of neurocognitive disorder (dementia). Based on data abstracted from Kazui et al. [46]. *Panel* **a**: agitation. *Panel* **b**: depression. *Panel* **c**: hallucinations

Prevalence of NPS in NCD Due to Parkinson Disease and Lewy Body Disease

Caputo et al. [51] profiled NPS (using NPI scores) of hundreds of older adults with NCDs by comparing vascular NCD with NCD with Lewy bodies and NCD due to Alzheimer disease. Vascular NCD had lower total and domain-specific NPI scores and a lower frequency of NPS than both NCD due to Alzheimer disease and Lewy body disease. The frequency of NPS increased with disease severity in Alzheimer disease and, to a lesser extent, in Lewy body disease [51]. In a recent retrospective case-control study, clinical data revealed that NPS in NCD due to Parkinson disease occurred at a higher frequency than in NCD due to Alzheimer disease or Lewy body disease, with a lower NPI total score than the Lewy body disease group [52]. It should be noted that hallucinations, primarily visual, during the early stages of NCD with Lewy bodies represent a defining characteristic of this disorder. (See ▶ Chap. 20.) However, one or more NPS of major NCD were reported in more than 90% of the individuals, regardless of the type of NCD. The Alzheimer disease group had a lower frequency of delusions, hallucinations, agitation, anxiety, irritation, and aberrant motor behavior compared to the Lewy body disease group. In addition, the most severe NPS were associated with a younger age, more advanced stage of illness, and a diagnosis of NCD with Lewy bodies [52]. Others have found that patients with NCD with Lewy bodies present with psychosis, including hallucinations, at a higher rate than patients with NCD due to Alzheimer disease [53, 54]. Hallucinations are also more common in NCD with Lewy bodies compared to those with NCD due to Parkinson disease [55].

Prevalence of NPS in Frontotemporal NCD

This illness is discussed further in ▶ Chap. 19. Frontotemporal NCD affects up to 20% of patients presenting with major NCDs [56] and is found to be most prevalent in individuals with major NCD below 60 years of age [57]. Of the two clinical categories of frontotemporal NCD (primary progressive aphasia and behavioral variant frontotemporal NCD), NPS manifestation is early in behavioral variant frontotemporal NCD and may occur in isolation or in addition to executive dysfunction [58]. The illness presents with significant changes in personality and behavior early in the illness. Different symptoms of aphasia occur early in primary progressive aphasia and remain most prominent over the course of illness [59].

Studies that examined differences in NPS between NCD due to Alzheimer disease and frontotemporal NCD point to higher NPS for the stage of the illness (i.e., earlier in frontotemporal NCD), higher rate of delusions, disinhibition, and abnormal motor behavior [45]. Caregiver reports of early personality change, unconcern, and inappropriate behavior reliably distinguished frontotemporal NCD from NCD due to Alzheimer disease [60]. Using the NPI, patients with frontotemporal NCD had total scores higher than NCD due to Alzheimer disease and illustrated more apathy, disinhibition, euphoria, anxiety, and aberrant motor behaviors [61]. Apathy, disinhibition, and compulsive and repetitive behavior appear to be common in frontotemporal NCD, whereas mood changes are more rare [58].

Teaching Point

Neuropsychiatric symptoms (NPS) occur in nearly all patients with NCDs during the course of the illness, regardless of type. However, the frequency of the individual NPS appears to vary both by the type and stage of NCD. Variation in the frequencies of NPS across studies may be due to selection bias, differences in diagnostic accuracy or criteria, and the instrument(s) used to identify and classify NPS.

22.1.4 Etiology and Mechanism

The underlying mechanisms of NPS are not well understood, which makes developing specific interventions challenging. In this section we will briefly discuss possible mechanisms involved.

Non-Disease-Specific Factors

A useful conceptual framework to understand the generation and maintenance of NPS of NCD incorporates three elements:

1. *Unmet needs of the patient:* patients with more advanced NCD may have difficulty expressing their medical and physiological needs (e.g., pain, need to void, hunger, thirst) and psychosocial needs (e.g., boredom, loneliness, fear, anxiety). In care facilities, busy or poorly trained staff may overlook these needs. The result is that the patient's unmet needs may manifest as behavioral disturbances [62].
2. *Lower stress tolerance threshold:* e.g., due to loss of executive skills, the patient is less likely to tolerate stress and emotional signals [63].
3. *Learned behavior:* this refers to classic behavioral conditioning, for example, a behavior can be inadvertently enforced if the consequences reward the behavior (e.g., screaming in the dining room results in getting meals in bed, which reinforces screaming in the dining room) [64].

Beyond neuropathological characteristics and trajectories of NCDs, each patient is unique with his/her own baseline temperament and coping skills, biography, and distinct health needs, and this person exists in and responds to a unique social environment in which the individual and the caregivers have their own perceptions, values, and often shared histories that can influence the nature of interactions and contribute to the generation of behavioral symptoms [65].

Disease-Specific Factors

Here we summarize some of the neurobiological factors in NPS identified through several lines of investigations.

Neurochemical Changes

Underlying neurochemical changes have been investigated from several angles including neuropathological studies (post-mortem), genetic polymorphism, probing central neurotransmitters, and neuroimaging.

There is evidence that abnormalities within the serotonergic system contribute to behavioral symptoms in patients with Alzheimer disease. Neuropathological (postmortem) studies have looked at changes in brain structure and chemistry in patients with confirmed NCD due to Alzheimer disease. Evidence of serotonergic neuron loss has been demonstrated in the brain stem of patients with Alzheimer disease [66–68]. Involvement of the serotonergic system has been further implicated in NPS through other lines of evidence related to genetic polymorphisms. Polymorphism in the 5-HT transporter gene was associated with behavioral symptoms of NCD due to Alzheimer disease, including agitation/aggression and psychosis in some studies [69–71] but not in others [72–74]. Serotonergic receptor polymorphism, mainly 5-HT_{2A}, has been associated with agitation/aggression and psychosis in Alzheimer disease in some studies [72, 73]. The association between 5-HT2A and 5-HT2C with depressive disorder in Alzheimer disease was reported in one study [75], but another study did not find an association between 5-HT2A or 5-HT transporter polymorphism and depression in NCD due to Alzheimer disease [76]. Other serotonergic receptors including 5-HT1A, 5-HT1B, 5-HT1D, and 5-HT6 have also been implicated in behavioral symptoms of Alzheimer disease [77, 78].

The involvement of central serotonergic neurotransmission in agitation/aggression and psychosis has important implications for pharmacological interventions and opened the door for selective serotonin reuptake inhibitors (SSRIs) as agents to treat these symptoms [79–81]. A relationship between cholinergic deficit and serotonergic transmission was reported in a study that showed association between acetylcholine deficit and aggressiveness in Alzheimer disease [82]. The fact that abnormalities in the serotonergic system play a role in agitation/aggression and psychosis in Alzheimer disease is also supported by the efficacy of SSRIs in reducing these symptoms in clinical trials (see ► section Pharmacological Interventions for NPS in NCD).

A smaller set of research studies has implicated norepinephrine in the behavioral symptoms of NCD due to Alzheimer disease [83, 84]. The role of dopamine in agitation/aggression of frontotemporal NCD was reported in one study [85], and reduction in striatal D2 receptors was reported in NPS of Alzheimer disease in another study [86]. Glutamate/GABA imbalance has also been linked to behavioral disturbances in Alzheimer disease in general [87] and to depression in Alzheimer disease specifically [88].

Neuroimaging Evidence of Network Involvement in NPS of NCD

The explosion of neuroimaging literature in NCD and initiatives like the Alzheimer Disease Neuroimaging Initiative (ADNI) have offered the opportunity to examine correlates of cognitive and non-cognitive symptoms of NCD due to Alzheimer disease and related disorders [89, 90]. Disruption of large-scale neural networks including the salient network and central-executive networks can be seen in relation to NPS. (For a review of brain networks and other neuroimaging correlates, please refer to ► Chap. 3.) For example, delusions in Alzheimer disease have been associated with gray matter atrophy in the anterior insula [91, 92] and the anterior cingulate cortex [93], both of which are part of the salient network. Delusions also have been associated with abnormalities in the frontal and parietal cortices, areas that represent the central-executive network [93, 94]. A systematic review pointed to the association of paranoid delusions in NCD due to Alzheimer disease with right frontal areas, while misidentification delusions have been linked to temporal-area abnormalities [95]. Hallucinations have been associated with right anterior insula abnormalities in addition to bilateral prefrontal areas [96]. Supramarginal region thinning was predictive of hallucinations in another study [97]. Agitation has been associated with abnormalities in salient network structures, including anterior insula, anterior cingulate, and their connectivity with the prefrontal cortex [94, 98, 99]. Deficits in blood flow and metabolism of prefrontal areas have been reported in patients with Alzheimer disease and depressive symptoms [100–104]. On the other hand, apathy in Alzheimer disease has been associated with gray matter atrophy in the left and right anterior cingulate cortex [94], hypoperfusion in the left anterior cingulate cortex and right orbitofrontal area, relative hyperperfusion in the hippocampi and temporal areas [87], and hypometabolism in the left orbitofrontal area [104].

Efforts are underway to define the different pathological factors leading to the disruption of brain structure and circuitry in NPS. For example, an amyloid PET study using the Pittsburgh compound B (PiB) of patients with subcortical vascular NCD found that both vascular changes and amyloid burden had comparable associations with NPS [105]. Murray et al. showed that Alzheimer disease patients with psychosis tended to have higher phosphorylated tau burden at autopsy compared to those without psychosis [106]. Although the latter was a neuropathological study, ligands to image phosphorylated tau are under development and can expand this work to in vivo brain imaging. Although structural and functional brain imaging continues to inform our understanding of cognitive and emotional processing in NCD, there are several limitations to this literature related to clinical definition, differences in imaging methodology used, and the cross-sectional nature of the majority of these studies. There is a need for standardization of imaging protocols and the use of multimodal (or hybrid) imaging and longitudinal design to allow mapping of the course of NPS in different NCDs [107].

Teaching Points

- Growing evidence implicates an imbalance of neurotransmitters, especially serotonin, in the pathophysiology of the NPS of NCD.

- Neuroimaging studies have been able to map types of behavioral symptoms to specific regions of the brain and link them to abnormalities of cerebral blood flow and metabolism.
- Using neuroimaging techniques, the burden of vascular changes and amyloid have been associated with NPS in vascular NCD, while in NCD due to Alzheimer disease, the burden of phosphorylated tau has been linked to psychosis.

22.1.5 Clinical Description

A Framework for the Assessment of NPS in NCD

The Physician Consortium for Performance Improvement has recommended that those with NCD be assessed at least annually by a physician for the occurrence of NPS with reliable instruments and psychometrically sound measures of NPS [108].

Because of the complexity of these symptoms and the multitude of factors that can contribute to their development and maintenance, it is essential for practitioners to use a framework to allow a comprehensive and systematic approach taking into account all possible factors operating in the specific case being assessed. Several models have been developed to do just that. It is likely that the patient's behavior comes from the interplay of the underlying illness and a combination of unmet needs, low stress tolerance, and learned behavior [64]. A care plan to address unmet needs of the patient that takes into account his/her individual physical, sensory, and cognitive characteristics and lifelong habits and roles has been shown to be more effective than care as usual [109]. A validated and practical model that was developed to facilitate a systematic approach to behavioral challenge stemming from NCD is the "DICE" model (see Table 22.3) [110]. In this model, an individualized assessment and management plan within a collaborative interprofessional framework that includes the patient and family is developed and evaluated [110, 111]. The DICE approach includes the following sequential steps:

1. Describe: to define the behavior through detailed inquiry with patient and caregivers (family and professional). Identify the specific behavior, any antecedents, which aspect is the most distressing or impose harm, and the consequences of the behavior (perceived and actual). To do this reliably, it is advisable to use standardized tools to identify specific symptoms and have a common language between practitioners and caregivers.
2. Investigate: to identify factors that might be contributing to the behavior identified, including:
    1. Patient factors:
        1. Unmet needs, e.g., lack of adequate sleep, hunger, toileting needs, fear as a result of confusion about the environment, and others
        2. Acute medical illness, e.g., infections, dehydration, depressive disorder, and medication side effects
        3. Sensory deficit: visual impairment (e.g., need for vision correction, surgical treatment of cataracts) and hearing impairment (e.g., assess need for hearing aids, speak to patient slowly, loudly, and clearly)
    2. Caregiver:
        1. Distress/burnout/depression
        2. Lack of knowledge/skills, inappropriate expectations for level of cognitive impairment
        3. Communication issue
    3. Environment:
        1. Level of stimulation and noise (e.g., high, low)
        2. Safety (e.g., access to sharp objects, risk of falls)
        3. Level of activity available
        4. Routines and structure available
3. Create a collaborative plan: to address the underlying causes and the behaviors.
    1. Non-pharmacological plan: all guidelines recommend using non-pharmacological interventions geared to address unmet needs of the patient and caregiver and environmental factors before using pharmacological agents except in some circumstances (see ► section Non-pharmacological Interventions for NPS of NCD for review of non-pharmacological interventions).
    2. Pharmacological plan: when there is a diagnosable additional comorbid psychiatric illness like major depressive disorder in the moderate to severe range, and/or when there are distressing psychotic symptoms or when aggression can potentially result in harm to patient or others, psychotropic drugs can be used to specifically target these symptoms. Risks and caveats need to be considered and weighted against potential benefit (see ► section Pharmacological Interventions for NPS in NCD for review of pharmacological interventions).

Table 22.3 Summary of the "DICE" model [110]

Components of DICE	Elements
D: Describe	Elicit details of the behavior including what, when, where, and who is affected: What is the distress level/safety issues Patient/caregiver perspective
I: Investigate	Patient factors Caregiver factors Environmental factors
C: Create/ collaborate	Create and collaborate on a treatment plan to address identified factors
E: Evaluate	Evaluate the treatment plan and modify accordingly

4. Evaluate the plan: to assess the outcome of the treatment plan, monitor for recurrence of the behaviors and adverse events from medications. The frequency of monitoring is somewhat setting specific, but the Canadian Consensus Conference on Dementia specifies at least every 3 months [112]. The decision on tapering off psychotropic medications is an important one with evidence of success in some studies [113], although recurrence is always a possibility for which monitoring is needed, given the chronicity of these symptoms, especially delusions, depression, and aberrant motor behavior [114, 115].

When faced with NPS of NCD, following an approach like the DICE has the potential to facilitate individualized assessment and care plan and reduce suffering and harm and inappropriate interventions.

Differential Diagnosis

The framework described above covers the process to rule in or out other causes of NPS. Here we emphasize several important considerations:

1. *Delirium.* Given the vulnerability of patients with NCD to develop delirium and given the grave consequences of undiagnosed and untreated delirium, it is essential to rule out the possibility that a change in behavior is due to delirium superimposed on the major or mild NCD. To do this it is important to establish if the current presentation is a relatively sudden departure from the patient's behavioral, cognitive, or functional baseline. Tools like the confusion assessment method (CAM) have been used to screen for delirium with good sensitivity and specificity [116]. This method relies on the presence of core features of delirium including criteria A (acute change from baseline and fluctuating course), criteria B (inattention), criteria C (disorganized thinking), and criteria D (altered level of consciousness). A positive screen requires both criteria A and B plus either criteria C or D. (See also ► Chap. 17, *Delirium in Older Adults*.)
2. *Other comorbid psychiatric illness.* Depressive episode due to major depressive disorder or bipolar disorder, manic episode due to bipolar or schizoaffective disorder, and psychotic episode due to schizophrenia or related illnesses can mimic features of the NPS of NCD. A recurrence of episodes of these illnesses in the context of NCD is likely and needs to be considered and managed accordingly.
3. *Use of psychotropic substances and medications.* This could take the form of delirium, but at times NPS can be triggered by the use of substances such as alcohol, benzodiazepines, and anticholinergic drugs with presentations that may be subsyndromal for delirium per se.
4. *Differentiation among types of NCD.* Accurate diagnosis of the NCD is important for the management of NPS, given that some illnesses like NCD due to Lewy bodies can have fluctuations as an inherent part of the illness, which may result in ongoing consideration of delirium with repeated unnecessary and costly investigations for delirium.

Teaching Points

Successful assessment and management of NPS depend on a framework for assessing and defining behavioral and psychological symptoms that emphasizes standardized definitions for clinicians and caregivers as well as an interdisciplinary approach. The Physician Consortium for Performance Improvement has recommended at least annual physician assessment for NPS using validated assessment instruments, such as the Neuropsychiatric Inventory (a general screening tool) and the Cohen-Mansfield Agitation Inventory. Other validated instruments exist, and the choice of instrument should be based in part on applicability to the clinical setting and need. When a behavioral problem is identified, the clinician should follow the DICE approach:

- Describe the behavior in detail.
- Investigate possible contributing factors: unmet patient needs, an acute medical change, sensory deficits like impaired hearing, caregiver factors that can precipitate or exacerbate the behavior, and environmental factors like too much or too little stimulation.
- Creation of a collaborative plan involving non-pharmacological and pharmacological interventions.
- Evaluation of the interventions.

22.1.6 Treatment

Treatment strategies for NPS are symptomatically driven, based on the incomplete understanding of the biological mechanisms for these symptoms. The lack of a mechanistic understanding of NPS has informed an empirical, rather than a mechanistic development of treatments. Management of NPS now relies on the use of both non-pharmacological and judiciously selected pharmacological therapies.

Pharmacological treatments for NPS of major NCD have limited efficacy [117], and adverse effects such as increased death and stroke risk have been associated with antipsychotic drug use [117–120]. Therefore, all consensus practice guidelines agree that non-pharmacological intervention should be tried first and pharmacological interventions should be reserved for certain conditions where there is imminent risk of harm to the patient or caregiver from aggressive agitated behavior and/or distressing psychosis.

Non-pharmacological Interventions for NPS of NCD

These include a set of interventions aimed to modify patient, caregiver, and environmental factors that are thought to contribute to the genesis and maintenance of NPS of NCD. These interventions are often driven by the conceptual framework described above, taking into account patient factors, including unmet needs, learned and enforced behaviors, and low stress threshold within the social and physical environment. This section summarizes the evidence for non-pharmacological interventions based on the findings from several systematic reviews and meta-analyses [8, 64, 121, 122].

The goal from non-pharmacological interventions includes prevention, amelioration/reduction, or elimination of NPS and preventing/reducing harm and distress for patients and others. Therefore, optimizing the patient's health, environment, and caregiver knowledge and skills, coupled with ongoing monitoring of patient, caregiver, and environmental factors, could help in prevention and early detection of these symptoms. Interventions can be divided into patient interventions, caregiver interventions, and environmental interventions:

1. *Patient interventions:*
    1. *Activation.* This includes engaging the patient with purposeful physical, cognitive, and/or social activities that are in keeping with the patient's previous interests. The feasibility of implementation in different settings needs to be considered. Examples include supervised routine walks, recreation therapy activation programs, and supervised physical exercise programs.

        Agitation has been attributed, in part, to a lack of physical activity [123]. However, research results of the benefits of exercise to treat the NPS in NCD have been mixed. A 12-week, high-intensity exercise program for mild to moderate major NCD in 170 nursing home patients in 18 Norwegian nursing homes found statistically significant improvements after 12 and 24 weeks in agitation and a trend toward sustained improvement in the total NPI score. No significant benefit was found for depression as assessed by the Cornell Scale for Depression in Dementia [124]. In contrast, among community-dwelling patients with clinically significant NPS, an individually tailored, progressively intensive walking regimen for the patient and caregiver did not improve NPI scores after 12 weeks, but paradoxically did decrease caregiver burden [125]. In a meta-analysis of global NPS scores in four studies, Barreto et al. found a strong trend in favor of exercise based on robust results in one study and a net benefit on depressive symptoms based on seven studies [126]. Brett et al. conducted a systematic review of exercise for NPS in nursing home patients in 12 studies meeting their inclusion criteria [127]. Overall, exercise interventions, which were heterogeneous, yielded modest improvement in physical functioning, particularly balance, and led to modest improvement in depression/affect, consistent with the Barreto et al. review [126]. So-called sundowning, defined as an increase in behavioral symptoms at the end of the day and measured by the Cohen-Mansfield Agitation Inventory, has been inversely correlated with daily walking time. Similarly, sleep quality has been shown to improve with longer daily walking times based on the Pittsburgh Sleep Quality Index [128]. Overall, physical activity for patients with NCD may prevent or ameliorate NPS overall and agitation and sleep quality specifically, with the accompanying benefit of improved physical functioning. An important point is that agitation appears to occur less frequently when patients are engaged in activities and receiving rewarding attention [129].
    2. *Sensory stimulation.* This includes a host of interventions that are provided individually or in combination such as music therapy, massage/touch, white noise, soothing multisensory stimulation (e.g., "Snoezelen room"), and aromatherapy [64, 130]. Among these therapies, music therapy seems to hold the most promise, while others have had mixed results.
    3. *Social contact.* This includes real one-to-one contact with a person, simulated contact with family via recorded media, and pet therapy.
    4. *Behavioral interventions*. These include behavioral reinforcement, stimulus control, and cognitive compensation training. These interventions have not been studied rigorously and have yielded mixed results [64, 130].
    5. *Medical and nursing care interventions*. These interventions are geared to correct the patient's medical and physiological needs. For example, treating pain, constipation, and incontinence, promoting sleep hygiene and maintaining normal circadian rhythm through bright light therapy (preferably using the spectrum of natural daylight), and providing aids for hearing and vision impairment may be helpful. Chronic pain affects 20–50% of older adults, and the prevalence is higher in long-term care facilities [131]. Acute and chronic pain has been associated with agitation and aberrant motor behavior and when treated can significantly reduce these symptoms [132]. Pain in patients with mild NCD can reliably be assessed by conventional pain scales like the numeric rating scale (0 = no pain, 10 = severe pain), but conventional scales have low sensitivity and tend to underestimate pain [133]. Some improvement in recognition has been achieved by pain scales developed specifically for patients with advanced major NCD, which tend to emphasize signs suggestive of pain, such as vocalizations like moaning, facial expression, motor restlessness like swaying or rubbing a body part, distress on movement,

irritability, poor appetite, and withdrawal/apathy [133]. Unless medically contraindicated, when a patient with major NCD is suspected of having chronic pain, empiric treatment with acetaminophen (paracetamol) given 3–4 times daily is appropriate (taking care not to disrupt nighttime sleep). Bedtime dosing of an analgesic may improve sleep quality.

2. *Caregiver interventions:*
   1. *Education for families.* This enhances awareness regarding symptoms of NCD and their impact on function (this is especially relevant in community-dwelling patients).
   2. *Staff training.* This includes a range of educational and skill training to facilitate better communication with patients and to enhance patient-centered care.
3. *Environmental interventions*:
   1. *Safe place.* Provision of a safe place for the patient to wander without the possibility of leaving the premises and getting lost is essential.
   2. *Adequate living space.* This includes an enriched and natural living space (e.g., to make patient's room in nursing home more like their home environment with family pictures and plants).
   3. *Adequate stimulation.* This provides an optimal space including reduction of excessive stimulation (e.g., noise, excessive activity).

Overall, the quality of non-pharmacological intervention studies has been limited by small sample size and risk of bias due to difficulty blinding the intervention. The effects of these interventions have to be considered relative to the stage of the NCD and the setting. For example, a review of non-pharmacological interventions in the nursing home setting showed some evidence of benefit for staff training and geriatric psychiatric consultation, in addition to psychosocial and sensory stimulation activities [121]. Non-pharmacological interventions can also be divided into generalized vs. targeted interventions. The former refers to interventions that aim to reduce various behavioral challenges by engaging a group of patients in a range of activities (e.g., music therapy). On the other hand, a targeted approach focuses on one specific behavior within a specific context (e.g., nursing home) and individualizes the approach to the specific situation. In a review by Gitlin et al., the authors conclude that the best evidence is for activation, caregiver education/training, music therapy, and adult day services [122]. Two large community studies investigated a targeted approach to behavioral problems most distressing to caregivers and have shown significant benefit on behavior and caregiver well-being [134, 135].

Overall, non-pharmacological interventions are relatively safe with no major safety risks involved, and the evidence suggests modest efficacy, although methodologically, the studies are not of the best quality. It is important to individualize these interventions to the patient and use a combination of targeted approaches in collaboration with the institutional or community care practitioners.

Teaching Points

- Non-pharmacological interventions remain the mainstay for managing NPS in NCD, although supporting data are limited.
- Ideally, a multipronged approach should be utilized that includes interventions directed toward the patient (e.g., addressing medical needs, managing incontinence, pain, exercise programs, social contact, pleasurable sensory stimulation), educating and empowering the caregiver, and optimizing the patient's environment.
- Physical activity may help control agitation, such as "sundowning," and may improve sleep quality.
- Given the high prevalence of chronic pain in geriatric patients, pain should regularly be assessed, preferably with validated instruments that promote the recognition of physical signs of distress. When chronic pain is suspected, it should be treated empirically, using regularly scheduled safe analgesics like acetaminophen (paracetamol).

Pharmacological Interventions for NPS in NCD

There are circumstances when pharmacological interventions become necessary to manage NPS arising in the context of NCD, especially when these symptoms result in significant risk of harm and/or cause significant distress to the patient or others. The choice of pharmacological agents used should be governed by a proper risk-to-benefit assessment. It is important to identify, measure, and monitor the specific target symptom(s), in addition to risks and adverse events associated with the use of these agents. Before a pharmacological treatment is tried, the target symptom must be adequately described, and the circumstances leading up to the behavior (the context) must be explored, in addition to assessing the severity of the consequences. Managing a patient whose disruptive behavior entails the use of foul language directed at the caregiver is different than managing a patient who hits or bites the caregiver. (See the DICE model of assessment, ► section A Framework for the Assessment of NPS in NCD)

Agitation and aggression arising from Alzheimer disease and mixed Alzheimer and vascular disease-related NCDs are the best studied, with several randomized controlled trials with subsequent meta-analyses and consensus guidelines. In developing a pharmacological approach to the broad construct of agitation, it is helpful to conceptualize potential contributors to the individual behaviors subsumed under agitation (Fig. 22.2). Once a detailed description of the behavior has been obtained, it may be possible to attribute it to one of four categories:

- Is the behavior a sudden, catastrophic, or explosive reaction? Commonly, angry outbursts, verbal aggression, and physical assaults arise abruptly after a provoking action due to executive dyscontrol (disinhibition).

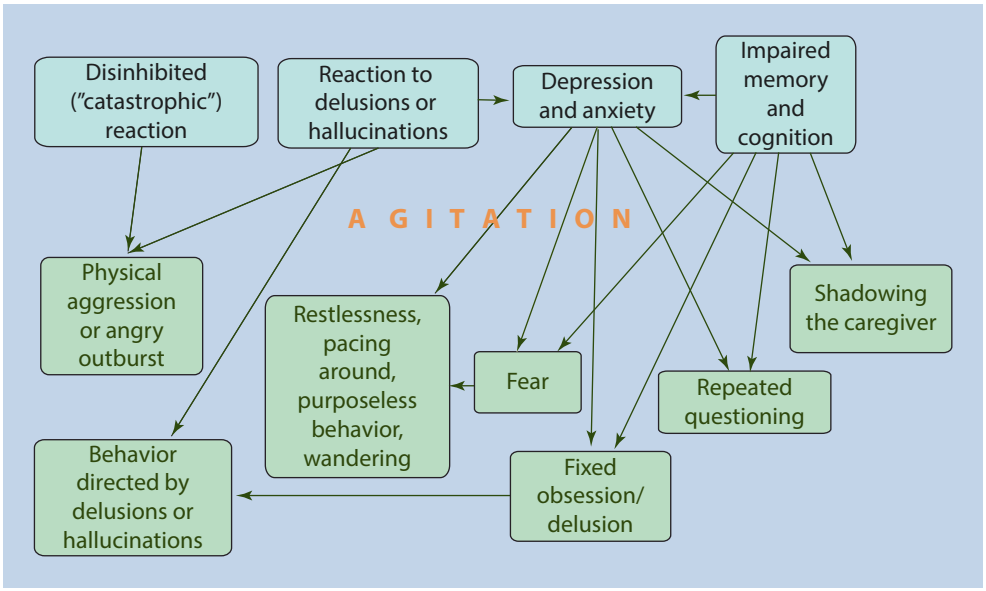

Fig. 22.2 Conceptual schema for agitation in neurocognitive disorders (dementia)

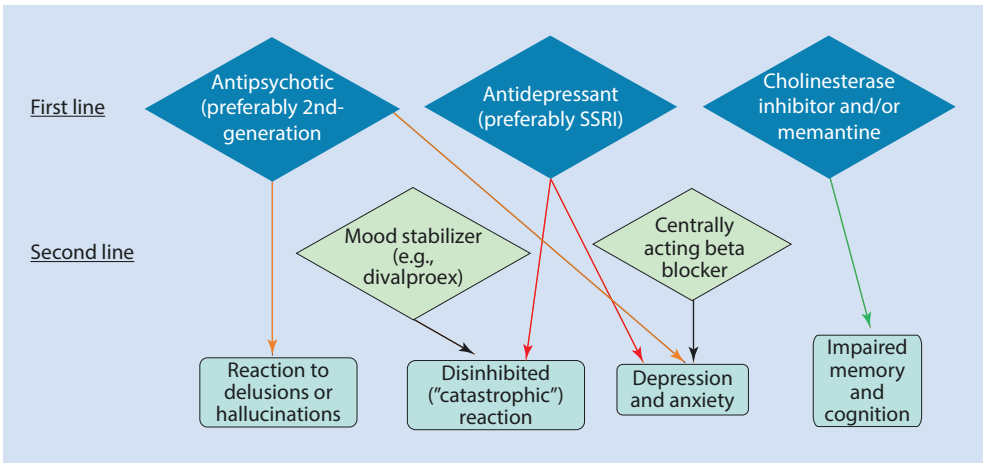

Fig. 22.3 Targeting drug therapy to the causes of distressing behaviors

- Is the behavior a result of delusions or hallucinations? An example of such a behavior is the patient calling the police out of a belief that her children are still toddlers and missing or angrily confronting a family caregiver based on a delusional belief that the caregiver has stolen property that the patient actually has misplaced.
- Could the behavior be driven by depression or anxiety? Anxiety can be provoked by delusions and hallucinations, leading to fear or motor restlessness. Depression and anxiety can be linked to a fixed obsession or delusion that, in turn, can precipitate distressing behaviors.
- Are impaired memory and cognition underpinning anxiety? For example, a patient may become worried about a missing pet because he cannot remember that it died, and repeatedly asks the caregiver where the pet has gone, or develops the delusion that it has become lost in the neighborhood, demanding that the caregiver go look for it. No amount of explanation can shake the patient's belief that the pet is alive and lost.

Figure 22.3 conceptually demonstrates how the pharmacological intervention is targeted to the suspected underlying cause(s) of the disruptive or distressing behavior.

Depression in the context of NCD can be a target for pharmacological interventions, although severe depression in the context of NCD has not specifically been studied. Because the patient often cannot describe symptoms consistent with a dysphoric mood, a reported history of a subacute (days to several weeks) change in behavior, such as social withdrawal, irritability, disinterest in formerly pleasurable activities, loss of appetite, new sleep disturbances, unexplained crying, and other vegetative symptoms, should raise suspicion of depression once delirium and other neuropsychiatric conditions have been excluded. Other symptoms like anxiety and apathy are sometimes targeted with pharmacological agents, but the evidence is still very limited as to benefit and risks.

Below is a summary of the evidence for psychotropic medications used to treat agitation and aggression related to NCD:

1. *Antipsychotic Medications*

These agents have been studied in randomized controlled trials. The efficacy of these agents is modest but significant over placebo. Meta-analyses have shown that the overall effect size for atypical antipsychotic drugs is between 0.13 and 0.16 on the NPI scale based on trials ranging from 8 to 12 weeks in duration [136, 137]. A more recent meta-analysis confirmed superior efficacy of atypical antipsychotic drugs on several measures of agitation with equivalent discontinuation rates compared to placebo, but with significantly higher rates of somnolence (odd ratio, OR 2.95), extrapyramidal symptoms (OR 1.74), cerebrovascular adverse events (OR 2.50), urinary tract infection (OR 1.35), edema (OR 1.80), gait abnormalities (OR 3.35), and all-cause death (OR 1.52) [138]. Among atypical antipsychotic drugs, the best evidence is for risperidone (five randomized controlled trials) and aripiprazole (three randomized controlled trials), although these studies included mainly long-term care (nursing home) patients. Olanzapine had mixed results with one meta-analysis showing it is not superior to placebo based on five randomized controlled trials [136] and another showing efficacy on agitation and aggression, but not psychosis [117]. A third meta-analysis showed higher efficacy for risperidone in patients with psychosis [139]. There is presently insufficient evidence to support efficacy of quetiapine in NPS of NCD due to the size and heterogeneity of studies [140]. The Clinical Antipsychotic Trials of Intervention Effectiveness-Alzheimer's Disease (CATIE-AD), a 36-week double-blind placebo-controlled trial including 42 sites and 421 patients with behavioral symptoms of major NCD (mainly psychosis, aggression, or agitation), did not show differences between atypical antipsychotics and placebo in terms of clinical improvement or time to discontinuation of treatment [141]. Further analysis showed that risperidone and olanzapine were more likely to be discontinued earlier than placebo due to side effects and quetiapine was more likely to be discontinued earlier than placebo due to both side effects and lack of efficacy [140]. Taking the research as a whole, risperidone has the best evidence for efficacy and has a specific indication for NPS in some countries (e.g., Canada and the UK), but not in the USA.

Typical antipsychotic medications have been less rigorously studied, although there is evidence for modest efficacy of haloperidol on aggression compared to placebo. However, it is associated with relatively greater adverse effects, chiefly extrapyramidal symptoms including tardive dyskinesia when used chronically, as a result of degree of irreversible dopamine receptor D_2 binding, compared to the atypical antipsychotics as a class [142, 143].

Given the significant risk of serious adverse events associated with these drugs, counterbalanced by only modest efficacy, practitioners need to go through individual risk-benefit assessment and discussion of these issues with patients and/or surrogate (substitute) decision makers for decisionally incapacitated patients before prescribing these agents. Below are important risks that need to be discussed when prescribing them [117, 140, 144]:

- Falls
- Extrapyramidal side effects
- Excessive sedation
- Worsened cognitive impairment
- QTc prolongation (a measure of delayed ventricular repolarization) leading to ventricular dysrhythmia or sudden death
- Metabolic abnormalities, especially weight gain and impaired glucose tolerance
- Stroke
- Increased all-cause mortality

Based on analyzing the data from 17 randomized controlled trials including over 5000 patients, in 2005, the US Food and Drug Administration (FDA) issued a black box warning around the use of atypical antipsychotic medications for the treatment of behavioral symptoms in NCD. The FDA estimated that atypical antipsychotics were associated with a 1.6–1.7-fold increase in the risk of mortality compared to placebo in older adults (▶ http://www.fda.gov/drugs/drugsafety/postmarketdrugsafetyinformationforpatientsandproviders/ucm053171). A similar warning was added for typical antipsychotic drugs in 2008, based on retrospective database studies, two from Canada and one from the USA, all of which suggested similar or even higher risk of mortality with typical compared to atypical antipsychotic drugs [145, 146]. Further support for the risk of mortality from typical antipsychotic medication came from sub-analysis of the meta-analysis by Schneider et al. [118] and a more recent retrospective cohort study among US veterans [147].

Published practice guidelines agree that antipsychotics are best reserved for cases where there is a risk of harm from physical aggression and/or severe distress to the patient (e.g., persistent and distressing psychotic symptoms), and it is preferable to give atypical over typical antipsychotic drugs. It is important to identify specific and measurable treatment targets and to monitor and review progress frequently. The risk of mortality has been assessed over longer-term exposure to any antipsychotic drug in a study from the UK. The study found that those who remained on antipsychotic medications instead of randomly being switched to placebo had a significantly greater risk of mortality that increased over time, with a cumulative probability of survival between groups at 12 months (70% vs. 77%), 24 months (46% vs. 71%), and 36 months (30% vs. 59%). It is therefore imperative to attempt to taper off these agents as soon as possible, given the apparent cumulative mortality effect [148]. Correcting systemic medical, pharmacological, and environmental factors and optimizing non-pharmacological interventions can help reduce the need for these agents. Unfortunately, serious NPS often are persistent, requiring longer use of psychotropic medications [114, 115].

2. *Antidepressant Medications*

Other symptoms, including depression/dysphoria, irritability/lability, and anxiety, are common in NCD. Studies have demonstrated a role for serotonin deficiency in the generation of NPS (see previous section on mechanism). Therefore, serotonergic antidepressants including SSRIs and trazodone

have been studied for the treatment of NPS of NCD. A 2011review of the literature on the use of antidepressants for NPS of NCD concluded that the evidence for sertraline is mixed (six total studies, two out of five favoring sertraline over placebo and one study favoring sertraline over haloperidol). The evidence for trazodone is also mixed (two out of three studies favoring trazodone over haloperidol and one out of two favoring trazodone over placebo), although this drug is still commonly prescribed in this context [149]. The evidence for citalopram is more robust, with favorable results compared to risperidone (two studies) and against placebo with or without perphenazine (three studies). Evidence of the efficacy of the antidepressants citalopram and sertraline in reducing agitation in NCD due to Alzheimer disease has also been reported in a 2011 Cochrane review of antidepressants for depression and psychosis in NCD [149].

The multicenter Citalopram for Agitation in Alzheimer Disease Study (CitAD), funded by the US National Institute on Aging and the National Institute of Mental Health, randomized patients with Alzheimer disease-related NCD and frequent agitation to citalopram titrated up to 30 mg daily or placebo. On the Clinical Global Impression of Change, 40% of citalopram users showed moderate or marked improvement versus 26% of placebo participants at 9 weeks. Standardized agitation ratings on the Neurobehavioral Rating Scale-Agitation Subscale improved significantly more in the citalopram group [150]. In that trial, response to citalopram was more likely in patients with mild to moderate cognitive impairment, patients with agitation of moderate severity, and patients in the middle age group of the study (76–82 years), while response to placebo was more likely in those in long-term care (nursing home) settings, those having more cognitive impairment, those having more severe agitation, and those receiving as-needed lorazepam [151]. The effect of citalopram on the 12 NPS captured in the NPI was evaluated in a planned secondary analysis. Citalopram recipients had significantly fewer delusions, less anxiety, and less irritability/lability than recipients of placebo [152]. Among responders, the onset of effectiveness tended to be after the third week in the 9-week trial [153]. The effect of citalopram was only partially explained by sedation, but largely due to other possible mechanisms of action [154]. Worsening of cognition and prolongation in QTc interval was seen significantly more in the citalopram group [150]. Electrocardiograms were available only on 48 out of the 186 participants (all over age 60) who were taking the 30 mg daily dosage of citalopram, which limits the ability to assess the effect of lower dosages on the QTc interval [155]. Additionally, a significant placebo effect was noticed in the trial, which might have been due to regression to the mean effect of psychosocial interventions, or other non-specific trial participation factors [156].

3. *Mood-Stabilizing Medications*

Due to the benefits of mood stabilizer drugs on mood in bipolar disorder and as adjunct treatment in depression, they have been used in the context of agitation and aggression of NCD. Most evidence to date is based on small case series. Valproic acid received significant attention, but despite initial promise in open-label and small trials, it failed to show benefit in well-designed trials and therefore is not recommended in all the published guidelines [157]. Carbamazepine received less attention, but showed robust benefit in two small 6-week trials [158, 159]. Due to its problematic side effects and drug-drug interactions, it is usually reserved for patients who have failed other pharmacological interventions.

4. *Cognitive Enhancers*

Although clinical trials of cholinesterase inhibitors in Alzheimer disease over the course of 6 months have shown statistically significant improvement on behavioral instruments like the NPI [160], the benefit is often not clinically meaningful and does not warrant routine prescription of these agents for acute management [161]. Possibly by delaying symptomatic cognitive decline, cholinesterase inhibitors may prevent or delay manifestation of some of the NPS when given over the long term. In NCD with Lewy bodies and Parkinson disease-related NCD, the benefit of cholinesterase inhibitors on NPS, including psychosis, has been found, although the evidence is not robust [162].

Memantine is another cognitive enhancer showing initial promise for helping behavioral aspects of NCD, specifically in Alzheimer disease [163, 164]. However, subsequent trials specifically examining the efficacy of memantine for agitation in Alzheimer disease have failed to confirm its efficacy [165].

5. *Benzodiazepines*

These are agents that have a significant role in emergency psychiatry given the quick response and ease of administration. In the context of NPS of NCD, these agents are still being used for acute management and/or for special circumstances when an intervention is planned (e.g., tooth extraction, MRI), but there is no evidence that they are effective in managing NPS in the long term, and their use is problematic because of the risk of excessive sedation, impaired coordination, falls, fractures, delirium, and accelerated cognitive impairment from NCD [166].

6. *Other Agents*

A host of other agents have been used, with reports of efficacy limited to case reports and a few small studies. For example, prazosin, an alpha-1 adrenergic blocker, has shown some efficacy for agitation and aggression in a small study of Alzheimer disease patients [167]. A recent, relatively large 10-week, phase 2 trial investigated the efficacy and tolerability of a dextromethorphan-quinidine combination drug on agitation in patients with probable Alzheimer disease. In this trial, a total of 220 participants were randomized to the active drug versus placebo at a ratio of 3:4; then participants in the placebo arm were stratified based on response and re-randomized at 1:1 ratio to active vs. placebo arm. This increased the number of participants who ultimately received the dextromethorphan-quinidine combination to 152, while those who received placebo numbered 127. In both stages of the study, the dextromethorphan-quinidine combination was more efficacious than placebo in reducing NPI scores. The combination drug was relatively well tolerated and was not associated with cognitive impairment, sedation, or QTc

interval changes but did have some adverse effects, including more falls, diarrhea, and urinary tract infections, compared to the placebo arm [20].

In summary, the majority of published practice guidelines recommend that non-pharmacological interventions should be tried first to help patients presenting with NPS of NCD. Pharmacological agents should be reserved for situations in which there is significant risk of harm and/or significant distress to the patient and/or caregiver. Most guidelines agree that antipsychotic medications have the best supporting evidence and recommend atypical antipsychotic medications such as risperidone, aripiprazole, or olanzapine as first-line treatment when medications are indicated. They also recommend short-term use and active efforts to discontinue as soon as possible. Other pharmacological interventions such as antidepressant medications are used as second-line agents based on current recommendations. The second-line status of SSRI antidepressants may change as published evidence accumulates. They remain appropriate when there is significant depression. Carbamazepine remains a third-line treatment when patients do not respond to other interventions. None of the guidelines recommend combination therapy or the use of sedating antidepressants like mirtazapine. In a recent time-series retrospective study from Ontario, Vasudev et al. reported that despite the 2005 implementation of the black box warning regarding increased mortality risk with antipsychotic medications, there continues to be problematic prescribing patterns for NPS related to NCD in long-term care (nursing home) settings in Ontario, Canada, whereby the use of sedating antidepressants like mirtazapine and trazodone, non-sedating antidepressants like SSRIs, and multi-psychotropic combinations has increased significantly. There was a significant decrease in benzodiazepine prescription, which was reassuring, and a modest decrease in antipsychotic and anticonvulsant drug prescription [168]. This supports the need for ongoing monitoring of prescription patterns and regular updates of practice guidelines to help practitioners faced with the task of caring for patients with agitation and aggression related to NCD.

22.2 Case Studies

This section highlights case studies to illustrate common neuropsychiatric symptoms (NPS) of major or mild neurocognitive disorders (NCDs), diagnostic challenges, and management concerns that are associated with treating geriatric patients with NCDs.

22.2.1 Case 1

Case 1 History

The police brought a 72-year-old Caucasian woman into the emergency department after she became agitated and accused her husband of conspiring with the neighbors to harm her. She had multiple chronic medical illnesses including hypertension (for 15 years), type 2 diabetes mellitus (for 20 years), neurogenic bladder and recurrent urinary tract infections (with indwelling catheter replaced monthly by a personal support worker), bladder cancer (with regular cystoscopy; no recurrence), status post-bilateral total hip arthroplasties, significant lumbar and sacral spine degenerative arthritis, chronic kidney disease, and chronic bilateral open-angle glaucoma and cataracts.

Upon further questioning, the patient stated that her neighbors continuously break in to her house, move things around, put children on her bookcase shelves and leave them there, and point guns at her from the window. She is very frightened by this and has called the police several times to investigate. Her husband had initially been supportive and nonconfrontational, but this changed after she called the police. His frustration peaked after he demanded that she not call the police again because they would not find anything. After that she started accusing him of colluding with the neighbors and threatened to kill him before he killed her. He felt unsafe and called the police for help.

The patient reported seeing the neighbors doing what she accuses them of doing; she also reported seeing their small children on her bookcase shelves. The first report of seeing little children and dogs in her house was about 2 months earlier when she was prescribed duloxetine for chronic back pain. These experiences improved when she was tapered off the duloxetine, but they recurred within the same month. These experiences were more intense during the evening and overnight, interfering with her sleep.

Her husband seemed visibly upset, and his growing impatience became evident when he angrily interjected during her interview, "Don't you get it? There's nothing there!" When interviewed separately, her husband indicated that he was unaware of any actual conflict with the neighbors or any more than average activity of the neighbors' children or pets. He confirmed that her behaviors worsened at night. When asked about her premorbid personality, he stated that she always had been a bit bossy and opinionated.

A computed tomographic (CT) brain scan with contrast did not show any tumors, but identified a chronic right occipital stroke with surrounding encephalomalacia, some scattered white matter hyperintensities, but relatively symmetrical and preserved hippocampal volume. An electroencephalogram (EEG) to rule out seizure activity and delirium was normal.

Her medications included over-the-counter extended release acetaminophen 2000 mg in the morning and bedtime, pregabalin 25 mg twice a day (started 2 months earlier when duloxetine was discontinued), rosuvastatin 5 mg daily for prevention of recurrent stroke, perindopril (angiotensin-converting enzyme inhibitor) 4 mg daily, vitamin D and B_{12} supplements, latanoprost ophthalmic solution one drop each eye at bedtime, and insulin glargine 10 units in the morning (previously had been 13 units) and 4 units before supper.

On examination, she was a 1.37 m (4.5 ft) tall, 73.5 kg (162 lbs) woman with kyphosis, somewhat disheveled with unkempt hair and dirty long nails, cooperative with the

examination but suspicious at times. She appeared in distress with a restricted affect. There was slight loss of her right lower quadrant visual field on confrontation examination. Her visual acuity was diminished (10/60 in the right eye and 10/20 left eye after correction with glasses), but her hearing was intact. Her supine blood pressure was 121/54 mmHg, and pulse was 67 beats/minute and regular. It initially dropped to 110/61 mmHg (pulse 69 beats/minute) on standing, but after several minutes of standing increased to 125/62 mmHg (pulse 80 beats/minute).

On neurological exam, other than for visual acuity and visual field deficits described previously, cranial nerve exam was grossly normal. She had a somewhat halting speech pattern, which her husband stated was not new but had become worse over the past year. She had difficulty with rapid alternating movements bilaterally (worse on the left side) and also some generalized impairment with coordination on the left side. Deep tendon reflexes were normal and symmetrical in the upper extremities, but absent at the knees and ankles. Both plantar responses were downgoing. There was mild weakness of her left side and reduced grip strength in the left hand. She also had decreased hip flexion on the left side but movement was limited because of pain. Using a borrowed walker, she was able to take a few steps, but her Timed Up and Go test was prolonged at 35 seconds (normal $\leq$ 10 seconds) [169], and she was quite unsteady. She could stand unsupported without the walker for only 7 seconds and was unable to do a step and then stand or stand with her feet together. There was no resting tremor, but flexion of her elbows by the psychiatrist revealed mild, symmetrical cogwheel rigidity.

Mental status examination showed that she continued to describe how her neighbors were breaking in to her house and moving things around, leaving their children there unsupervised. She reaffirmed that a male neighbor liked to point a gun at her from outside the window and would bring his young daughter to practice doing that as well. She indicated that she saw these people and at times heard them talking to each other but not to her or about her. There was no indication that she was having hallucinations in other sensory modalities. She denied feeling depressed but expressed her concern about what her neighbors were doing and that her husband might be colluding with them. Her fixed and consistent delusions and hallucinations demonstrated very limited insight and judgment.

Cognitive function was tested using the Mini Mental State Examination (MMSE) [170], on which she scored 26 out of 30, missing one point on place orientation (not knowing the country), one on delayed recall, one on copying the pentagons, and one on writing a sentence (she wrote an unintelligible sentence). On clock drawing test, she could complete the circle but failed to place the numbers and hands correctly.

The neuropsychiatric inventory questionnaire (NPI-Q) was completed by her husband, reflecting symptoms over the previous 2 weeks; the NPI-Q was positive for delusions (severity 3/3, distress 3/5), hallucinations (severity 3/3, distress 3/5), agitation/aggression (severity 1/3, distress 4/5), anxiety (severity 2/3, distress 3/5), irritability/lability (severity 2/3, distress 4/5), and nighttime behavior (severity 2/3, distress 2/5).

The Cohen-Mansfield Agitation Inventory (CMAI) was completed in interview format with the husband and was positive for "grabbing at others" several times a week (rated 4), "throwing things" several times a week (rated 4), "pace and aimless wondering" several times a day (rated 6), "general restlessness" several times a day (rated 6), "cursing or verbal aggression" several times a day (rated 6), and "complaining" several times a day (rated 6). A delirium screen using the Confusion Assessment Method (CAM) revealed disorganized thinking and fluctuating course but failed to meet criteria for syndromal delirium.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. Using the DICE model, describe the main behavioral challenges in this case.

? Question 2. What is the next step in the assessment and management?

? Question 3. What interventions need to be considered?

? Question 4. Considering the new data, what is your evaluation of the plan?

Case 1 Answers

Case 1 Answer 1 (Question 1—Using the DICE model, describe the main behavioral challenges in this case.)

The "D" in the DICE model refers to *description* of the behavior and the surrounding circumstances. In this case the clinician was able to elicit a detailed description of the behaviors by systematically interviewing the patient and her husband. The use of systematic questionnaires added important information about the behaviors, revealing delusions, hallucinations, anxiety, agitation, and nighttime behavioral difficulties. The CMAI showed that her agitation included physically and verbally aggressive behaviors in addition to physical and verbal nonaggressive behaviors. The negative CAM result made delirium diagnosis unlikely. Although occurring throughout the day, her NPS worsened in the evening, with some day-to-day fluctuation over the previous several months.

Applying an antecedent-behavior-consequences analysis can provide a framework for approaching the clinical management of her behaviors. History from her husband did not elucidate any specific antecedents except for a temporal association with the evening and night. This raises the possibility of a relationship with her sleep-wake cycle and/or darkness. There did not appear to be any basis for the patient's paranoid delusions. These NPS clearly were imposing significant distress to the patient but also significant risk of harm to the patient, her husband, and the neighbors. Furthermore, her repeated calls to the police represented a public nuisance and a misuse of community resources.

Case 1 Answer 2 (Question 2—What is the next step in the assessment and management?)

The "I" in the DICE model stands for *investigate*. This includes searching and profiling patient, caregiver, and environmental factors. In this case we can identify the following:

A2.1. *Patient factors.* In this case there are both modifiable and unmodifiable or semi-modifiable patient factors:

1. Modifiable factors:
    1. Possibility of a urinary tract infection: due to her indwelling catheter, there is an ongoing risk for urinary tract infection that needs to be evaluated and treated if found.
    2. Pain: due to her degenerative disk disease, pain can increase her emotional distress and contribute to her agitation.
    3. Centrally acting analgesics and analgesic agonists like opioids, serotonin norepinephrine reuptake inhibitors, and anticonvulsants; over-the-counter and prescription anticholinergic medications; and certain antibiotics like the cephalosporins (which have been associated with neurotoxicity [171]) can contribute to neurocognitive dysfunction and NPS. The patient was taking pregabalin, which has been associated with delirium and psychosis [172].
    4. Sleep disturbance: this is likely caused by the NPS but also can contribute to their worsening.
    5. Lack of structure and limited physical and social activity.
2. Unmodifiable or semi-modifiable factors:
    1. Stroke: risk can be somewhat modified via prevention of further cerebrovascular events by cardiovascular risk factor management.
    2. Neurodegenerative illness: given her chronic progressive course of cognitive impairment and decline involving memory and executive function, her visual hallucinations, her chronic fluctuating course, and parkinsonism (gait changes and bradykinesia), this syndrome could represent a NCD due to Lewy body disease. This factor is semi-modifiable by providing current standard of treatment with cognitive enhancers.
    3. Premorbid characteristics: this patient was described as a very assertive in-control person premorbidly. This likely contributed to her desire to regain control over the situation she perceived by taking charge, calling the police, and trying to get rid of the threat. It is difficult to modify this factor, but being mindful of it can allow building a better therapeutic alliance with the patient with validation of her experience of distress and supporting her in a non-threatening, respectful way.

A2.2. *Caregiver factors.* The husband in this case was very supportive and able to stay calm and nonjudgmental in the face of the patient's psychosis until, after several months of sleep deprivation and tension, he showed signs of caregiver burnout, as evidenced by his spontaneous angry outburst against the patient during her examination. The husband's impatience and angry reaction to her calling the police demonstrate how caregiver reaction to NPS can lead to their escalation. The patient started perceiving his distress as hostility toward her, and she integrated him into her delusional beliefs, which created more risk as described previously. This factor is modifiable through supporting the husband emotionally (psychological counseling), psychoeducation, and counseling in communication skills (how to respond to questions from the patient about her delusional beliefs). It can also be modified via respite placement to reduce the caregiver burden. The husband became a target of a homicidal threat. If outpatient management were desired, a safety plan would need to be in place to avoid harm.

A2.3. *Environmental factors.* The NPS arose within a relatively stable environment in the community. The patient and her husband lived in the same house for many years, and there were no recent changes in immediate neighbors or the overall neighborhood. However, the patient's current health, cognition, and function no longer were compatible with living in her home and neighborhood. She did not have social support other than her husband, and when he was out doing errands, she was alone and vulnerable. Given the nighttime worsening of her behaviors, better indoor and possibly outdoor lighting to reduce shadows and increase visibility of objects (e.g., tree branches) that could be misidentified as children or prowling neighbors might be helpful.

Case 1 Answer 3 (Question 3—What interventions need to be considered?)

The "C" in the DICE model refers to *collaborate on care plan* that attempts to address identified modifiable or semi-modifiable factors. Some of these factors have been identified in the discussion previously. It is important to note that potentially contributing factors may not individually be causing the NPS, but they may be exacerbating one or more NPS. They can also act additively or synergistically to collectively cause or exacerbate behaviors or the underlying NCD.

A.3.1. *Patient factors:*

1. Perform a urinalysis with culture and sensitivity to screen for a urinary tract infection and treat accordingly. Even if her urine merely was colonized without infection, the bladder catheter represents a major risk factor for future urinary tract infections, and problem-solving around optimal catheter management and reducing urinary tract infection recurrence should involve collaboration with the patient's primary care

physician or urologist as well as the patient and her husband.
2. Monitor and optimize pain control while minimizing psychotropic analgesics.
3. Other medications should be reviewed and adjusted to optimize psychotropic medications and to eliminate all anticholinergic medications, which can cause cognitive impairment. Although the patient's only prescribed psychotropic medication was pregabalin, over-the-counter medications should be included in the medication reconciliation. Also, because she had a sleep disorder, it is possible that she or her husband had purchased a non-prescription sleep aid, which commonly contains the potent anticholinergic, diphenhydramine.
4. Enhance sleep hygiene; factors that could contribute to nighttime wakefulness should be controlled, such as caffeine and other psychostimulant consumption, sleeping with the TV or radio on, and daytime napping. Agents to restore the sleep-wake cycle such as melatonin and bright light therapy during the daytime can be helpful. Physical activity during the day can also help promote restful sleep.
5. Continue with stroke prevention strategies.
6. Enhance patient's sense of control by involving her in the treatment planning.
7. Optimize the patient's hearing and vision.
8. Weigh the risks and benefits of using psychotropic medications in this case (to be discussed further).

A.3.2. *Caregiver factors:*
1. Add psychosocial support for her husband, including education on reducing emotional tone and enhancing concrete supportive communication.
2. Facilitate access to respite care.
3. Advocate for more support from community agencies such as the local chapters of the Alzheimer Society of Canada or the US Alzheimer's Association.

A.3.3. *Environmental factors:*
1. Consider adding more structure at home with added services.
2. Consider adult day program referral to add structure and provide caregiver respite.
3. Optimize lighting to eliminate shadows that could be misconstrued as intruders. Closing window shades at night potentially could prevent objects like tree branches from forming the nidus of a hallucination. "White noise" (e.g., soothing, constant background sounds like falling rain can be produced by inexpensive tabletop sound machines). A recreational therapist, if available, could help design a program of music therapy or other calming environmental factors.

Case 1 (Continued)

Due to the significant risks and distress associated with the patient's psychosis, as well as concern about parkinsonism contributing to her impaired mobility, the atypical antipsychotic, quetiapine, was selected and titrated up to 200 mg daily over 6 weeks, with negligible benefit on psychosis at the 4-week and 6-week follow-ups, but dose-dependent excessive sedation and orthostatic lightheadedness reported by the husband. Also, because she was becoming more agitated due to psychosis and because of additional calls she made to the police, she was hospitalized and taken off quetiapine. In its place, risperidone was initiated at 0.25 mg twice daily and titrated up to 0.5 mg twice daily over 1 week. Although her psychosis improved, she developed involuntary movements in her oral and jaw area 2 weeks after discharge and started falling, indicating significant sensitivity to the risperidone. The risperidone was tapered off and she was switched to aripiprazole 5 mg daily, with substantial improvement in her NPS but only modest improvement in her oral and jaw abnormal movements over 3 weeks. On MMSE testing 8 months later, her score had declined to 15 out of 30, missing 2/5 on time orientation, 3/5 on place orientation, 4/5 on serial 7s, 3/3 on recall, 1/1 on repetition, 1/1 on writing a sentence, and 1/1 on copying pentagons. Her clock drawing test was now severely impaired with a small circle without numbers inside and meaningless scribbling outside the clock face. A trial of cognitive enhancer was considered, but unfortunately the patient had bradykinesia and second-degree heart block, which made it unsafe to trial acetylcholinesterase inhibitors in this case. Memantine was also considered, but the patient and her husband did not wish to pursue it due to the cost associated with it.

Case 1 Answer 4 (Question 4—Considering the new data, what is your evaluation of the plan?)

Evaluation is the final step in the DICE model. Scheduled follow-up visits and telephone calls enable her clinicians to adjust the care plan to balance control of her NPS with the side effects of her antipsychotic medication. At 6 weeks it was evident that quetiapine was ineffective with untoward sedation and lightheadedness. Follow-up after replacement of the quetiapine with risperidone resulted in improvement of her psychosis and less agitation at the expense of significant extrapyramidal side effects, prompting a change to treatment with aripiprazole.

The treatment team reviewed the course of her illness and confirmed that the patient met criteria for major NCD with Lewy bodies (i.e., visual hallucinations, fluctuation of the course, parkinsonism at baseline, and sensitivity to antipsychotic medications). The location of the stroke was not strategic to cause a full-blown NCD but likely contributed to the clinical picture. A diagnostic criterion for NCD with Lewy bodies historically has been exquisite sensitivity to the extrapyramidal effects of dopamine-antagonist antipsychotics, principally butyrophenones (e.g., haloperidol) and phenothiazines (e.g., perphenazine). Although classified as an atypical antipsychotic, risperidone, like haloperidol, *irreversibly*

inhibits the dopamine D_2 receptor. As a result, it was decided to taper off risperidone gradually, replace with modest dose aripiprazole, and refer the patient to a movement-disorder neurologist to consider local botulinum injection of jaw muscles to reduce the impact of the involuntary movements on her ability to eat and drink. Monitoring for relapse of psychotic symptoms closely is essential in cases like this patient and ideally should be followed every month in the clinic with outreach nurse follow-up in between. Ongoing support of her husband through a senior day program and in-home supportive services helped him to keep her at home. He was referred to the local Alzheimer Society and to their website (► http://www.alzheimer.ca/en; Alzheimer's Association in the USA: ► http://www.alz.org) for information about the stages of progressive degenerative neurocognitive disorders (dementia) and tips on behavioral management. The need for assessment of safety and function on regular basis was also emphasized. In this case, the rapid decline in cognitive scores raises the possibility of delirium. On the other hand, patient's sensorium was clear, EEG was normal, and no active factor was identified to cause delirium (urines were clear when tested sporadically and her medications monitored carefully for unwanted mechanism). The rapid decline in MMSE scores in this case is likely related to Lewy body disease, which is known to have fluctuations in cognition and/or a rapid course in many cases.

Case 1 Analysis This case discusses the late-onset psychosis, making the diagnosis and controlling the symptoms. In real-world clinical practice, clinicians often encounter older patients who develop late-onset paranoia, hallucinations, or other psychotic symptoms. Evaluating the etiology of these symptoms and creating a better diagnostic framework for understanding them are imperative. This case framed our discussion of an older adult who presented with paranoia, visual hallucination, and agitation. This case highlighted the diagnostic complexities of late-life psychosis and allowed us to address issues of diagnosis and treatment. (For further details on late-life psychosis, see ► Chap. 15.)

The most common causes of late-onset psychosis are major NCDs, delirium, drug-induced psychosis, and primary psychiatric disorders, most commonly major depressive disorder. Major NCD is the greatest risk factor for development of psychotic symptoms in the geriatric population both as a result of major NCD process itself and through an increased vulnerability to developing delirium. Determining the etiology of late-onset psychosis is the first step. The work-up for delirium is paramount and generally includes identification of potentially offending prescription medications (especially anticholinergics and sedative/hypnotic medications), infections (e.g., urinary tract infection, pneumonia), and metabolic causes. Once delirium is excluded as an etiology, the next step is to determine whether the psychotic symptoms stem from a major NCD or from another neuropsychiatric disorder. A careful history taking from the patient and collateral information from family members or caregivers, along with cognitive and functional assessments, can assist in establishing a working diagnosis and a treatment plan. In this case, major NCD with Lewy bodies is likely given due to the presence of cognitive disorder with visual hallucinations, parkinsonism, fluctuation of the course, and sensitivity to antipsychotic medications. An approach to integrating non-pharmacological and pharmacological treatments in order to fully institute tailored treatments for this patient with NPS due to NCD, including family caregiver interventions, has been emphasized.

22.2.2 Case 2

Case 2 History

Mrs. E., a 78-year-old Filipina, was referred to the geriatrics clinic by her primary care physician for assistance in the evaluation and management of "dementia with behavioral disturbances." The patient is accompanied by her daughter and son-in-law, with whom she lives. The patient herself is unable to provide a history. She persistently talks about how much she loves America and repeatedly asks, "Would you like to hear me sing?" After which, without waiting for a response, she starts singing "God Bless America." The patient then insists on standing and trying to leave the room. The daughter or son-in-law have to rise and patiently follow Mrs. E. and gently escort her back into the room. The patient's inability to sit still or cooperate limits the physical examination. Mrs. E. is very thin, weighing 40.8 kg (90 lbs) with a height of 1.5 m (4.9 ft) (BMI = 18.1 kg/m^2). Her seated blood pressure is 90/62 mmHg, and heart rate is 74 beats/minute and regular. Her chest and heart examination is compromised by her incessant talking. On observation, there is no evident cranial nerve or motor abnormalities. She is able to stand easily from her chair, which she does repeatedly, and her gait appears within normal limits. The MRI scan of her brain performed 1 year prior showed global cerebral atrophy with predominant hippocampal and medial temporal lobe atrophy. The MoCA test was attempted but the patient was agitated and uncooperative. A MoCA score from 5 months earlier was 12 out of 30.

Because the patient will not sit still or keep quiet while the daughter provides a history, a nursing assistant is asked to take orthostatic vital signs so that the geriatrician, resident physician, and social worker can interview the daughter and son-in-law separately. The daughter appears tired and haggard. She explains that her mother began to show impaired memory several years earlier, but remains independent in her activities of daily living. However, the daughter had recently noticed that her mother's underwear frequently is smeared. Her mother denies that her underwear is dirty and will angrily insist on wearing the same panties the next day. Mrs. E. still attempts to prepare Filipino specialties, but will forget key ingredients or get distracted and burn the food. More and more she wanders aimlessly around the house and attempts to go outside to go to the store. Because she has wandered off and gotten lost in the neighborhood twice in the last 3 months, the family (including two grandchildren

ages 9 and 12) has been vigilant for the sound of the front door opening. An earlier attempt to keep the doors locked using double-sided keyed deadbolts resulted in angry outbursts from the patient. Mrs. E. also interrupts the children when they are doing homework, scolding them for keeping their rooms messy, and regularly interrupts the daughter or son-in-law. Often the interruptions are centered around the delusion that the grandchildren are lost or kidnapped, and Mrs. E. becomes quite agitated when the daughter does not call the police or go searching for them. If a family member tries to prevent Mrs. E. from leaving the house, she sometimes attempts to slap them. The patient remains constantly physically active during the day. Although she goes to bed at 9 or 10 PM, she regularly gets up around 1 AM and can be heard wandering around the house or knocking on the daughter's bedroom door to tell her to hurry up and make breakfast for the grandchildren or to demand the daughter help her with some trivial task like finding old photographs of her deceased husband. The daughter already has devised strategies for keeping her mother busy, such as assigning her to fold laundry. However, Mrs. E. tends to put the folded laundry in the wrong places, such as on the pantry shelves and inside the entertainment center. When the daughter is asked about Mrs. E.'s near-cachectic appearance, she replies that her mother "eats like a horse, twice as much as me, and look at *me*!" (The daughter is obese.)

Case 2 Questions and Answers

Case 2 Questions

? Question 1. What are Mrs. E.'s neuropsychiatric symptoms?

? Question 2. How would you manage Mrs. E.'s NPS?

? Question 3. What can be done for the patient's NPS at this point?

Case 2 Answers

Case 2 Answer 1 (Question 1—What are Mrs. E.'s neuropsychiatric symptoms?)

Using the NPI-12 item instrument as a guide, the patient has *delusions*, consisting of the belief that the grandchildren must be lost or kidnapped when they are not present in the house. She also manifests *agitation*, frequently being resistive, stubborn, uncooperative, aggressive, and hyperactive. The patient displays *anxiety*, worrying about the grandchildren as part of her delusion that they are lost or kidnapped. Some *disinhibition* is apparent by the way the patient impulsively gets up and wanders or starts talking to strangers (e.g., the resident physician) about how much she loves America and then singing (always the same tune). Mrs. E. is periodically *irritable*, getting angry easily over being prevented from engaging in an inappropriate or unsafe activity, and is argumentative. She constantly paces around the house without purpose and fidgets, as exemplified by getting up and down repeatedly from her chair in the exam room, thus demonstrating *aberrant motor behavior*. Her *sleep* is severely impaired. Although she goes to bed and falls asleep, she awakens and paces, awakening others in order to get help with inappropriate nighttime activities. The patient also displays *appetite and eating disorders* consisting of eating an excessive amount of food yet apparently losing weight.

Case 2 Answer 2 (Question 2—How would you manage Mrs. E.'s NPS?)

The first step in treatment is to ascertain which behaviors are the most disruptive or distressful to her caregivers. Antecedents should be sought for her agitation so that nonpharmacological approaches might be tried. For example, for her wandering, the front door might be kept locked, but the door to a backyard enclosed by a fence with a lockable gate might be kept open. To mitigate nighttime wakefulness and inappropriate activities, greater efforts might be taken to tire the patient during the day, such as taking her for long walks, provided that family members have the time to do this. Mrs. E.'s caregivers should ensure that the patient does not receive caffeine that might exacerbate her insomnia. A pharmacological approach might be considered to help the patient sleep and to reduce her delusions. A clinician should be considering an unmasked manic episode from bipolar disorder in the differential diagnosis at this time and direct questions to test this hypothesis. If such a diagnosis is supported by the history, quetiapine or olanzapine could be started at bedtime for its sedating, antipsychotic, and antimanic effects. Valproic acid or other antimanic agents could be considered as additional therapy, given Mrs. E.'s severely distressful behaviors.

The well-being of Mrs. E.'s family must be considered. Adult day care might be an option, if available and affordable to the family. The daughter and son-in-law should be educated about how their responses to the patient can escalate the patient's behavior and that reasoning with her is counterproductive due to her major NCD.

Case 2 (Continued)

The daughter indicates that the patient's nighttime wandering and occasionally unsafe behaviors, such as attempting to cook breakfast and letting the pan burn on the stove, are the most distressing. They know that she has a major NCD due to Alzheimer disease, because the patient's older sister developed "Alzheimer dementia" in her late seventies. They are willing to try adult day health care, but worry that Mrs. E. may try to wander off. The attending geriatrician, suspicious of underlying mania, asks the daughter about any prior psychiatric history. The daughter denies any, but when pressed admits that, while she was growing up, her mother seemed to have endless energy for months at a time, cooking large meals for her five children and husband while tending a large flock of hens whose eggs she sold. She never seemed to sleep. Sometimes, however, her mother would "just wear out" and take to bed for days and could be very tearful. Based on this history, she is referred to geriatric psychiatry and a manic episode with psychotic features versus NPS of major NCD remains the working diagnosis. Quetiapine 25 mg at bedtime is prescribed.

After discussion with the daughter, valproic acid will not be started simultaneously.

Over the ensuing month, the dose of quetiapine is increased to 100 mg at hs and 50 mg in the AM. Although the patient now tends to nap during the day, her nighttime sleep only increases to 4 or 5 hours, and she still awakens and paces at 2 or 3 AM, continuing to disrupt the son-in-law and daughter and occasionally the children, whom she sometimes mistakes for her own children when they were little. Valproic acid 125 mg twice daily is started in light of the patient's small size, with the intent to titrate upward for effect. The nighttime dose of quetiapine is continued, but the AM dose is stopped. After 2 weeks, the daughter calls, concerned that her mother is not eating and is losing weight. A serum ammonia is drawn and is 102 μg/dL (59.9 μmol/L; high). The valproic acid is stopped, and after 1 week the patient's ammonia and her liver enzymes have normalized, and her appetite has returned. Because of the hyperammonemia caused by valproic acid, the patient was started on carbamazepine 100 mg twice daily. The daughter notices slight improvement in the patient's behavior after 1 week, and the dose is increased to 200 mg twice daily. Six days later the patient is hospitalized for an acute, life-threatening Stevens-Johnson allergic dermatitis and mucositis, which are attributed to the carbamazepine. She experiences acute kidney injury due to dehydration. After 16 days she is discharged home on a prednisone taper and a nasogastric feeding tube, along with quetiapine. Her creatinine has improved but now reflects stage 3 chronic kidney disease, with an estimated creatinine clearance of 41 mL/minute/1.73m^2.

When seen in follow-up in the geriatric psychiatry clinic 1 month later, the patient no longer is ambulatory but eating well. She continues to be awake most of the night and calls out for her daughter, who dutifully gets up and goes to her mother's room. She cannot get out of bed on her own, although sometimes attempts to use the bathroom and has fallen while trying to stand up. She still is verbally disruptive and irritable and periodically attempts to leave her wheelchair to walk, resulting in additional non-injurious falls. The patient no longer is having delusions about her grandchildren being lost, but appears worried about their safety and wants her daughter to check on them frequently at night. Since it was not helpful for the insomnia, the quetiapine 100 mg qhs is switched to olanzapine 5 mg qhs, but her sleep disturbance continues, her napping increases, and she develops significant extrapyramidal symptoms with increasing risk for falls. Subsequently, olanzapine is tapered off without recurrence of the delusions or an increase in agitation. Lithium is considered inappropriate, given the patient's unpredictable consumption of fluids and her chronic kidney disease.

Case 2 Answer 3 (Question 3—What can be done for the patient's NPS at this point?)

Pharmacotherapy for the presumed mania versus NPS of major NCD has been unsuccessful. Although carbamazepine showed promise, Mrs. E.'s life-threatening allergic reaction precludes its restart. Another antipsychotic agent (like risperidone or aripiprazole) is unlikely to be helpful or tolerated. At this juncture, the focus of therapy should be on reducing caregiver burden, the patient's safety (given the falls), and the patient's anxiety. An antidepressant could trigger more manic behavior, so it is appropriate to restart low-dose quetiapine if the anxiety worsens. The choice of bed could influence nighttime fall risk. Based on past unsafe behaviors, a hospital bed with raised bedrails could be dangerous if the patient attempts to climb over or around them. Thus, placing the mattress directly on the floor would be advisable, provided the daughter is able to help her up. A bed alarm or a simple baby monitor could alert the family to the patient's attempts to get out of bed. If putting the mattress directly on the floor is not feasible, then a bedside pad to cushion a fall would be a consideration, with the caveat that such pads can adversely affect balance. A bedside commode would facilitate nighttime toileting. Because diapers do not alter the sensation of needing to void, they would not necessarily prevent attempts to get out of bed. Melatonin could be tried to facilitate sleeping longer at nighttime. A benzodiazepine and diphenhydramine are both strongly contraindicated because of the risk of increasing confusion. At some point, however, the ability of the family to obtain restful sleep, thus enabling ongoing caregiving, may outweigh the side effects of a sleeping aid medication. As an antidepressant, trazadone should be used cautiously due to potential for mood switch, postural hypotension, and risk for falls.

Adult day health care should be resumed, now that the patient no longer is an elopement risk. Home physical therapy aimed at strengthening and restoring safe ambulation should be a high priority, since restraining the patient in her wheelchair using a "postural restraint" or belt could lead to agitation and is considered elder mistreatment in many jurisdictions.

Case 2 Analysis The patient presented with a constellation of symptoms, which could be part of an undiagnosed bipolar disorder with mania and psychotic features, or represented NPS of major NCD. Disinhibited behaviors and agitation related to NCD are important to distinguish from mania, which may represent a recurrence or relapse of underlying psychiatric disorder, which will have significant treatment implications. Although this was unclear in Case 2, in patients with a personal or family history of bipolar disorder or major depressive disorder, a successful trial of a mood stabilizer may provide diagnostic clarification, but this should not be done routinely and should prompt a referral to a geriatric psychiatrist for diagnostic clarification and management.

However, psychotic symptoms such as hallucinations and delusions can frequently occur in patients with major NCD, but they also occur in delirium, which must be excluded. Psychotic symptoms in NCD can vary in severity, and they may not require active pharmacological treatment if present without causing harm or distress to the patient or others. The most commonly used scale for detection of NPS of NCD is the NPI, which assesses symptoms in 12 domains (see Sect. ► 1.2).

Treatment with anticonvulsant mood stabilizers (e.g., valproic acid, carbamazepine) can be considered in the treatment of NPS of NCD, but these agents are not routinely used unless the patient has a comorbid diagnosis of bipolar disorder, as suspected in this case. Valproic acid has limited efficacy on NPS and is less recommended. Carbamazepine is a strong enzymatic inducer, with a high likelihood of drug-drug interactions, making the benefit-risk ratio too great to be considered on a routine basis in the geriatric population. In this case, carbamazepine was considered as an alternative treatment. Although carbamazepine can cause blood dyscrasias, hepatic failure, pancreatitis, and exfoliative dermatitis (e.g., Stevens-Johnson syndrome), oxcarbazepine may have a lower rate of side effects and is well tolerated, but there is no high-quality evidence that oxcarbazepine has benefit in the acute treatment of bipolar disorder [173]. The anticonvulsant mood stabilizers have been associated with hyponatremia due to syndrome of inappropriate antidiuretic hormone secretion (SIADH), particularly in older adults, which sometimes necessitates anticonvulsant discontinuation. Hyponatremia may be related to water retention caused by anticonvulsant's antidiuretic effect. Judicious use of medications in patients with major NCDs, with or without comorbid psychiatric disorders, and monitoring for treatment response and side effects are imperative.

22.3 Key Points: Neuropsychiatric Symptoms of Major or Mild Neurocognitive Disorders

- NPS of major or mild NCD are very common and result in significant consequences to the patient, caregivers, and system of care.
- These symptoms are diverse and occur at variable frequency in different NCDs and at different stages of these illnesses.
- There are several clinical scales to profile these symptoms including the NPI, NBRS, CMAI, and BEHAVE-AD.
- Underlying mechanism of these symptoms remains to be elucidated, but evidence point to neurochemical changes involving serotonin and other neuromodulators.
- Assessment and management of these symptoms requires a comprehensive and systematic approach in order to identify contributing factors and allow the development of an individualized care plan to optimize gain and reduce harm.
- There are several published treatment guidelines from several international groups, all of which agree to start with identifying and managing correctible factors and non-pharmacological interventions (including educational interventions) and use pharmacological interventions only if needed.
- Pharmacological interventions and mainly antipsychotic drugs have evidence in treatment of severe NPS with psychosis and/or aggression, but they carry significant risk and need to be considered with caution.

22.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which one of the following is the *best* first step to help a 70-year-old woman with advanced Alzheimer disease in nursing home presenting with constant loud nonsense vocalization?

A. Start an SSRI to reduce anxiety
B. Use the DICE model for assessment and management
C. Start a small dose atypical antipsychotic medication
D. Start acetaminophen
E. All of the above

Answer: B

Before prescribing any agents, we need to profile the behavior and factors contributing and attempt non-pharmacological interventions unless it is indicated for specific illness like pain or depression of the like.

MCQ 2. You are assessing an 80-year-old woman with history of cognitive decline over the last 3 years. Her family thinks she is depressed, as she does not want to do anything. The patient herself appears calm and not concerned. She has no premorbid history of depression, and she already had two adequate trials of antidepressants (sertraline and venlafaxine) with no significant change in her symptoms. Which of the following would be the *best* option:

A. A trial of ECT
B. A trial of lithium augmentation of an antidepressant
C. A trial of combination of two antidepressants with complimentary mechanism of action
D. Consider alternative explanation of her behavior before changing medications

Answer: D

As in MCQ 1, before prescribing any agents, we need to assess the behavior and factors contributing and implement non-pharmacological interventions unless it is indicated for specific illness like pain or depression.

MCQ 3. You are consulted on a patient that has advanced NCD who is residing in a nursing home. He is a physically strong man and has been quite agitated and aggressive imposing risk to others. His behavior seems to be stemming from delusion that others are taking his belonging, and all attempts to modify his behavior with environment modification have failed so far. His physician is considering pharmacological options to reduce his behavior. Considering current evidence and expert consensus, which of the following agents/dosages would you recommend?

A. An SSRI at the regular dose used to treat depression

B. A small dose of a typical antipsychotic as it allows you to use an IM route
C. An anticonvulsant at half the dose used in seizure disorders
D. An atypical antipsychotic at a low dose

Answer: D

Before prescribing any agents, we need to evaluate the behavior and factors contributing and employ non-pharmacological interventions, but with the failure of all of that and with the distressing psychotic symptoms resulting in risk of harm, the best evidence is for antipsychotic medications. Careful assessment and monitoring of the risk is important, and attempt to reduce and discontinue these agents as soon as feasible would be of utmost importance.

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Neuropsychiatric Manifestations of Systemic Medical Conditions

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23.1 Background

23.1.1 Definition

Systemic medical conditions frequently present with neuropsychiatric symptomatology that may be incorrectly attributed to a primary psychiatric disturbance. According to prior editions of the *Diagnostic and Statistical Manual of Mental Disorders* [1], the psychiatric presentation of another medical disorder can be defined as "the presence of mental symptoms that are judged to be the direct physiological consequences of a general medical condition".

Evidence that a neuropsychiatric disturbance is the direct physiological consequence of another medical condition requires an index of suspicion. In older adults, the index of suspicion should be relatively high given the age-related dampening or modulation of common indicators of physiological disturbance. There are no pathognomonic features that reliably direct clinicians toward a general medical condition versus a psychiatric disorder [2–4]; however, factors such as those illustrated in Table 23.1 should certainly raise suspicion of medical etiology [3–5].

Clinicians must remain cognizant that neuropsychiatric symptoms stemming from systemic medical conditions may present in muted, varied, or unusual ways in older adults [6]; thus it is imperative to ensure a careful workup to rule out an underlying or contributory medical condition. This can be further complicated by issues such as polypharmacy, iatrogenic factors, and comorbid psychiatric disorder.

Teaching Point

Robust presentations that are typically described as "classic" features of a number of common disorders are less likely to be seen in older adults.

A broad spectrum of medical conditions can present with neuropsychiatric manifestations as illustrated in Table 23.2 [3, 4, 6–9]. In particular, tumors, autoimmune disorders, metabolic abnormalities, endocrinopathies, infectious processes, and neurologic conditions can induce neuropsychiatric symptomatology. Many of these conditions also occur at a higher frequency in the geriatric population.

Common neuropsychiatric symptoms associated with underlying medical conditions include psychosis, anxiety, depression, unusual personality changes, and behavioral disturbance. Given that these symptoms are also hallmark features of common psychiatric conditions, it can undoubtedly present a challenge to distinguish primary from secondary causes of psychiatric disturbance. Thus, in evaluating older adults presenting with neuropsychiatric symptoms, a wide differential diagnosis can be considered in order to avoid incorrect and potentially dangerous attribution to primary psychiatric disorders as the chief cause of the presenting symptomatology. Although the spectrum of medical conditions in older adults that mimic psychiatric disorders is broad, this chapter will focus on the most common medical conditions that present with neuropsychiatric features and conditions for which early diagnosis and treatment are imperative.

Table 23.1 Neuropsychiatric symptomatology: features suggestive of a systemic medical origin [3–5]

Absence of risk factors and precipitants; e.g., absence of personal and family history of mental illness, absence of substance use
Medication use: long term, rapid titration, "direct" route of administration (IV or intrathecal) or high-dose use of high-risk medications, polypharmacy
Late age of onset
Sudden onset and/or rapid progression
Atypical presentation, course, or response to treatment for the putative psychiatric diagnosis
Abnormal vital signs
Altered sensorium
Unexplained laboratory results
Relapsing and remitting cognitive dysfunction
Refractory or atypical response to treatment
Poorly controlled or refractory comorbidities

Table 23.2 Systemic medical conditions with neuropsychiatric manifestations in older adults [3, 4, 6–9]

Systemic origin	Disorder
Autoimmune	Multiple sclerosis Paraneoplastic syndromes Sarcoidosis Systemic lupus erythematosus
Endocrine	Hypo/hyperparathyroidism Hypo/hypercortisolism Thyroid dysfunction
Infectious	Arboviral encephalitides: SLE and WNV encephalitis HIV/AIDS and associated opportunistic CNS infections Lyme neuroborreliosis Syphilis Tropical diseases in patients with positive travel history
Metabolic	Electrolyte abnormalities: Ca, Mg, Na Hepatic encephalopathy Hypo/hypercalcemia Micronutrient deficiencies: Fe, vitamins B_1 and B_{12}
Neoplastic	CNS tumors Paraneoplastic syndromes

Note: *CNS* central nervous system, *SLE* St. Louis encephalitis, *WNV* West Nile virus

23.1.2 Epidemiology

Risk Factors

There are some notable risk factors for misattribution of neuropsychiatric presentations to primary psychiatric disorders in older adults. Older adults with cognitive or functional impairment present a particularly vulnerable group who are at the greatest risk for developing atypical presentations of illness [10] and consequently having their symptoms misattributed. Similarly, advanced age (over age 85), polypharmacy, and multiple medical comorbidities are risk factors for atypical presentation [10] and misattribution of the etiology of illness.

Iatrogenic risk factors are particularly important as they can obscure the diagnostic lens. Cognitive biases inherent in viewing aging as the chief explanatory model for disability and morbidity can detract from a more thorough and directed workup [10]. Similarly, patients and their families may dismiss seemingly vague symptoms as part of the aging process and thus delay seeking medical attention. Admission medications are often not wholly known or are not adequately reviewed, thus making it difficult to rule out medication as an underlying or contributory cause to the clinical presentation.

Finally, comorbid psychiatric disorders paradoxically increase the likelihood of misattribution to psychiatric illness. Assumptions are often made that older adults with an active chronic psychiatric illness or a history of psychiatric illness are presenting with an exacerbation or recurrence of the condition. Similarly, nonspecific symptoms suggestive of a depressive disorder may be incorrectly viewed as a "normal" part of the aging process and not merit further investigation. This is certainly problematic given that neurovegetative symptoms often herald an evolving medical condition.

Presentations with frank psychotic symptomatology may overshadow cardinal neurocognitive features of delirium [3, 11, 12], thus making a strong case for routinely ruling out delirium in every older adult presenting with psychosis. Misattribution of etiology in older adults with neuropsychiatric presentations to some degree also reflects systemic issues of limited clinical time and resources in addition to being a reflection of cognitive bias associated with patient age.

Etiology

Autoimmune Disorders

Autoimmune disorders are a common cause of neuropsychiatric symptoms and should be considered an important source of medical mimicry. Although innumerable, some important or more common autoimmune conditions include systemic lupus erythematosus (SLE), other autoimmune vasculitides with central nervous system (CNS) involvement, multiple sclerosis, sarcoidosis, and autoimmune phenomena associated with paraneoplastic processes [3, 4, 13]. Autoimmune mechanisms underlying neuropsychiatric manifestations include intracranial vascular lesions (vasculitis and autoimmune complex deposition resulting in thrombosis); production of autoantibodies to neuronal antigens, ribosomes, and phospholipids; and cytotoxic effects of local cytokine production [9, 14, 15].

SLE will be explored in some detail as most patients with SLE develop neuropsychiatric symptoms and SLE is one of the more common autoimmune disorders that cause neuropsychiatric symptoms. The prevalence of SLE varies among populations and also varies based on the diagnostic criteria utilized. Some sources suggest an approximate prevalence of 50 in 100,000 persons [14]. Estimates for the prevalence of neuropsychiatric manifestations in patients with SLE range from 17 to 75% [9, 15]. Neuropsychiatric symptoms of SLE often manifest before SLE is recognized, as exemplified in the advanced case study (see ▶ Sect. 23.2.2).

Teaching Point

Neuropsychiatric symptoms of SLE may well precede recognition of the disorder. In fact, most patients experience seizures, acute confusion, cognitive dysfunction, psychosis, and depressive symptoms well before SLE is diagnosed.

Neuropsychiatric SLE remains the least understood manifestation of lupus [15]. Symptoms of neuropsychiatric systemic lupus erythematosus (NPSLE) may range from mild diffuse symptoms to acute life-threatening events [4, 9, 15, 16]. Neuropsychiatric manifestations of SLE are common and are associated with worse prognosis, more cumulative organ damage, and decreased quality of life [17]. Certain symptoms correlate with disease activity. For example, antineuronal antibodies correlate with cognitive dysfunction and depression, antiribosomal antibodies correlate with psychosis, and antiphospholipid antibodies correlate with stroke and vascular dementia [16, 18]. It is important to note that these autoantibodies are not definitive indicators of NPSLE.

The neuropsychiatric sequelae of SLE are defined in the diagnostic criteria established by both the original American College of Rheumatology (ACR) diagnostic criteria [19] and the revised criteria proposed by the Systemic Lupus International Collaborating Clinics [20]. The ACR classification of NPSLE (see ◘ Table 23.3) is likely the most widely referenced although none of the ACR criteria are specific to NPSLE [19].

The most common features in NPSLE are cognitive dysfunction, headache, depressive disorders, and cerebrovascular disease; however these features are also the least specific [15]. Furthermore, non-lupus causes of neuropsychiatric symptoms such as treatment complications, metabolic dysfunction, and drug intoxication may contribute to the manifestation of some of the criteria. Determination that SLE is the underlying cause of neuropsychiatric symptomatology is consequently a diagnosis of exclusion [4], thus underscoring the importance of a comprehensive and appropriate workup in order to appropriately direct treatment.

Table 23.3 Case definitions for neuropsychiatric lupus syndrome (NPSLE) based on the American College of Rheumatology recommendations [19]

Central NPSLE syndromes	Peripheral NPSLE syndromes
Acute confusional state Anxiety disorder Aseptic meningitis Cerebrovascular disease Cognitive dysfunction Demyelinating syndrome Headache Mood disorder Movement disorder Myelopathy Psychosis Seizure disorder	Acute inflammatory demyelinating polyradiculoneuropathy (Guillain-Barré syndrome) Autonomic dysfunction Cranial neuropathy Mononeuropathy Myasthenia gravis Plexopathy Polyneuropathy

In patients with NPSLE, treatment of acute lupus exacerbations typically includes the use of high-dose systemic corticosteroids and immunosuppressant agents like cyclophosphamide and azathioprine for lupus disease activity, in combination with symptom-directed treatment for neuropsychiatric symptoms [15, 21]. Unfortunately, the disease-modifying agents can also cause neuropsychiatric symptomatology including psychosis, depression, and anxiety [9, 16, 22] as illustrated in the advanced level case study (see Case 2). In addition to immunosuppressive therapy, ancillary treatments are also required in the management of NPSLE. Antipsychotic, antianxiolytic, and antiepileptic agents are often required for controlling neuropsychiatric symptoms such as psychosis, anxiety, and seizures [9].

Metabolic Disorders

Vitamin deficiencies present an important and relatively common cause of secondary neuropsychiatric symptoms in the geriatric population. Vitamin deficiencies can cause neuropsychiatric symptoms, particularly B vitamin deficiencies like cobalamin (vitamin B_{12}) and thiamine (vitamin B_1) deficiencies. Older adults are at increased risk of such deficiencies for a variety of reasons, notably dietary, physiological, and lifestyle-related factors.

Thiamine deficiency will be mentioned only briefly in this chapter. Thiamine deficiency is most commonly associated with excessive alcohol use concomitant with malnutrition and malabsorption secondary to both alcohol abuse and inadequate nutrition. The neuropsychiatric sequelae of thiamine deficiency manifest as the Wernicke-Korsakoff syndrome which includes Wernicke encephalopathy in the acute setting and Korsakoff syndrome, a chronic amnestic condition of anterograde and retrograde memory impairment with conservation of long-term memory [4]. (Please refer to ▶ Chap. 28, ▶ Sect. 28.1.2. Confusion, for further coverage of these essential conditions.)

Cobalamin deficiency is common and has potentially serious hematological and neurological complications [7].

Table 23.4 Neuropsychiatric manifestations of vitamin B_{12} deficiency [4, 7, 8]

Neurological symptoms	Psychiatric symptoms
Cerebellar ataxia	Anxiety
Cognitive impairment	Insomnia
Dorsal column signs (sensory polyneuropathy associated with dorsal column dysfunction)	Depression (with marked neurovegetative symptoms such as fatigue, anorexia, insomnia)
Decreased visual acuity	Mania
Abnormal reflexes: Babinski sign	Psychosis

Prevalence rates of cobalamin deficiency are variable due to the use of variable serum level thresholds. Epidemiological studies in industrialized nations show a cobalamin deficiency prevalence ranging from 5% to 60%, depending on the definition of cobalamin deficiency used [7, 8, 23–25]. In the older adult age group, the deficiency is noted to occur frequently, with a prevalence of at least 20% in the community and higher rates in institutionalized or hospitalized older adults [7, 23, 24]. However, the deficiency is often unrecognized because the clinical manifestations are subtle [4, 7], resemble a number of other disorders, or occur in the context of a broader syndrome such as failure to thrive.

Cobalamin deficiency in older adults primarily stems from food-cobalamin malabsorption syndrome (over 60% of all cases), pernicious anemia (15–20% of all cases), other malabsorption problems, and poor dietary intake [7, 23]. Inadequate dietary intake may variably constitute a key factor in some older adults who, for a variety of socioeconomic reasons, may not be able to obtain adequate micronutrient coverage in their diets. The *tea and toast lifestyle* is often commented on and should certainly be considered in older adults with limited budgets, vegetarian diets, and single-person households. The case of Mrs. T. (see ▶ Sect. 23.2.1) highlights a number of such factors. Neuropsychiatric symptoms of vitamin B_{12} deficiency are broad and include both central and peripheral nervous system disorders, as well as psychiatric manifestations including depression, psychosis, and anxiety, as illustrated in Table 23.4 [4, 7, 8].

It is important to note that there may be no hematologic evidence of deficiency [4, 7, 8, 25] as there can be at least a 5-year lag between the onset of insufficient intake and the onset of clinical illness, with the delay attributed to hepatic stores and enterohepatic recycling of cobalamin [7, 8]. Certain high-risk groups may develop clinical deficiency sooner and should regularly be monitored for vitamin B_{12} levels. Gastric atrophy increases with age and is a key factor in food-cobalamin malabsorption as are other risk factors outlined in Table 23.5 [7, 8]. The prevalence of these risk factors in older adults certainly underscores the need to screen B_{12} levels routinely in this age group.

Table 23.5 Predisposing factors for cobalamin deficiency in older adults [7, 8]

Anatomic factors	Atrophic gastritis: associated with age and chronic *Helicobacter pylori* infection Anatomic: gastrectomy, gastric bypass surgery Microbial proliferation: chronic antibiotic use Chronic alcohol abuse
Functional factors	Hypochlorhydria: chronic antacid use (H2-receptor antagonists, proton pump inhibitors), biguanides Pancreatic exocrine failure Chronic alcohol abuse
Other factors	Autoimmune and inflammatory processes: Sjogren's disease, Crohn's disease, pernicious anemia Immune and neoplastic processes: AIDS, lymphoma, tuberculosis Idiopathic: age-related factors

Teaching Point

Body stores of vitamin B_{12} can last 3–5 years; hence clinical evidence of vitamin B_{12} deficiency anemia is likely a reflection of prolonged deficiency.

Treatment of cobalamin deficiency in older adults typically involves parenteral administration of cyanocobalamin until serum levels are corrected, followed by ongoing supplementation depending on the underlying cause of the deficiency. Deficiency related to pernicious anemia requires lifelong supplementation. The most important aspect of treatment is the involvement of hematology specialists to rule out non-dietary causes and to initiate treatment. As diet alone (i.e., without any of the other risk factors identified in Table 23.5) is not a common cause of vitamin B_{12} deficiency anemia in older adults in industrialized nations [7, 23], it is imperative to attempt to involve hematology in identifying the underlying cause of cobalamin deficiency as there are potentially serious complications associated with this vitamin deficiency. Of note, neurologic damage caused by cobalamin deficiency is often irreversible; thus early identification and correction are imperative [23, 24].

In terms of other metabolic disorders that may potentially result in neuropsychiatric symptoms, the list of possibilities is infinite and cannot be covered in depth here. However, it is important to make brief mention of calcium disorders as they can cause severe neuropsychiatric symptomatology and are more common in the geriatric age group [26]. Hypocalcemia can cause emotional lability, psychosis, anxiety, depression, and seizures depending on the degree of hypocalcemia and the rapidity of decline in serum calcium levels [27]. In contrast, hypercalcemia can manifest with confusion, psychosis, lethargy, and weakness and progress to serious outcomes like coma and death [26]. In older adults, hypercalcemia is usually secondary to primary hyperparathyroidism as described below.

Endocrine Disorders

Endocrine disorders can frequently cause neuropsychiatric symptoms. The most commonly encountered endocrine disorders in older adults are diabetes mellitus which is associated with increased rates of depression and thyroid dysfunction which is associated with a broad spectrum of neuropsychiatric symptoms as discussed below. Clinicians should also be aware of hyperparathyroidism as it presents with neuropsychiatric symptoms and can cause serious morbidity [26]. Primary hyperparathyroidism is a disorder of calcium homeostasis that occurs most commonly in older adults and results in a hypercalcemic state [28]. Neuropsychiatric manifestations of the resultant hypercalcemic state may range from mild depression and cognitive changes to extreme agitation and psychosis.

Teaching Point

Clinical suspicion of secondary hyperparathyroidism should be raised in patients with a history of chronic lithium treatment, prolonged or severe vitamin D deficiency, or neck radiation therapy [29].

Hypothyroidism can present with symptoms suggestive of a depressive disorder with associated pseudodementia, while hypothyroidism caused by autoimmune thyroiditis is associated with delirium and recurrent episodes of psychosis [30]. Hypothyroidism should be suspected in patients presenting with systemic symptoms of the disorder, including cold intolerance, fatigue, lethargy, dry skin, brittle hair, and weight gain. Associated neurological symptoms include proximal muscle weakness and pain, ataxia, and peripheral neuropathies such as carpal tunnel syndrome [3, 30]. Typically in older adults, there is a known history of hypothyroidism, so it is important to assess thyroid status and medication adherence as part of the initial approach workup.

In older adults, hyperthyroidism can also present with depression and lethargy, while in younger adults anxiety and irritability are more common. Other neuropsychiatric symptoms of hyperthyroidism include cognitive impairment, psychosis, and peripheral nervous system manifestations such as sensory polyneuropathy and myopathy [3, 4, 30]. Restoration of the euthyroid state results in resolution of symptoms, but it is unknown what proportion of patients experience incomplete recovery with both hypothyroidism and hyperthyroidism.

Infectious Disorders

Infectious disorders constitute an important source of neuropsychiatric morbidity. While a number of infectious processes declare themselves relatively quickly, some infections are more occult, particularly in the aging adult. The age-related modulation in constitutional symptoms of infection can obscure presentation and timely detection. Similarly,

cognitive biases and lack of attention to epidemiological trends may steer clinicians awry. Sexuality, sexual activity, and the shifting patterns in sexually transmitted infection epidemiology constitute one such blind spot that should become more routine considerations on the history, particularly with the aging of the human immunodeficiency virus (HIV) epidemic and the recently observed rise in sexually transmitted infections across all age groups [31, 32].

The evolution of highly active antiretroviral therapy (HAART) has significantly prolonged the life span of those living with HIV [33, 34]; thus clinicians can expect to encounter a small but steadily growing proportion of older adult patients living with HIV. To this end, the recognition of neuropsychiatric manifestations of HIV is necessary as a number of HIV-related syndromes present with neuropsychiatric symptomatology including depression, neurocognitive impairment, mania, and psychosis. The etiology of neuropsychiatric symptomatology in HIV is manifold and includes the direct activity of primary HIV disease, opportunistic infections and malignancies, neurotoxic effects of medication, and the psychosocial consequences associated with the infection [3, 34, 35].

The need for heightened awareness of the aging of the HIV epidemic is underscored by recent disease estimates. In 2005, 25% of those infected with HIV were older than age 50, and older adults accounted for 15% of new HIV cases [34], largely due to ongoing advances in treatment. American projections estimated that by 2015, 50% of HIV-infected individuals in the United States were likely to be aged 50 and older [33].

Although 50 years is significantly younger than the conventional definition of the geriatric age group, HIV-positive individuals above the age of 50 and uninfected individuals above the age of 65 are in fact comparable when one considers that those infected with HIV age at a much faster rate and experience clinical conditions typically encountered in the geriatric population.

Teaching Point

Clinicians should have increased awareness of the aging of the HIV epidemic, particularly as neuropsychiatric presentations of the underlying immunological condition are relatively common.

Regrettably, despite the increasing prevalence of HIV in older patients and favorable cost-effectiveness for HIV testing [33], clinicians are not routinely considering the possibility of HIV in older patients presenting with unexplained neuropsychiatric symptomatology nor testing for HIV infection with the result that older patients have more advanced disease than do younger patients by the time they are diagnosed [33]. This lag allows further progression of the underlying disease and in fact makes it more likely that patients are misdiagnosed with primary neuropsychiatric disorders, which are certainly high on the list of differential diagnoses to consider. To complicate matters even further, primary psychiatric disorders coexist with secondary psychiatric disorders in those living with HIV and AIDS (acquired immune deficiency syndrome). For example, depression can develop as a primary underlying disorder or as a result of the HIV infection, its treatment, substance abuse comorbidity, or the stigma of living with the disease [36, 37]. The prevalence of depressive disorders in seropositive individuals is at least twice that of the general population [36].

The CNS is often one of the first targets of HIV infection [38]. The effect of chronic immune activation and accelerated senescence on the CNS is manifested in an impairment of cognition, known as HIV-associated neurocognitive disorder (HAND). HAND is characterized by memory impairment, depressive symptoms, and movement disorders such as ataxia, tremor, weakness, and bradykinesia [39]. The prevalence of neurocognitive impairment associated with HIV is quite significant, with some degree of neurocognitive impairment detected in as many as a quarter to half of all patients infected with HIV in one large study [39].

The spectrum of HAND is broad, ranging from milder forms, such as asymptomatic neurocognitive impairment and mild neurocognitive disorder, to the most severe form, HIV-associated major neurocognitive disorder [38]. Currently, no therapy other than combined antiretroviral therapy is recommended for routine treatment of HAND in the clinical setting [38]. Recognition of the HAND spectrum is difficult if a diagnosis of HIV has not been made. In patients with a known diagnosis of HIV, distinguishing HAND from other neuropsychiatric disorders requires a systematic assessment, including the history; physical examination including cognitive screening; and laboratory investigations, particularly brain imaging, cerebrospinal fluid studies, and blood tests including testing for common coinfections and opportunistic infections.

In terms of the history, it is important to elucidate both the pattern and course of progression of neurocognitive impairment. Rapid progression combined with a pattern of prominent difficulties in learning new information, rapid forgetting, and language problems (e.g., deficits in naming and comprehension) are suggestive of an underlying neurocognitive disorder such as Alzheimer disease as such features are not prominent in HAND [38]. The most severe form of HAND, known as HIV-associated dementia (HAD), is characterized by profound abnormalities in neuropsychological testing and significant impairment in a patient's ability to perform activities of daily living [4, 35, 39]; however, unlike Alzheimer disease and other primary major neurocognitive disorders, the neurocognitive deficits of HAD are generally reversible with HAART and supportive management [4, 38].

In terms of the physical examination, fluctuating or atypical patterns of cognitive deficits in the absence of a delirium should certainly raise clinical suspicion for autoimmune and infectious processes when more common causes of neurocognitive impairment have been ruled out. No specific cognitive screening tools have been identified for HAND [38]. Attention to the presence of signs and symptoms suggestive of opportunistic or AIDS-defining conditions is an important

indicator of disease progression and activity at specific sites, in combination with viral load, CD4+ counts, and neurotoxicity of the HAART regimen in use. In patients on a regimen including a HAART agent with relatively high CNS penetration effectiveness, neurotoxicity secondary to the HAART should be suspected in patients presenting with neuropsychiatric symptomatology.

The mainstay of treatment for HAND is combined antiretroviral therapy [38]. The approach to treatment should initially involve confirmation of treatment adherence, particularly as neurocognitive disorders can interfere with treatment adherence. In untreated patients, specialist consult for initiation of a HAART regimen with high CNS penetrance is necessary. A modest degree of improvement in neuropsychiatric functioning can be expected with HAART treatment for at least 1 year, particularly with respect to attention, processing speed, and executive performance [38]. Adjunct treatment such as antipsychotics, psychostimulants, and supportive care may be required at the outset to manage symptoms. In patients with HAD, psychological support and rehabilitation therapy are essential for functional recovery, as HAD may result in significant impairment in a patient's ability to perform activities of daily living [4, 40].

In patients in whom HIV is suspected or known, investigations should also include screening for syphilis as the rates of HIV and syphilis coinfection are on the rise [31]. Similarly, if neurosyphilis is suspected, concurrent HIV testing should be done. Syphilis has historically been described as *the great pretender* due to its variable manifestations including prolonged periods of indolence over the course of illness and nonspecific symptomatology like the flu-like symptoms that characterize the secondary stage. Neurosyphilis is commonly a late-stage presentation of syphilis; however it can occur at any stage of infection and has manifold presentations [31]. Late neurosyphilis can present with a variety of clinical CNS syndromes, including neurocognitive disorder, paresis, and locomotor ataxia (known as tabes dorsalis) [4, 31]. No single laboratory test or clinical feature can diagnose neurosyphilis; rather the diagnosis is based on a combination of clinical presentation and serum or cerebrospinal fluid evaluation.

In terms of the approach to suspected neurosyphilis, involvement of an infectious disease specialist is essential to the appropriate workup and subsequent treatment of patients, particularly given the elusive nature of syphilis and the psychometric properties associated with diagnostic tests. Only 30–40% of patients with primary syphilis are diagnosed at the primary stage of infection [31] and may subsequently fail to recognize or seek medical attention for manifestations indicative of the secondary stage of infection; they may also be misdiagnosed given the "flu-like" nature of a number of secondary stage symptoms. Thus, patients may remain unaware of the infection well into their advanced years, as tertiary syphilis may remain latent for decades. The tertiary stage of infection may manifest as neurosyphilis or less commonly as cardiovascular or gummatous disease [31]. It is unclear how long it takes to develop clinical neurosyphilis after the central nervous system becomes infected [31].

Patients suspected of having syphilis are usually screened with nontreponemal tests initially, including the Venereal Disease Research Laboratory (VDRL) and Rapid Plasma Reagin (RPR) tests, but specific treponemal testing is also required, particularly in patients with strong risk factors such as infection with HIV or unexplained neuropsychiatric symptoms in the setting of risk factors [4, 31, 32]. Syphilis is considered a reemerging infection [32], and given its above-noted properties, it is imperative to consider it on the differential. Sexuality and sexually transmitted infections are not often considered in the geriatric population, but this cognitive bias needs to be remediated, particularly in light of recent epidemiologic trends as the bias may result in prolonged morbidity and potential mortality. Finally, as part of the management plan, it is essential to discharge the duty to report to public health authorities, a requirement in most jurisdictions.

Paraneoplastic Processes

Paraneoplastic syndromes are autoimmune-mediated processes, with antineuronal antibodies directed at organ and tissue sites distant to a primary malignancy or metastases [3, 4]. Paraneoplastic syndromes may precede the diagnoses of cancer and cause an innumerable variety of symptoms, including neuropsychiatric symptoms like fluctuating levels of consciousness, cognitive dysfunction, psychosis, hypomania/mania, and depression [4]. In paraneoplastic limbic encephalitis, neuropsychiatric symptoms arise as a result of autoantibodies directed toward neuronal intracellular or cell membrane antigens [3, 41]. Suspicion of a paraneoplastic process should arise in refractory neuropsychiatric syndromes and trigger a tumor search as the key principle of management is treatment of the underlying tumor in conjunction with the use of immunosuppressants. Paraneoplastic limbic encephalitis is most commonly associated with small-cell lung cancer, but various other tumors have also been implicated [3].

Iatrogenic Factors

Iatrogenic factors constitute an important source of secondary neuropsychiatric symptomatology. Iatrogenic factors can be diverse but chiefly include the choice of treatment (in particular pharmacological treatment) and the role of cognitive bias. In terms of pharmacologic treatment factors, the propensity of pharmacological agents to cause neuropsychiatric effects is significant, with the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition* [42], describing a number of categories of medication-induced syndromes. (See ► Chap. 5.) In older adults, some of these categories are noteworthy, including medication-induced neurocognitive disorders. The role of medication cannot be underscored enough given the prevalence of polypharmacy among older adults.

In prior editions of the *Diagnostic and Statistical Manual of Mental Disorders*, "persisting dementia induced by sedatives, hypnotics, or anxiolytics" [1] was described and is highly relevant among older adults whom are often prescribed such

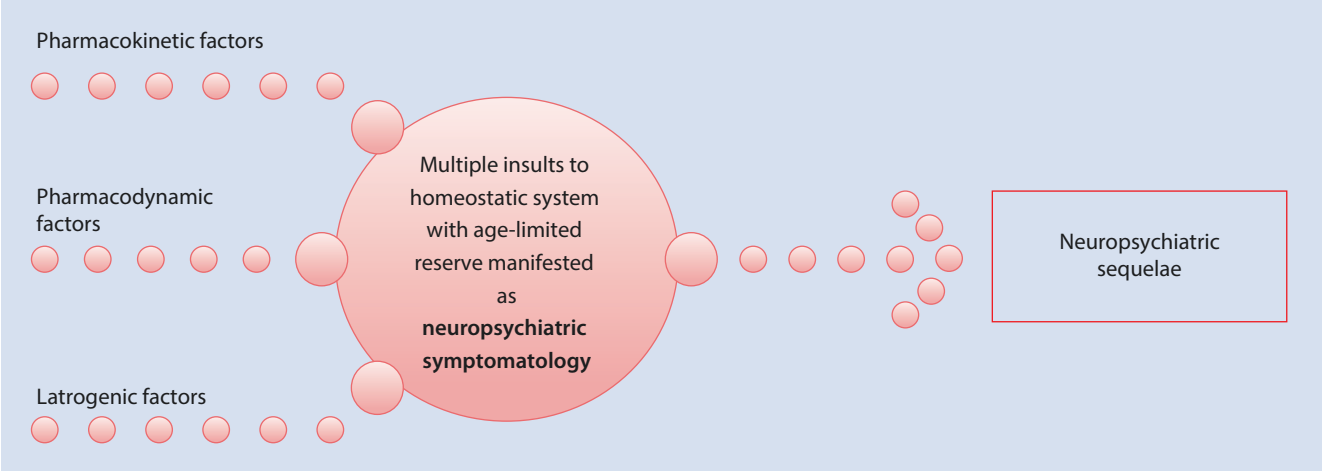

Fig. 23.1 Age-related risk factors contributing to neuropsychiatric manifestations of medical conditions [43–45]

agents both in primary care and during hospitalizations. Subsequent tolerance to these agents results in long-term use which creates the setting for dementia-like presentations. As age is the leading risk factor for major neurocognitive disorder, these presentations are more likely to be attributed to a primary neurocognitive disorder, with failure to recognize sedatives, hypnotics, or anxiolytics as the underlying issue. As such, active medication reviews should be routinely prioritized in the care of the geriatric patients. Furthermore, the process should not focus on psychotropic agents alone. While psychotropic medications are certainly more likely to cause neuropsychiatric effects given that the CNS is the chief site of action, psychotropic medications will not be explored here as they fall outside the scope of the chapter and will be discussed elsewhere (see ▶ Chaps. 5 and 26).

The mechanisms underlying the neuropsychiatric effects of pharmacological agents relate to pharmacokinetic, pharmacodynamic, and patient-specific factors as summarized in Fig. 23.1 [43–45]. In terms of pharmacokinetic factors, drug absorption may be impaired for certain medications and micronutrients, notably vitamin B_{12} absorption in the small intestine. Drug distribution is also affected, with fat-soluble drugs distributed more widely and water-soluble drugs less extensively [44]. Age-related decline in hepatocytes and microsomal activity [43, 45] results in decreased metabolism and elimination, particularly with drugs that are eliminated by the hepatic cytochrome enzyme system [45]. Finally, drug excretion is decreased with decreasing kidney function; thus dose adjustment and titration must be carefully considered. In terms of patient-specific factors, individual health state, genetic liabilities (particularly with respect to isoforms of cytochrome P450 enzymes), and behavioral factors including comorbid substance use are important considerations with respect to the neuropsychiatric liability of medications.

Although it is understood that medications can present an important causal or contributory factor in psychosis associated with delirium, pharmacotherapy as a source of psychosis outside the context of delirium is not as well recognized as it should be. Furthermore, a number of the pharmacological treatments utilized in internal medicine can result in side effects that mimic symptoms of depression, anxiety, mania, and psychosis [5]. Extreme effects including suicidal ideation can also occur [5]. Although medication-induced neuropsychiatric symptoms are more likely to occur at high doses or with rapid titration or discontinuation, it is important to note that neuropsychiatric side effects also occur at therapeutic doses. Certain pharmacological agents are more likely to cause neuropsychiatric side effects, notably corticosteroids; disease-modifying biologic agents, some of which can directly affect neurotransmission; anticholinergic agents; antiviral agents; and sympathomimetic agents as illustrated in Fig. 23.2 [5]. The important role of pharmacotherapy is more extensively reviewed in ▶ Chap. 5.

In terms of the other iatrogenic factor noted above, the role of cognitive bias can be significant. Cognitive biases implicit in clinicians' approach to older adults may shape multiple layers of the clinical encounter from the type of history requested to the choice of investigations and the differential diagnoses considered. As discussed above in the HIV section, there is a tendency to overlook infectious causes such as HIV and syphilis despite epidemiological evidence to the contrary. Such cognitive blind spots are certainly problematic given the delay in diagnoses and initiation of appropriate treatment. Misattribution to a primary neuropsychiatric disorder further exposes patients to unnecessary psychotropic medication.

23.1.3 Approach to Neuropsychiatric Presentations

The evaluation of the patient presenting with neuropsychiatric symptoms and the extent of medical workup should be guided by clinical and epidemiological context [3]. Conducting a workup for what is initially a very broad differ-

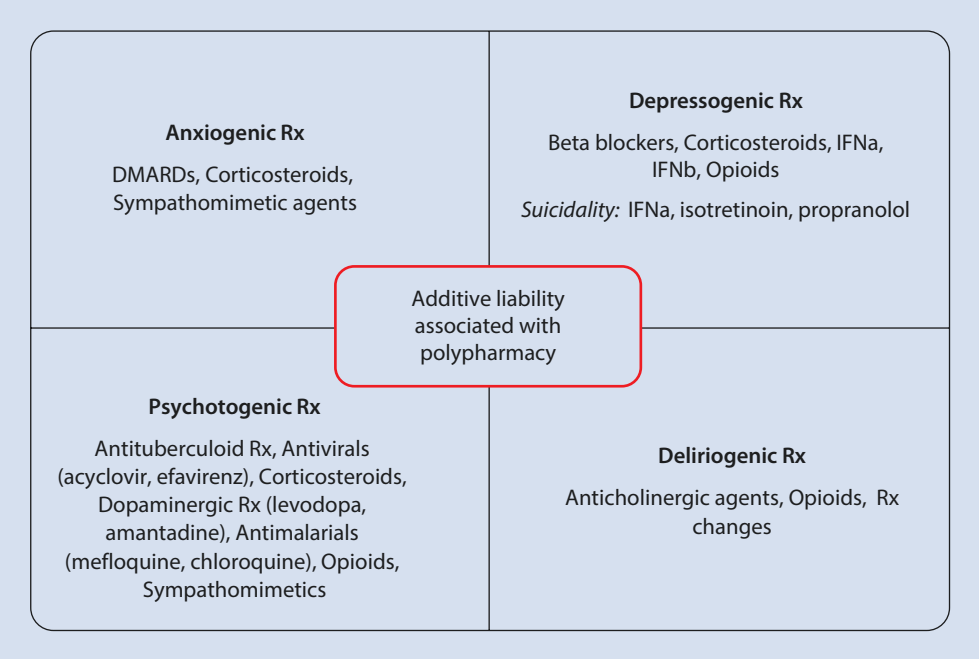

Fig. 23.2 Medications with high propensity to cause neuropsychiatric side effects in older adults [5]. *DMARD* disease-modifying antirheumatic drug, *IFN* interferon, *Rx* treatment

ential diagnosis can prove to be unwieldy and uninformative in the absence of clinical and epidemiological context to help avert indiscriminate investigative tests. Although there is no standardized workup for neuropsychiatric symptomatology, the foundation of the initial approach rests on a thorough evaluation as exemplified in ▶ Chap. 2.

Laboratory investigations should be conducted if not done recently, and attention should be paid to serial vitals and serial cognitive screens in patients presenting with neuropsychiatric symptoms suggestive of a medical etiology. In terms of parameters to include in the investigations, this should be informed by the history and physical examination, particularly the presenting signs and symptoms, past medical history, and medication regimen. In patients presenting with an unusual history, atypical or profound symptoms, and treatment-refractory symptoms, brain imaging should be considered, particularly when there are focal/lateralizing neurological symptoms [3].

As mentioned above, there is no standardized approach to the workup of patients presenting with neuropsychiatric symptoms. The general approach should be to start broadly with respect to differential diagnoses, particularly in older adults with no prior history of neuropsychiatric symptoms, narrow down based on clinical and epidemiological factors, and then refine the diagnostic inquiry further based on serial evaluations and response to treatment or lack thereof. Given that certain conditions are easily tested for and readily treatable, it is recommended to specifically exclude conditions such as B_{12} deficiency and thyroid dysfunction in every older adult presenting with neuropsychiatric symptoms, particularly as these conditions are relatively common in the older adult population.

23.2 Case Studies

Autoimmune disorders and endocrine disorders present an important source of medical mimicry given the broad spectrum of associated symptomatology. Neuropsychiatric mimicry by such medical conditions is notable in complexity, morbidity, and, regrettably, in the ease of misattribution despite the fact that these disorders are not uncommon. The following cases illustrate the preponderance and complexity of neuropsychiatric comorbidity associated with these medical conditions.

23.2.1 Case 1

Case 1 History

Mrs. T. is an 80-year-old widow who resides alone in an apartment. She was admitted for failure to thrive at home after her apartment superintendent found her apartment to be in a poor state during a visit to replace smoke detectors. She was noted to have no food in the refrigerator beyond a few loaves of bread, the apartment was malodorous with the smell of urine and feces although no soiled items were visible, and the smoke detectors had been dismantled. Mrs. T. indicated that she had to dismantle the carbon monoxide and smoke detectors as they contained hidden cameras that had been monitoring her. An ambulance was called, and Mrs. T. was transported to a hospital where she was admitted to the internal medicine service with a diagnosis of failure to thrive, which was subsequently revised to a diagnosis of mild neurocognitive disorder due to Alzheimer disease.

She has a history of upper gastrointestinal bleed, hypertension, osteoporosis, hypothyroidism, depression, and recently had shingles. She has a remote history of treatment for chronic *Helicobacter pylori* infection diagnosed following immigration for Poland at the age of 47. She also has a remote history of alcohol use disorder. Her current medications include pantoprazole, aspirin, hydrochlorothiazide, levothyroxine, sertraline, and an over-the-counter omega supplement.

On the internal medicine ward, she was noted to be withdrawn and dysphoric and complained that she was too weak and tired to engage in physiotherapy. During an attempted occupational therapy assessment, she was noted to be unsteady on her feet and clumsy with items requiring fine grip. Mrs. T. attributed her unsteady gait and clumsiness to weakness and light-headedness because of the "water pill". The psychiatric consultant was requested to adjust Mrs. T.'s antidepressant as she appears profoundly depressed despite being on an adequate dosage of sertraline at 175 mg po daily. Sertraline was initiated for depression 5 years ago following her husband's death. As the psychiatric consultant, on evaluating Mrs. T., you are struck by the degree of lassitude and fatigue. Mrs. T.'s daughter also happens to be present and reports that the psychotic symptoms evolved gradually over the past 6–9 months. Both Mrs. T. and her daughter deny any psychotic symptoms accompanying her depressive symptoms prior to that.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What additional information would you like to elicit on history?

Question 2. What investigations should be ordered?

Question 3. What is your differential diagnosis?

Question 4. What is your approach to treatment?

Case 1 Answers

Case 1 Answer 1 (Question 1—What additional information would you like to elicit on history?)

Inquiry should be made about the following items:

- Dietary information: this reveals that Mrs. T. stopped cooking after her husband's death as she did not see any point to cooking for one. She largely subsists on sandwiches, cereal, and crackers with peanut butter. However, she does get a hot meal once a week during the apartment building's weekly community meal.
- Last alcohol use and history of medical complications with alcohol: this reveals that Mrs. T. relapsed for a 31-month period after her husband died 5 years ago. Mrs. T. has a history of complicated alcohol withdrawals, with three prior medical admissions for the same.
- Medication adherence: this reveals that she is adherent with all her medications although she stopped taking her bisphosphonate 3 years ago contrary to her primary care physician's advice.

Case 1 Answer 2 (Question 2—What investigations should be ordered?)

The following should be included in the initial investigations:

- CBC with differential: this is to rule out anemia contributing to neurovegetative symptoms. Mrs. T. has a history of *H. pylori* infection, malnutrition, and alcohol use disorder, all of which are risk factors for cobalamin and other micronutrient deficiencies. Cobalamin deficiency could generate all of the above neuropsychiatric symptoms.
- Extended electrolyte panel: this is to rule out electrolyte disturbances contributing to neurovegetative symptoms. Mrs. T. is an older female on an SSRI medication (sertraline) and would be at increased risk of hyponatremia due to syndrome of inappropriate antidiuretic hormone (SIADH). Similarly, she is malnourished, is not taking vitamin or mineral supplements, and does not take her bisphosphonate, so one wonders about prolonged, severe calcium, magnesium, or vitamin D deficiencies, all of which can affect calcium homeostasis. You find out that the abnormal results on the laboratory investigations include a low sodium level (Na + 129 mmol/L or 129 mEq/L), but other electrolytes are within normal limits.
- Vitamin B_{12} level: this is to rule out deficiency given the history of malnutrition, alcohol use disorder, and previous chronic *H. pylori* infection as these contribute to food-cobalamin malabsorption, and the latter two are risk factors for atrophic gastritis. You learn that the B_{12} level is found to be at the lowest end of the hospital laboratory's reference range.
- Parathyroid hormone (PTH) and thyroid-stimulating hormone (TSH) level: this is to assess current thyroid status in a patient with known history of hypothyroidism and to rule out parathyroid dysfunction.
- Serial cognitive screening: this is to help identify baseline cognition at admission and repeat screening to track any changes with treatment; robust recovery in the cognitive screen concurrent with improved performance on the occupational therapy assessment would put in question the diagnosis of Alzheimer-related neurocognitive disorder.
- Consider magnetic resonance imaging (MRI) of the brain: this is to rule out structural defects given the patient's neurological symptoms.

Teaching Point

Red blood cell indices like mean corpuscular volume (MCV) do not rule out clinical cobalamin deficiency. In fact, the severity of neuropsychiatric complications is thought to inversely correlate with the severity of megaloblastic anemia [4]. Neuropsychiatric complications can occur in the absence of any hematologic evidence of megaloblastic anemia or other conditions

associated with B_{12} deficiency [4]. It is recommended to maintain plasma vitamin B_{12} levels in the mid-normal range (400–500 pg/mL or 295–369 pmol/L) to reduce the risk of cobalamin-related neuropsychiatric disorders [24].

Case 1 Answer 3 (Question 3—What is your differential diagnosis?)

The differential for Mrs. T.'s neuropsychiatric symptoms is broad given the complex medical history and polypharmacy but would include in descending order:

- Vitamin B_{12} deficiency anemia: Mrs. T. has multiple risk factors for cobalamin deficiency as described above in Answer 2. In addition, her neuropsychiatric symptoms including the diagnosis of major neurocognitive disorder may all stem from advanced B_{12} deficiency. The features noted by the occupational therapist (i.e., ataxia, clumsiness which may reflect a polyneuropathy) also support the possibility of a vitamin B_{12} deficiency.
- Major depressive disorder with associated pseudodementia.
- Korsakoff syndrome: despite reported discontinuation of alcohol use in this case, the cerebellar signs and amnestic symptoms may reflect persisting effects of chronic alcohol abuse, in addition to which there may still be undisclosed ongoing alcohol use due to shame.
- Hyponatremia: hyponatremia associated with sertraline should be considered given the history of weakness, cognitive disturbance, and hyponatremia, particularly in an older female. Hyponatremia due to SIADH is associated with the use of serotoninergic medications. Evaluation of hyponatremia requires assessment of the volume status (typically euvolemic in SIADH) as well as serum and urine osmolalities and urine sodium.

Teaching Point

Clinicians should consider screening for cobalamin deficiency in (i) all older adults suspected to be malnourished, (ii) all older adults with risk factors identified in Table 23.5, and (iii) all institutionalized or hospitalized older adults.

Case 1 Answer 4 (Question 4—What is your approach to treatment?)

The treatment approach will depend on the findings of the above-recommended investigations and further history elicited, including the following:

- Treat like alcohol use is still present. Initiate the Clinical Institute Withdrawal Assessment for Alcohol (CIWA) at admission and ensure thiamine is administered in addition to a multivitamin given the history of malnourishment.
- Replenish vitamin B_{12}.
- Consult neurology specialty given the above-noted neurological findings.
- Immediately discontinue sertraline given symptomatic hyponatremia and history of gastrointestinal bleed; assess volume status, urine and serum osmolalities, and urine sodium to confirm a diagnosis of SIADH; and recommend that a non-SSRI antidepressant be initiated if mood symptoms do not subside appreciably with vitamin B_{12} replenishment.
- Serial cognitive and functional assessments throughout the course of treatment.
- Response to treatment may be gradual; therefore recommend transfer to a rehabilitation ward to optimize level of function once acute treatment is completed.

Teaching Point

Structural brain damage can occur with advanced cobalamin deficiency; hence early identification and correction are imperative.

Case 1 Analysis The case above demonstrates the subtle and indolent nature of cobalamin deficiency, in keeping with the gradual depletion of an estimated 5–10-year hepatic storage capacity that is supplemented by the enterohepatic cycle [23]. The case also emphasizes the multifactorial nature of presentations in geriatric patients of advanced age as they typically present with multiple subtle concurrent medical derangements with neuropsychiatric manifestations. Mrs. T.'s vitamin B_{12} level was at the low end of the normal range but still within "normal" limits which may suggest a low likelihood of clinical deficiency. However, a low normal serum B_{12} level does not rule out clinical deficiency as variable reference ranges are used. Since vitamin B_{12} deficiency can occur despite normal serum cobalamin levels, some recommend that in patients treated for neuropsychiatric B_{12} deficiency, homocysteine and methylmalonic acid levels should also be measured to decrease false-negative findings, in addition to which cobalamin levels should be monitored annually in at-risk patients, patients who discontinue supplementation after resolution of symptoms, and patients with confirmed replenishment [24]. The potential seriousness of the complications associated with cobalamin deficiency (particularly neuropsychiatric and hematological) requires investigation of all patients in whom malnourishment is suspected or reported [7, 25].

23.2.2 Case 2

Case 2 History

Mrs. G. is a 69-year-old female who presented to the emergency department with a history of what her family described as suspiciousness, transient episodes of confusion that were becoming more frequent, debilitating clusters of headaches,

and intermittent rapid-onset psychotic symptoms. She is agitated on presentation and is not able to provide a useful history. In fact, she appears to have trouble comprehending questions and is transiently inattentive or internally preoccupied during intake at the emergency department triage. She has a history of recurrent depressive episodes with postpartum onset at the age of 28. Some of the recent episodes of depression coincided with psychotic symptomatology, but most of her psychotic symptoms were not accompanied by depressive symptoms. In addition, her psychotic episodes in the past few years have changed in quality in that their onset was rather abrupt. At present, she only partially meets criteria for a major depressive episode.

Her medications are confirmed to include phenytoin 200 mg po tid, citalopram 20 mg po od, aspirin 81 mg po od, and ramipril 2.5 mg po od, with no changes in the past 3 years. Her family reports that they ensure adherence as Mrs. G.'s husband dispenses her medications. Although her primary care physician had recently prescribed donepezil (for memory decline), Mrs. G. had refused to start it due to concerns about side effects.

Her past medical history is also positive for hypertension, 30-pack-year history of smoking, a decade-long history of recalcitrant epileptic seizures, and a 5-year history of "memory trouble sometimes but then she becomes a bit better again" according to the history elicited from her husband and son. The patient had recently been diagnosed with early major neurocognitive disorder by her primary care physician and was referred to a geriatrician for a second opinion. The patient's family was concerned about the wait to see a geriatrician, in addition to which the family was finding it increasingly challenging to cope with the patient's suspiciousness and acute episodes of psychosis, with prior episodes precipitating two emergency department visits in the past 18 months. These visits precipitated 3–7-day admissions for presumed delirium, but no underlying causes were ever identified.

On presenting to the emergency department this time, the patient was medically cleared and admitted to the psychiatric ward with an admitting diagnosis of major depressive disorder, with psychotic features. She was seen by the geriatrics service who concluded that her presentation was atypical and likely not in keeping with major neurocognitive disorder despite a grossly abnormal MoCA score of 18 out of 30. Note was made of a history of spontaneous recovery in cognitive function off and on in the past few years as the geriatrician was able to obtain some prior cognitive screens from Mrs. G.'s primary care physician. The geriatrician suggested a neurology consult to rule out cognitive impairment associated with undertreated seizure disorder.

Once on the psychiatric ward, Mrs. G. began complaining of various somatic symptoms, including fatigue, headaches, myalgias, and arthralgias. She accused her nurses and her psychiatrist of injecting her joints with noxious substances while she was asleep and reported observing her psychiatrist adulterating her body lotion, hence the new-onset arthralgias and myalgias. She refused to allow vital signs to be done but was noted to be diaphoretic and complained of "burning inside" because of being poisoned by her doctors and nurses. She eventually allowed her temperature to be taken and was febrile (37.7 °C or 99.8 °F).

Although some of the somatic features were thought to be associated with an evolving episode of depression, note was made of mild swelling in her wrists and febrile leukopenia. Blood cultures were negative. The constellation of unusual signs and symptoms prompted further laboratory investigations, including an autoimmune panel. The autoimmune panel was positive for markedly elevated ESR, CRP, and a positive ANA titer, so the internal medicine service was consulted. Further autoimmune bloodwork was requested and showed the presence of the following autoantibodies: antiphospholipid antibodies, anti-double-stranded DNA, anti-ribosome P, and anti-Sm. The patient was evaluated by the rheumatology service and diagnosed with systemic lupus erythematosus (SLE), based on the American College of Rheumatology (ACR) diagnostic criteria.

The patient was transferred to an internal medicine ward where she was treated with a regimen of high-dose corticosteroids and cyclophosphamide. She was also treated with antipsychotic agents as her mental status deteriorated rapidly, with frank psychosis and significant worsening in depressive symptoms. However, her arthralgias, myalgias, and headaches concurrently improved, and the swelling in her joints resolved. Eventually there was gradual but significant improvement in serial cognitive screens, and her depressive and psychotic symptoms resolved.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. What conditions would you consider in the differential diagnoses?

? Question 2. How likely is it that Mrs. G.'s psychosis is associated with a primary seizure disorder?

? Question 3. What is the most likely cause of Mrs. G.'s initial psychiatric decompensation on transfer to the internal medicine service? Has she been misdiagnosed with SLE given that treatment for SLE worsened her mental status?

Case 2 Answers

Case 2 Answer 1 (Question 1—What conditions would you consider in the differential diagnoses?)

Perhaps the most challenging presentation occurs with patients who like Mrs. G. have a known history of primary psychiatric disturbance, as the question is then whether the presentation reflects an acute decompensation of a preexisting chronic or recurrent psychiatric disorder. Once more, the role of a careful workup and consideration of factors identified in ◘ Table 23.1 should steer clinicians to consider a medical process in the differential diagnosis. In Mrs. G.'s case, her prior history of both concurrent and nonconcurrent mood and psychotic symptoms suggests a schizoaffective

disorder, but this should not detract from consideration of a broader differential in light of her constellation of symptoms.

In terms of nonpsychiatric differential diagnoses, consideration of broad causes such as the following is important given Mrs. G.'s past medical history and presenting symptoms: neurological disorders including seizure disorder (see Question 2), infection, autoimmune disorder, paraneoplastic process, endocrine/metabolic processes, and iatrogenic causes. Her initial presentation in the emergency department suggests an episode of delirium, and this should always remain on the differential given the associated morbidity and mortality. The history should rule out B symptoms like fever, night sweats, and weight loss (i.e., constitutional symptoms suggestive of a neoplastic process), toxic exposures, iatrogenic causes like medication changes, and serial neurocognitive screening. Initial laboratory investigations should at minimum include evaluation of extended electrolytes, urinalysis, thyroid activity, vitamin B_{12} level, chest X-ray, and MRI of the brain in addition to baseline parameters like the CBC, electrolytes, blood urea nitrogen, and creatinine.

Teaching Point
Delirium is a medical emergency. Any older adult presenting like Mrs. G. with inattentiveness, confusion, and preoccupation with internal stimuli should be worked up to rule out a delirium.

Case 2 Answer 2 (Question 2—How likely is it that Mrs. G.'s psychosis is associated with a primary seizure disorder?)

Mrs. G. carries a diagnosis of major depressive disorder with psychotic features but has episodes of psychosis in the absence of depression and a history of refractory seizures, confusion, and cognitive impairment which raises the question of a primary seizure disorder with persisting postictal or interictal neuropsychiatric symptoms. Epilepsy is one of the most common chronic neurological diseases and may result in a conclusion of a primary seizure disorder, even in the setting of concurrent albeit vague or nonspecific concurrent symptomatology that suggest otherwise. Psychiatric symptoms are overrepresented in patients with epilepsy, making it more likely that Mrs. G.'s presentation is mistaken for a primary neuropsychiatric disorder. It is important to note that the rate of seizures in patients with SLE is three times the rate in the general population, and seizures reflect the sequelae of disease activity [16]; hence treatment response to traditional antiepileptic drugs is poor in patients with SLE.

Teaching Point
Seizures due to SLE respond poorly to antiepileptic drugs because seizure activity is typically precipitated by thrombotic sequelae of lupus cerebritis. As such, management of seizures is directed at SLE disease activity through anticoagulation.

In terms of Mrs. G.'s history of refractory seizures, this is often seen in patients with SLE, hence the recognition of seizures as a diagnostic item in the ACR criteria [19]. Mrs. G.'s seizures well predate the presentation of other symptoms of her underlying autoimmune disorder. This pattern is in fact quite common in patients with SLE, with seizures and nonspecific symptoms like fatigue, confusion, and cognitive impairment presenting years before recognition of SLE [15, 16].

Case 2 Answer 3 (Question 3—What is the most likely cause of Mrs. G.'s initial psychiatric decompensation on transfer to the internal medicine service? Has she been misdiagnosed with SLE given that treatment for SLE worsened her mental status?)

The initial worsening in Mrs. G.'s psychosis is likely associated with high-dose intravenous steroids, particularly as her physical symptoms of SLE concurrently improved despite worsened psychosis. Corticosteroids have a high propensity to induce neuropsychiatric side effects. Approximately 6% of all patients develop some psychiatric side effects with administration of corticosteroids [5]; the rate is increased depending on the route, rapidity, and dosage administered. Side effects may occur as quickly as 1 day after initiation of high-dose steroids, with prednisone having a higher propensity than other systemic steroids, although methylprednisolone, dexamethasone, and beclomethasone also cause neuropsychiatric side effects [5]. It is often difficult to distinguish medication-related neuropsychiatric effects from disease process, with the issue being further obscured by the contribution of polypharmacy.

Teaching Point
Patients with SLE develop psychosis secondary to lupus cerebritis, and psychosis is correlated with markers of SLE disease activity. Psychosis as a result of corticosteroid treatment also occurs but less frequently than psychosis associated with disease activity.

Case 2 Analysis The case highlights the complexity of neuropsychiatric presentations, particularly in patients with preexisting psychiatric disorders and complex medical histories. In this case, the initial emergency department presentation is highly suggestive of a delirious process which remained elusive and resulted in the patient being deemed medically clear for psychiatric admission. However, a number of red flags should have been raised in light of the acuity of neuropsychiatric symptoms precipitating the emergency room visit. The rapidity of psychotic symptoms, transient episodes of confusion, and report of "memory trouble sometimes but then she becomes a bit better again" are certainly suggestive of an underlying medical process. The utility of serial cognitive screens is underscored in this case as the waxing and waning of cognitive symptoms reflect disease activity in lupus cerebritis.

While the nonprogressive nature of Mrs. G.'s cognitive dysfunction rules out a primary neurodegenerative process, it should also direct the workup toward medical imaging, including MRI of the brain and electroencephalogram, particularly given the patient's refractory seizure disorder. MRI would be useful in ruling out some conditions on the differential. In the early stages of disease, the MRI of the brain is normal in over half of patients [46]. However, as the disease progresses, more patients have abnormal MRI studies, with MRI studies showing cerebrovascular disease, myelitis, and focal hyperintensities in both white and gray matter [47], although there are no specific NPSLE patterns recognized yet on MRI images.

Mrs. G.'s course of illness on the psychiatric ward is highly suggestive of an infectious or autoimmune process, although the congruence of her persecutory delusions with her somatic complaints may inadvertently misdirect care providers toward more intensive management of psychosis initially. The case further highlights the importance of interdisciplinary liaison in the approach to the evaluation and management of older adult patents presenting with complex medical histories, unclear neuropsychiatric symptoms, and treatment refractoriness.

23.3 Key Points: Neuropsychiatric Manifestations of Systemic Medical Conditions

- Neuropsychiatric presentations of systemic medical conditions are common and may herald serious underlying illness.
- Age-related physiological changes can cloud "typical" presentations of medical conditions; thus common medical conditions may present in vague, varied, or unusual ways in aging adults.
- Systemic medical conditions that are common sources of neuropsychiatric symptoms include autoimmune, endocrinologic, infectious, paraneoplastic, and metabolic disorders.
- Pharmacotherapy is a particularly important and common cause of neuropsychiatric side effects due to age-associated changes in pharmacokinetics and pharmacodynamics.
- Iatrogenic causes of neuropsychiatric conditions are also common and require attention to treatment regimens, particularly with respect to pharmacologic interventions given the increased susceptibility of older adults to neuropsychiatric medication effects.
- Distinguishing primary from secondary neuropsychiatric symptoms requires careful, thorough evaluation as there are no pathognomonic signs that reliably indicate medical versus psychiatric etiology.
- Despite the lack of pathognomonic signs distinguishing primary versus secondary etiology, some important factors need to be taken into consideration: (i) patient factors and presentation factors (i.e., atypicality of onset, course, or response to usual treatment for psychiatric disorders), (ii) polypharmacy, and (iii) recent iatrogenic interventions.
- It is imperative to retain a degree of clinical suspicion about the possibility of contributory, exacerbating, or underlying systemic medical conditions in order to avoid an incorrect and potentially dangerous attribution to a primary psychiatric disorder.
- Older adults should be asked about sexual activity as the rates of sexually transmitted infections are rising across all age groups.
- The HIV epidemic is aging, and clinicians will need to consider HIV-related neuropsychiatric disorders in their differential where applicable.
- The prevalence of neurocognitive impairment associated with HIV is quite significant.
- Clinicians evaluating HIV-positive patients should check for syphilis coinfection. Similarly, patients in whom neurosyphilis is suspected should be tested for HIV.
- Neuropsychiatric complications can occur in the absence of any hematologic evidence of megaloblastic anemia or other conditions associated with B_{12} deficiency.
- Autoimmune disorders are a common cause of neuropsychiatric symptoms and should be considered an important source of medical mimicry.
- NPSLE correlates with disease activity although autoantibodies are not reliably predictive of specific NPSLE effect.

23.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Patients with vitamin B_{12} deficiency anemia may present with:

A. Paresthesia
B. Nystagmus
C. Confabulation
D. Ophthalmoplegia
E. None of the above

Answer: A

Paresthesia is the most likely of the above options. Options B, C, and D are more in keeping with Wernicke-Korsakoff syndrome.

MCQ 2. Which of the following statements is correct?

A. Neuropsychiatric manifestations of systemic lupus erythematosus classically include cognitive impairment, depression, tabes dorsalis, and acute confusional episodes.
B. The type of lupus autoantibody is usually predictive of the specific neuropsychiatric symptom.
C. Symptoms of limbic encephalitis typically reflect the effects of a locally situated tumor.

D. Neurosyphilis presents at the tertiary stage of infection with manifestations like major neurocognitive disorder, paresis, and gummatous disease.
E. The volume of distribution of lipophilic drugs declines gradually with aging.

Answer: D

Option A is incorrect as tabes dorsalis is not classically associated with SLE but rather with neurosyphilis. Option B is incorrect as the type of lupus autoantibody is only sometimes predictive of symptomatology. Option C is incorrect as limbic encephalitis usually reflects a distally situated tumor. Option E is incorrect as the volume of fatty tissue and therefore the volume of distribution of lipophilic stores increase with aging, while the opposite occurs with hydrophilic drugs. Therefore, option D is the correct statement.

MCQ 3. Which of the following pharmacological agents are least likely to cause neuropsychiatric side effects in older adults?
A. Disease-modifying biologic agents
B. Topical steroids
C. Anticholinergic agents
D. Antiviral agents
E. Corticosteroids

Answer: B

Topical steroids are not absorbed systemically and are thus unlikely to cause neuropsychiatric side effects in older adults. The rest of the drugs listed above are systemically absorbed and therefore present a risk of neuropsychiatric side effects in older adults.

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Sleep-Wake Disorders in Late Life

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24.1 Background

24.1.1 Definition and Diagnostic Criteria

Age-related sleep complaints (e.g., insomnia, with resulting daytime distress and impairment) are common, and associated with adverse outcomes [1, 2]. Age-related physiological changes and age-related increases in pathology prevalence are underlying mechanisms associated with sleep difficulties in older adults. Unless otherwise specified in this chapter, "geriatric" and "older adults" refer to those aged 65 or older. Normal aging leads to several sleep changes such as less restorative sleep and phase advancement of the sleep-wake cycle, manifesting as older adults being more alert in the morning but drowsier in the early evening [2]. Usual aging leads to decline in health status, physical function, and increased incidence of primary sleep disorders. Therefore, sleep-wake complaints of dissatisfaction regarding the quality, timing, and amount of sleep in older adults can be viewed as a consequence of multiple predisposing, precipitating, and perpetuating factors [1]. Sleep-related care in older patients with sleep-wake disorders includes the diagnostic assessment of sleep complaints and the multiple risk factors including medical, psychological, and social issues, with the goal of developing a therapeutic plan.

Sleep-related symptoms based on the *Diagnostic and Statistical Manual of Mental Disorders*, *5th Edition* (DSM-5), criteria include difficulties in sleep onset or maintenance, early morning awakenings, and non-restorative sleep [1]. According to the DSM-5 classification, sleep-wake disorders comprise different types of sleep disorders, with some being closely associated with age-related sleep changes (e.g., circadian rhythm sleep-wake disorders, rapid eye movement (REM) sleep behavior disorder, breathing-related sleep disorder). Table 24.1 summarizes the DSM-5 diagnostic criteria for common sleep-wake disorders encountered mostly in the geriatric population [1].

A clinical diagnosis of sleep-wake disorder requires a determination of duration for the complaint of sleep dissatisfaction and the resulting daytime symptoms of drowsiness [1]. Drowsiness is often established by self-reporting napping behavior and, less often, by the Epworth Sleepiness Scale (a brief self-administrated questionnaire with scores ranging from 0 to 24, with higher scores denoting greater drowsiness) [3].

Sleep disturbances are often present in depressive, anxiety, and neurocognitive disorders, but persistent sleep disturbances are also risk factors for subsequent development of neuropsychiatric disorders [4]. Sleep disturbance can also represent a prodromal phase of a psychiatric disorder, and thus early intervention may prevent or mitigate a full-blown episode. Possible coexisting systemic medical (e.g., congestive heart failure, chronic obstructive pulmonary disease, osteoarthritis) and neurological (e.g., Parkinson disease, Alzheimer disease, Lewy body disease) conditions are the rule, not the exception, in older adults with sleep disorders [1]. These disorders may contribute to disturbed sleep and sleep may worsen symptoms associated with the disorder itself (e.g., confusional arousals in Alzheimer disease patients). REM sleep behavior disorder is often an early indicator of alpha synucleinopathies (e.g., Parkinson disease or Lewy body major neurocognitive disorder) [5]. The DSM-5 classification system for sleep-wake disorders has included the use of biomarkers where indicated, e.g., formal sleep studies (i.e., polysomnography) for breathing-related sleep disorders and periodic limb movements during sleep, which often coexist with restless legs syndrome [1, 2].

24.1.2 Epidemiology of Sleep Disorders in Older Adults

Epidemiologic data have demonstrated a higher prevalence of insomnia in older adults when compared with younger patients [6]. As many as 40% of individuals over the age of 60 may experience insomnia, frequent awakening, and sleep disruption [6]. In an epidemiologic study that assessed the prevalence of sleep complaints across three communities of older adults aged 65 or older (mean age, 74 years), 57% reported chronic disruption of sleep, while only 12% reported no sleep complaints [7]. In this study, the prevalence of chronic sleep complaints included difficulty in sleep initiation or maintenance (43%), nocturnal waking (30%), insomnia (29%), difficulty falling asleep (19%), early waking (19%), unrestful sleep (13%), and daytime napping (25%) [7]. A 3-year longitudinal study in adults aged 65 or older reported an annual incidence rate of insomnia of about 5% [8]. In the Established Populations for Epidemiologic Studies of the Elderly (EPESE) of patients aged 65 or older, 43% reported difficulties in sleep initiation or maintenance, while 25% napped [9]. In general, insomnia symptoms are more prevalent in older females, with sex differences in napping being less clear [10].

24.1.3 Age-Related Sleep Changes

Sleep disturbances are particularly concerning in older adults as they affect quality of life, increase the risk of motor vehicle accidents, and are one of the leading reasons that older adults are placed into long-term care facilities [2, 11]. Patients with sleep difficulties present more frequently to their primary care physician, reinforcing that there is a greater use of healthcare resources because of disturbed sleep [12].

Before discussing the systemic medical and psychiatric causes of disturbed sleep, it is essential to understand that there are normal age-related changes that are expected with regard to the sleep cycle. As individuals age, the amount of sleep they get per night does not change, but rather, the sleep architecture changes. Older adults spend less time in slow-wave sleep

Table 24.1 Highlights of DSM-5 diagnostic criteria and clinical features for common sleep-wake disorders in older adults [1]

Sleep-wake disorder	Diagnostic criteria	Diagnostic features
Insomnia disorder		
	Dissatisfaction with sleep quantity/quality and one (or more) of: (i) difficulty initiating sleep, (ii) difficulty maintaining sleep, (iii) early morning awakening Frequency > 3 nights/week Duration > 3 months	Diagnosis is given when insomnia is not attributable to physiological effects of a substance/medication and when coexisting psychiatric and systemic medical conditions do not adequately explain the main complaint of insomnia. Maladaptive sleep habits (e.g., excessive time in bed, erratic sleep schedule, napping) and cognitions (e.g., fear of sleeplessness, clock monitoring) must be addressed
Circadian rhythm sleep-wake disorders		
Advanced sleep phase type	Advanced sleep onset and awakening times	Usually > 2 hours earlier sleep-wake times than desired/conventional times; more common in older adults; onset in late adulthood (earlier in familial form); prevalence 1% in mid-age adults
Delayed sleep phase type	Delayed sleep onset and awakening times	Usually > 2 hours delay in timing of the major sleep period; prevalence 0.17% in general population (can be familial); symptoms begin in adolescence/early adulthood and severity decreases with age
Irregular sleep-wake type	Disorganized sleep-wake pattern throughout the 24-hour period	Fragmented sleep and wake periods across 24 hours; commonly associated with major neurocognitive disorders
Breathing-related sleep disorders		
Obstructive sleep apnea-hypopnea	Either (1) or (2) on polysomnography: 1. Five (or more) obstructive apneas/hypopneas/hour of sleep *and* (a) nocturnal breathing disturbances and/or (b) daytime sleepiness, fatigue, unrefreshing sleep 2. Evidence of 15 (or more) obstructive apneas/hypopneas/hour of sleep, regardless of associated symptoms	Most common breathing-related sleep disorder. Key symptoms: snoring, daytime sleepiness; each apnea (total absence of airflow) or hypopnea (reduction in airflow) represents a decrease in breathing of > 10 seconds in duration in adults and drops in O_2 saturation of > 3% *Severity specifier* for apnea-hypopnea index (AHI): Mild: AHI < 15 Moderate: AHI 15–30 Severe: AHI > 30
Central sleep apnea	Evidence on polysomnography: Five (or more) central apneas/hour of sleep	Key features: sleepiness, insomnia, awakenings due to dyspnea; Cheyne-Stokes breathing may occur; obstructive sleep apneas may coexist; chronic long-acting opioid use can lead to central sleep apnea (e.g., 30% of nonmalignant pain cases)
Parasomnias		
REM sleep behavior disorder	Repeated episodes of arousal during REM sleep (uncommonly during daytime naps), with vocalization and/or complex motor behaviors. Either (1) or (2): (1) REM sleep without atonia on polysomnography; (2) history suggestive of this sleep disorder and an established synucleinopathy diagnosis	Key features: repeated episodes of arousal, with dream acting out behaviors, and significant distress/impairment; severity is based on the consequences of behavior than frequency; prevalence 0.5% in the general population (greater if taking psychotropics). Onset is gradual or rapid, and course is usually progressive; close monitoring because of high association with later underlying neurodegenerative disorders
Restless legs syndrome	Urge to move legs during periods of rest/inactivity, which is partially/totally relieved by movement and occurs/worsens in the evening or at night Frequency > 3 times/week Duration > 3 months	It can delay sleep onset, waken person from sleep, and lead to sleep fragmentation and daytime sleepiness; family history in first-degree relatives and reduction with dopaminergic treatment are supportive features; prevalence 2–7.2%, increases with age, females are twice more likely to be affected

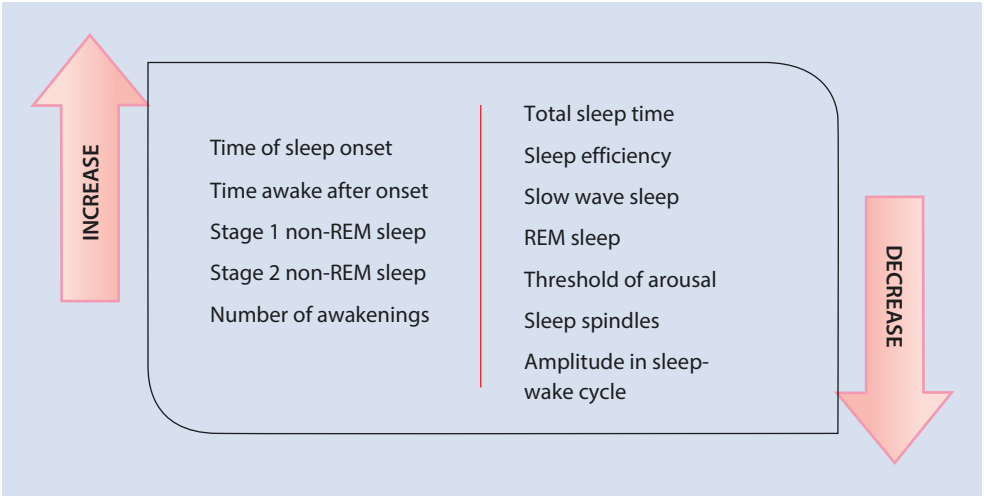

Fig. 24.1 Normal age-related sleep changes [2]

(stages 3 and 4) and REM sleep and more time in stages 1 and 2 sleep, which accounts for sleep being lighter and more shallow. Sleep efficiency (i.e., amount of sleep relative to the amount of time in bed) continues to decrease with increasing age and is more affected in older women versus men [13]. The time it takes for someone to fall asleep, called sleep latency, increases with age, but a significant difference is only noted when compared to very young adults [13].

The circadian rhythm system is responsible for many physiological functions, including sleep-wake cycle, responding to external cues (e.g., light exposure) and internal cues (e.g., hormones). With age, the sleep-wake circadian rhythm cycle becomes less effective at responding to cues, making the sleep-wake cycle less consistent across the 24-hour day. Additionally, the sleep-wake cycle in older adults becomes phase advanced resulting in earlier sleep and wake times [2]. Figure 24.1 lists common age-related sleep changes [2].

Teaching Point

Older adults spend less time in slow-wave sleep (stages 3 and 4) and rapid eye movement (REM) sleep and more time in stages 1 and 2 sleep, with resulting sleep being lighter and more shallow. Sleep efficiency decreases with age. The sleep-wake cycle becomes phase advanced, resulting in earlier sleep and wake times.

24.1.4 Disorders Contributing to Poor Sleep

The age-related changes in sleep architecture noted in ▶ Sect. 24.1.3, while expected, do not account for most of the disturbed sleep often seen in older adults. As the patient ages, systemic medical and psychiatric comorbidities contribute to disturbed sleep, as do primary sleep disorders described in the following section, which are more common in older adults [14].

Primary Sleep Disorders

Primary sleep disorders cannot be attributed to other psychiatric or systemic medical disorders or to the influence of medications or other substances. The most common primary sleep disorders experienced by older adults are restless legs syndrome, periodic limb movement disorder, REM sleep behavior disorder, and the breathing-related sleep disorders.

Restless Legs Syndrome and Periodic Limb Movement Disorder

Restless legs syndrome is a feeling of discomfort in the lower extremities, usually only present at rest, associated with the urge to move. There is a diurnal variation, with symptoms worsening in the evening and bedtime, making sleep a challenge. Restless legs syndrome, while present in 6% of adults, occurs in up to 20% of those aged 65 or older [15], and distress related to insomnia is often one of the biggest complaints in restless legs syndrome. The DSM-5 criteria for restless legs syndrome include the primary symptoms of the syndrome, namely, an urge to move the legs in response to uncomfortable and unpleasant sensations in the legs (paresthesias and dysesthesias), which is worse during periods of rest, worse in the evening, relieved with movement, and not attributable to other medical conditions [16]. Restless legs syndrome is often distressing to patients, given the inability to fall asleep and difficulty staying still during sedentary activities, but it is not usually described as painful [16]. It may present similar to other conditions including anxiety disorders, leg cramps, tic disorders, peripheral neuropathy, and drug-induced akathisia; thus, it is important to include these in the differential.

Restless legs syndrome frequently has a primary motor symptom that is characterized by the occurrence of periodic leg movements in sleep, which is distinct from periodic leg movement disorder. Periodic limb movements are stereotypical repetitive contractions of the legs, which occur in clusters throughout the night, lasting up to 5 seconds [17]. Periodic leg movements in sleep occur in 80–90% of patients with restless legs syndrome; their combined presence sup-

ports a diagnosis of restless legs syndrome [18]. Periodic limb movements in sleep also occur in other sleep disorders including narcolepsy and REM sleep behavior disorder [18]. Periodic limb movements, in contrast to restless legs syndrome, are not usually noticed by the patient and can only be diagnosed by polysomnography [17].

Periodic limb movements in sleep occurring in patients with otherwise unexplained insomnia and/or hypersomnia are defined as periodic limb movement disorder and occur in approximately 3% of the population [17]. Periodic limb movement disorder may be diagnosed when the frequency of limb movements is greater than 15 per hour and when accompanied by sleep disturbance or other functional impairments [19].

The cause of restless legs syndrome and periodic limb movement disorder is unknown, but hypotheses suggest a role for the dopaminergic system, with input from other neurotransmitters [16]. Unlike REM sleep behavior disorder, there is no evidence that older adults with restless legs syndrome or periodic limb movement disorder are at increased risk for neurodegenerative diseases (e.g., Parkinson disease). Both restless legs syndrome and periodic limb movement disorder are reported more frequently in patients with certain medical conditions, compared to the general population. Iron deficiency, with or without anemia, as well as ferritin levels less than 50 μg/L are commonly associated with restless legs syndrome. There are also higher prevalence rates in patients with hypothyroidism and diabetes mellitus [16].

Given the prevalence of both of these conditions and the impact on sleep and daily function, an accurate diagnosis is imperative. Additionally, the inappropriate prescribing of antipsychotic medications solely to improve sleep can actually exacerbate symptoms of restless legs syndrome and periodic limb movement disorder [17].

The treatment options for restless legs syndrome and periodic limb movement disorder will be further discussed at Case 1, but briefly, dopaminergic agents are considered first-line treatment, followed by opioid and benzodiazepine agents. Particularly in older adults, special attention must be paid when prescribing these medications due to side effects, most notably the development of sleep apnea when on long-term opioid treatment, and delirium, falls, and fractures associated with hypnotic use [17].

REM Sleep Behavior Disorder

REM sleep behavior disorder is characterized by the loss of normal atonia that occurs during REM sleep, resulting in patients acting out their dreams. Affected persons may walk, thrash or flail their limbs, or even engage in complex movements while sleeping, which can be harmful to themselves or their bed partner in extreme cases [5]. Idiopathic REM sleep behavior disorder typically has its onset between the ages of 50 and 70 years. Dream acting out can also be caused by antidepressant use, in which case the age of onset may be younger.

Several studies have shown that lesions to pontomedullary areas result in REM sleep behavior disorder through disinhibition of control of the motor cortex to extremities. Patients have also developed REM sleep behavior disorder after strokes affecting this lower brainstem area [5].

Idiopathic REM sleep behavior disorder is most often proven to be associated with one of the synuclein-mediated neurodegenerative diseases, including Parkinson disease, Lewy body disease, and multiple system atrophy [5]. It has also been linked to non-neurodegenerative disorders (e.g., narcolepsy, multiple sclerosis, Guillain-Barre syndrome, amyotrophic lateral sclerosis), as well as pharmacological agents (e.g., tricyclic antidepressants, selective serotonin reuptake inhibitors) [20].

REM sleep behavior disorder presents in 25–50% of patients with Parkinson disease and is considered a non-motor manifestation of Parkinson disease [21]. For this reason, REM sleep behavior disorder is an important and clinically relevant predictor (or prodromal marker) of Parkinson disease and other neurodegenerative synucleinopathies [5]. This will be discussed further in Case 2. Clonazepam 0.5–2 mg at nighttime or melatonin 3–12 mg at nighttime is a common treatment option for REM sleep behavior disorder [22].

Teaching Point

Up to 50% of patients with Parkinson disease have REM sleep behavior disorder, which is a non-motor manifestation of this disease [21]. REM sleep behavior disorder may be a strong predictor (or prodromal marker) of neurodegenerative synucleinopathies including Parkinson disease, neurocognitive disorder with Lewy bodies, and multiple system atrophy.

Advanced Sleep Phase Syndrome

This is a circadian disorder characterized by a phase advancement in the sleep-wake cycle beyond that which can be explained by normal aging alone [23]. Patients with advanced sleep phase syndrome fall asleep as early as 6:00 PM and wake up as early as 2:00 AM and are unable to resume sleep. Advanced sleep phase syndrome reflects a reduced ability to phase-delay the circadian rhythm in response to normal environmental cues that should reset the rhythms each day, called zeitgebers (e.g., effect of light-dark cycle) [23]. Because early morning awakening is commonly encountered in major depressive disorder, advanced sleep phase syndrome is a diagnosis of exclusion.

Breathing-Related Sleep Disorders

Sleep-disordered breathing includes snoring, obstructive sleep apnea, central sleep apnea, and sleep-related hypoventilation. Obstructive sleep apnea is the predominant type of sleep apnea seen in the older adults; its frequency increases with age, and it is the focus of this section [24].

Obstructive sleep apnea occurs when there is an obstruction to airflow, secondary to the narrowing in the pharynx and hypopharynx [24]. By comparison, central sleep apnea occurs due to a failure of the central nervous system to activate the respiratory muscles [24]. In both types of apnea, abnormal respiratory patterns can range from significant

snoring to episodes of complete airway obstruction where breathing ceases for a period of 10 seconds or more [25].

Risk factors for obstructive sleep apnea include increasing age, male sex, family history, obesity, craniofacial abnormalities, and menopause in women [26]. Symptoms commonly noticed include snoring, daytime sleepiness, awakening with gasps, and bed partners noticing periods of witnessed apneas, as well as falls and confusion in geriatric patients [26]. Obstructive sleep apnea is also associated with an increased risk for systemic medical conditions, including hypertension, heart disease, and stroke, as well as neurocognitive disorders.

Evaluation of a possible obstructive sleep apnea may include screening tools (e.g., the Berlin Questionnaire to estimate obstructive sleep apnea risk or the Epworth Sleepiness Scale to assess sleepiness), but these have not been validated in older adults. A more robust indicator is a combination of history and physical examination, noting the presence of the previously described symptoms, as well as obesity, increased neck circumference, comorbid cardiovascular risk factors, and unexplained falls, accidents, and cognitive decline [26]. When obstructive sleep apnea is suspected, diagnosis is confirmed through polysomnography. Regardless of apnea-hypopnea index (AHI), the disorder is considered to be more severe when more than 10% of the sleep time is spent at oxygen hemoglobin desaturations of less than 90%. Apneas are associated with a drop in airflow amplitude of greater than 90% for at least 10 seconds, accompanied by a sustained or increased respiratory effort [2]. Hypopneas are decreases in airflow amplitude greater than 50% but less than 90% of baseline lasting at least 10 seconds (See ◘ Table 24.1).

Teaching Point

Diagnosis of obstructive sleep apnea is confirmed through polysomnography. Apneas are defined as a decrease of baseline airflow amplitude of greater than 90% for at least 10 seconds, accompanied by a sustained or increased respiratory effort, whereas hypopneas represent a decrease greater than 50% but less than 90% of baseline airflow for at least 10 seconds. The severity of obstructive sleep apnea depends on the level of daytime sleepiness and frequency of respiratory events.

Sleep-disordered breathing is diagnosed by polysomnography, and treatment is recommended for geriatric patients who have obstructive sleep apnea and clinical symptoms.

Sleep-disordered breathing is associated with cognitive decline, where attention, episodic memory, working memory, and executive functioning are the cognitive domains most affected by obstructive sleep apnea [20]. Sleep-disordered breathing is also associated with an earlier age of onset of mild cognitive impairment [27], as well as elevated biomarkers of Alzheimer disease in the cerebrospinal fluid of patients with sleep-disordered breathing [27]. Although sleep-disordered breathing accelerates cognitive decline in later life, treatment via continuous positive airway pressure (CPAP) offers some protection by delaying the age of onset of mild cognitive disorder [27]. Additionally, in patients with a diagnosis of both Alzheimer disease-related neurocognitive disorder and sleep apnea, treatment with CPAP has been shown to reduce the rate of cognitive decline [28]. This information highlights the importance of treating patients with sleep apnea to minimize future cognitive impairment and screening all patients with Alzheimer disease-related neurocognitive disorder for sleep apnea.

CPAP is the treatment for obstructive sleep apnea, as it keeps the upper airways open using air pressure, thereby improving symptoms by decreasing hypoxemia and sleep fragmentation [20]. In terms of the cognitive impairment seen in obstructive sleep apnea, CPAP has been shown to improve sustained attention, some aspects of executive function (e.g., flexibility), and episodic memory [20].

Systemic Medical Conditions and Medications

Chronic Disease

As the aging population lives longer, the likelihood of having a chronic disease becomes greater. In North America, approximately 80% of patients over the age of 70 have at least one of the seven most common chronic diseases (heart disease, cancer, diabetes mellitus, hypertension, respiratory disease, cerebrovascular disease, and arthritis). Progressive neurocognitive disorders as chronic illnesses are discussed later in ▶ Sect. 24.1.4, Major or Mild Neurocognitive Disorders.

Sleep disturbances in older adults are frequently associated with existing systemic medical conditions, with perception of sleep quality being highly associated with the number of systemic medical comorbidities [29]. These specific chronic illnesses have all been found to be independently associated with sleep problems, including difficulty falling asleep, staying asleep, breathing pauses, and daytime sleepiness [29].

Patients with respiratory disease, particularly chronic obstructive pulmonary disease (COPD), objectively and subjectively have evidence of disturbed sleep which is unrelated to hypoxia and which is dissimilar to those with sleep apnea (it manifests clinically as increased daytime sleepiness) [30]. For this reason, polysomnography is not routinely done, but rather, the level of distress is evaluated, with management focusing on treatment of the disease symptoms, and then management of sleep. This is expanded on later in case-based discussions.

Both pain and obesity are important conditions in old age that, independent of other comorbidities, affect sleep. Adults who are obese have more frequent nighttime awakenings with breathing pauses, reaffirming that obesity is a risk factor for obstructive sleep apnea.

◘ Table 24.2 describes various chronic illnesses which are associated with sleep disturbances [2].

Medications

Given the number of illnesses and comorbidities seen in the aging population, polypharmacy is becoming increasingly more common among older adults [31]. In many cases, these

Table 24.2 Chronic illnesses associated with disturbances of sleep [2]

Illness group	Examples
Acute or chronic pain	Arthritis, fibromyalgia, neuropathic pain, cancer, chronic headaches
Cardiac disease	Nocturnal angina, congestive heart failure (nocturnal hypoxemia, nocturia)
Respiratory disease	COPD, nocturnal bronchospasm, sleep-related laryngospasm
Endocrine disease	Hypothyroid-associated central sleep apnea, diabetes mellitus (nocturia, neuropathic pain)
Genitourinary problems	Incontinence and resulting nocturia
Neurological disorders	Stroke (difficulty changing positions, aspiration), major neurocognitive disorders, nocturnal seizures, neuromuscular degenerative disorders

Table 24.3 Medications and other substances that can contribute to insomnia in older adults

Caffeine
Nicotine
Antidepressants
Psychostimulants
Diuretics
Angiotensin converting enzyme inhibitors
Alpha-blockers
Beta-blockers
Dopamine agonists
Theophylline
Bronchodilators
Corticosteroids
Statins
Cholinesterase inhibitors
H1 antagonists

medications contribute to or even cause insomnia. Therefore, medication review is a priority when addressing sleep disturbances.

Stimulants of the central nervous system (e.g., methylphenidate, modafinil) and antidepressant medications (e.g., selective serotonin reuptake inhibitors, atypical antidepressants such as mirtazapine and trazodone, monoamine oxidase inhibitors) often used to treat major depressive disorder and insomnia can be particularly problematic, having an adverse effect on sleep [31]. Additionally, common medications used to treat chronic illnesses such as antihypertensives (e.g., alpha and beta adrenergic blockers, angiotensin-converting-enzyme (ACE) inhibitors), respiratory medications (e.g., theophylline, albuterol), and hormones (e.g., corticosteroids, thyroid hormones) may also contribute to insomnia. A list of common medications and other substances contributing to insomnia is shown in Table 24.3.

When possible, reducing doses or eliminating unnecessary medications is advisable. The timing of medications is also important; stimulating medications and diuretics should preferably be taken earlier in the day, and sedating medications should be administered prior to bedtime [31].

Major or Mild Neurocognitive Disorders

Neurocognitive Disorder Due to Alzheimer Disease

The sleep disturbances seen in major or mild neurocognitive disorder due to Alzheimer disease are a challenging component of the illness, resulting in distress to patients and also to their caregivers [32]. In fact, sleep disturbance is one of the leading causes of institutionalization of Alzheimer disease patients [11]. Up to 45% of patients with Alzheimer disease may experience sleep disturbances, with frequent complaints of excessive awakenings, early morning awakening, and excessive daytime sleepiness [33]. Although these disturbances can occur early in the course of the disease, they tend to get worse with disease progression. Common sleep architecture changes seen in the patients with Alzheimer disease include decreased nocturnal total sleep time, decreased sleep efficiency, and decreased time in REM sleep [32].

Irregular sleep-wake disorder consists of fragmented sleep and wake periods and is commonly associated with major neurocognitive disorders including Alzheimer disease [22]. These patients lack a well-defined sleep period, sleeping on and off throughout the 24-hour day. This may be experienced as insomnia at night and excessive sleepiness in the day. Although circadian rhythm changes are seen in normal aging, those associated with Alzheimer disease are far more profound and disruptive, as seen by the effects of the Alzheimer disease process on the suprachiasmatic nucleus [22]. The suprachiasmatic nucleus, located in the hypothalamus, regulates and coordinates the circadian rhythms. In patients with Alzheimer disease, the suprachiasmatic nucleus has been shown to have neurofibrillary tangles, neuronal cell loss, and reduced production of vasopressin [22]. Interestingly, neuritic plaques and beta amyloid, the other neuropathologic features of Alzheimer disease, are not deposited in the suprachiasmatic nucleus [22].

Teaching Point

The most common sleep disturbance in patients with Alzheimer disease is the irregular sleep-wake rhythm, which is a circadian rhythm disorder that may be caused by the effects of the disease process on the suprachiasmatic nucleus.

Alzheimer disease patients have chronobiological changes in their sleep-wake cycles, as well as changes to other physiological markers of the circadian rhythm, including body temperature, blood pressure, heart rate, and melatonin levels [32]. The heart rate and blood pressure in patients in later stages of Alzheimer disease exhibit dulling of the normally robust diurnal variability and reflect the impact on hypothalamic function [32]. The amplitude of the melatonin rhythm and the overall melatonin levels are also reduced in patients with Alzheimer disease, compared to age-matched controls. Sundowning is the term given to describe the agitated behaviors seen in patients with Alzheimer disease and other neurocognitive disorders. Sundowning occurs around sunset and the nocturnal hours and may reflect these chronobiological changes. Since these behaviors occur specifically at night, they likely reflect changes to the body's ability to regulate the circadian timing system [32]. The nature of these changes is complex and depends on severity of illness, as well as individual cycle changes. (See ▶ Chap. 22.)

In addition to changes affecting the suprachiasmatic nucleus and circadian rhythm on a neuropathological level, patients with Alzheimer disease experience changes to the important environmental cues, which are critical in reinforcing regular circadian rhythm patterns [22]. These environmental cues include participation in social and physical activities and exposure to light. Whether in nursing homes or other care settings, patients with major neurocognitive disorders often have disturbed patterns of light exposure because of the environment, inactivity during the day, and excessive daytime sleepiness. The light they receive may also not reach brain centers as effectively because of visual disturbances (e.g., cataracts, macular degeneration), which are common in older adults [22].

Assessment of Insomnia in Neurocognitive Disorder Due to Alzheimer Disease

Prior to treating specific sleep changes on a symptomatic basis, it is important to address other issues that may be superimposed on the major or mild neurocognitive disorder (e.g., delirium, polypharmacy, other medical comorbidities). Ruling out the primary sleep disorders described previously (e.g., restless legs syndrome, REM sleep behavior disorder) is also important. Comorbid neuropsychiatric diseases must also be considered, as 50% of Alzheimer disease patients have symptoms of depressive disorder [33].

Management of Insomnia in Neurocognitive Disorder Due to Alzheimer Disease

As with most sleep disturbances, non-pharmacological approaches should be considered before pharmacological approaches. During the day, Alzheimer disease patients should be encouraged to exercise for at least 30 minutes daily, including walking outdoors, and naps should be limited to 30 minutes and avoided after 1:00 PM. Avoiding lying in bed without sleeping and keeping a regular schedule for going to sleep and waking up is important, but often challenging. In nursing homes, limiting nighttime noise and light exposure is very important and a well-established measure in those with Alzheimer disease. Bright light therapy has shown to have modest benefits when exposure occurs in the morning for 2 hours, improving sleep and circadian rhythms [32].

Pharmacological treatment of sleep disturbances in patients with major or mild neurocognitive disorder due to Alzheimer disease includes common use of drugs, such as melatonin, Z-hypnotics (e.g., zolpidem), sedating antidepressants, antipsychotics, and benzodiazepines. Melatonin has received attention not just for its potential role in improving sleep, but its role in the pathogenesis of Alzheimer disease and potential cognitive benefit [33]. Given the variability in the severity of neurodegenerative changes, benefits of medications have been inconsistent. However, melatonin has been shown to be effective in improving sleep onset latency and nocturnal sleep time, and subjective measures of sleep improvement have been positive [33].

The hypnotics include benzodiazepines and "Z-drugs". Benzodiazepines are not recommended due to the poor side effect profile including daytime sedation, confusion, risk of falls and fractures, and deleterious effects on cognition [33, 34]. The side effect profile of the Z-drugs (e.g., zolpidem) is slightly less concerning than that of the benzodiazepines, and can be cautiously considered for short-term use in patients with Alzheimer disease, but need to be used with caution [33].

Sedating antidepressants are usually considered when there is concomitant depressive disorder. Tricyclic antidepressants should be avoided given their anticholinergic properties, which may worsen cognition, and may cause dizziness and somnolence in the daytime. The noradrenergic and specific serotonergic antidepressants, mirtazapine, can have benefits for treating insomnia but have undesirable sedating side effects, and dosing requires close monitoring. Trazodone has been shown to increase nocturnal sleep time without significant daytime somnolence or negative effects on cognition.

Antipsychotics are frequently used to control the behavioral disturbances seen in Alzheimer disease. Their sedating properties make them an attractive option when nocturnal agitation is present; however, given the risk of sudden death, particularly in those with preexisting cardiac disease and prolongation of QT interval, they should be used judiciously [32, 33]. Additionally, antipsychotics carry significant risk of common side effects, including extrapyramidal symptoms, weight gain and metabolic disorders, and should be limited or avoided in those with Parkinson disease and other neurodegenerative synucleinopathies, and those with diabetes mellitus. The risks and benefits of the medications in these classes are summarized in ◘ Table 24.4.

Neurocognitive Disorder Due to Parkinson Disease

Parkinson disease is a neurodegenerative illness characterized primarily by motor symptoms of tremor, rigidity, and bradykinesia, as well as non-motor features. Sleep disturbances occur in

Table 24.4 Risks and benefits of medications used to treat sleep disturbances in Alzheimer disease

Medication	Risks and benefits
Melatonin	Improved total sleep time and sleep onset latency Improved benefits noted by caregivers No sedating or cognitive side effects Not effective in all patients Some studies found adverse effects on mood
Hypnotics/benzodiazepines	Role for Z-drugs (zolpidem, zaleplon) in the short term and when used cautiously Benzodiazepines not recommended given sedation, risk of falls, confusion, and other negative effects on cognition Avoid those with long elimination half-lives
Antidepressants	Improvements in total nocturnal sleep, without significant daytime somnolence or serious adverse side effects, seen with trazodone Modest benefit with mirtazapine, but poor side effect profile (increased appetite, dose-related morning sedation) Avoid tricyclic antidepressants due to anticholinergic side effects
Antipsychotics	May be effective in treatment of nocturnal agitation and behavioral disturbances Sedating properties assist with insomnia, but risks of daytime sedation, cardiac side effects, and sudden death—poor option when treating sleep disturbances

60–90% of patients with Parkinson disease and may be due to neurodegenerative changes related to the disease itself or side effects of antiparkinsonian medications [35]. As well, depressive disorder and major neurocognitive disorder are common sequelae of Parkinson disease and, as discussed in other sections of this chapter, both have negative effects on sleep.

The changes in the sleep architecture of patients with Parkinson disease are numerous. These patients have a reduced total sleep time, reduced sleep efficiency, and an increased number of awakenings [36]. The sleep fragmentation and insomnia may be in part due to sleep breathing disorders or periodic limb movements, which are common in Parkinson disease. As well, the motor symptoms of rigidity and bradykinesia cause discomfort and trouble changing sleep position, another contributor to frequent awakenings [36]. Nocturia is also commonly seen in Parkinson disease, affecting up to 80% of patients and becoming worse with disease progression and severity [37].

Teaching Point

Decreased total sleep time, decreased sleep efficiency, and increased number of awakenings are sleep-related changes seen in Parkinson disease. Sleep breathing disorders and periodic limb movements, motor symptoms of rigidity and bradykinesia causing discomfort and difficulty changing sleep position, and nocturia are all common in patients with Parkinson disease, which could explain, at least in part, the sleep fragmentation and insomnia.

Sleep Disorders in Parkinson Disease

REM sleep behavior disorder, restless legs syndrome, and periodic limb movement disorder are commonly associated with Parkinson disease. REM sleep behavior disorder, as discussed previously, is seen in 25–50% of patients with Parkinson disease, depending on stage of the disease [21, 22]. Perhaps one of the most important clinical aspects of REM sleep behavior disorder is its ability to predict the development of neurodegenerative disease [5]. Most patients who present to a sleep clinic with idiopathic REM sleep behavior disorder will eventually develop a neurodegenerative disease, usually Parkinson disease, Lewy body disease, or multiple system atrophy [5]. Independent studies suggest that REM sleep behavior disorder is a potential clinical indicator for future Parkinson disease for two main reasons. Firstly, idiopathic REM sleep behavior disorder compared to other symptoms that may predict future Parkinson disease shows a specificity of 50–65% in identifying a presymptomatic phase of neurodegeneration [5]. This suggests that if there was a neuroprotective agent for these neurodegenerative diseases, those with REM sleep behavior disorder would be potential candidates for this treatment. Secondly, latency from the onset of REM sleep behavior disorder to the presentation with Parkinson disease is on average 13 years, 6–9 years longer than what previous neuroimaging studies of the substantia nigra had suggested the time might be prior to clinical onset of Parkinson disease [5].

Restless legs syndrome and periodic limb movement disorder are also more common in Parkinson disease than in the general population, with prevalence varying between 8% and 50% for restless legs syndrome and up to 80% for periodic limb movement disorder in severe cases [35]. Unlike REM sleep behavior disorder, these sleep disorders are not a preclinical form of Parkinson disease, as they have differing pathophysiological mechanisms [35]. Although treatment of restless legs syndrome and periodic limb movement disorder is discussed later in Case 1, for Parkinson disease specifically, dopamine agonists (e.g., ropinirole and pramipexole) should be considered first line [35]. Levodopa should be avoided in

treating these sleep disorders to prevent further rebound and augmentation during the night, commonly experienced by Parkinson disease patients [35].

Teaching Point

Restless legs syndrome and periodic limb movement disorder are not a preclinical form of Parkinson disease, unlike REM sleep behavior disorder. First-line treatment of restless legs syndrome and periodic limb movement disorder in patients with Parkinson disease consists of dopamine agonists (e.g., ropinirole and pramipexole) [35]. Levodopa should be avoided to prevent rebound and augmentation during the night [35].

Neurodegenerative Sleep Changes

As Parkinson disease progresses, various changes contribute to poor sleep, including the neurodegenerative process itself, the development of sleep disorders discussed in ► section Sleep Disorders in Parkinson Disease, uncomfortable motor symptoms, and the complex medication regimen required to maintain quality of life [35].

Excessive daytime sleepiness, resulting in daytime somnolence with frequent periods of sleepiness, affects up to 50% of patients with Parkinson disease and increases with the progression of the disease [35]. From a neurodegenerative standpoint, the excessive daytime sleepiness occurs secondary to progressive cell loss in the dopaminergic and non-dopaminergic brain structures and circuits that modulate the sleep-wake mechanisms [38]. This is in keeping with the understanding that severity of excessive daytime sleepiness worsens with increased severity of the disease and longer disease duration [38]. Several findings indicate that the integrity of the central dopamine system is crucial for maintaining sleep-wake control and that dopamine cell loss occurring in Parkinson disease predisposes to excessive daytime sleepiness. This dopamine deficit occurring at the level of mesocorticolimbic circuits impairs the thalamocortical arousal state resulting in excessive daytime sleepiness and inappropriate intrusion of REM sleep into daytime naps [38]. The loss of hypocretin, the hypothalamic wake-promoting substance, is hypothesized to be responsible, as there are reduced levels of hypocretin in the ventricular cerebrospinal fluid and reduced hypocretin neurons in Parkinson disease patients [39, 40].

Antiparkinsonian Medication-Related Sleep Changes

Levodopa has been used to treat Parkinson disease. Alternatives to levodopa have been developed and are called dopamine agonists (e.g., ropinirole, pramipexole). Unlike levodopa, dopamine agonists do not have to be modified by brain enzymes in order to activate dopamine receptors. Dopamine agonists may be used in place of levodopa or in combination with it to treat Parkinson disease. Levodopa and dopamine agonists play a considerable role in the impairment of daytime consciousness. Levodopa and dopamine agonists exert their sedating effects through mesothalamocortical dopaminergic projections. While the sedating effects of dopaminergic agents cannot be helped, the severity of excessive daytime sleepiness in patients with Parkinson disease has been associated with longer duration of dopaminergic treatment, and those with higher doses of dopaminomimetics are at higher risk of developing hypersomnia [38].

A phenomenon called "sleep attacks" was coined to describe the onset of abrupt sleepiness with no warning signs, occurring with the use of dopaminergic drugs, and independent of the excessive daytime sleepiness related to other parkinsonian changes [41]. Sleep attacks, lasting seconds to minutes, can occur at any time- during meals, conversations, activities and while driving- and affect up to 6% of the Parkinson disease population [42]. Although sleep attacks can occur in patients taking any type of dopaminergic medication, patients taking levodopa alone had lower risks of sleep attacks than those on combination therapy or taking dopamine agonists [42]. The main factors influencing the occurrence of sleep attacks appear to be the intake of dopamine agonists and the duration one has had the illness. Concomitant sleep disorders do not predispose to increased risk of sleep attacks. Although doses of dopamine agonists conferring increased risk are unknown, there is some evidence suggesting that there is a dose effect for bromocriptine and pergolide [42]. Sleep attacks start to occur several days or months after the introduction of the offending agent, and they usually resolve or decrease after its withdrawal, reduction, or replacement [38].

Teaching Point

Sleep attacks are abrupt onset of sleepiness occurring with the use of dopaminergic drugs, independent of the excessive daytime sleepiness related to Parkinson disease changes. Sleep attacks can occur in patients taking any type of dopaminergic medication, but those taking levodopa alone had lower risks of sleep attacks than those taking combination therapy or dopamine agonists [42]. The main factors influencing the occurrence of sleep attacks appear to be the intake of dopamine agonists, dose, and the duration of the illness.

Neurocognitive Disorder with Lewy Bodies

Neurocognitive disorder with Lewy bodies is characterized by cognitive impairment, neuropsychiatric symptoms, motor dysfunction, and both sleep and autonomic disturbances. The sleep disturbances, as in Alzheimer disease and Parkinson disease, while not considered a core feature of the illness, are particularly distressing and warrant the appropriate treatment.

The primary sleep disturbances seen in patients with Lewy body neurocognitive disorder include REM sleep behavior disorder, restless legs syndrome, and hypersomnia (see ► Sect. 24.1.4, Primary Sleep Disorders).

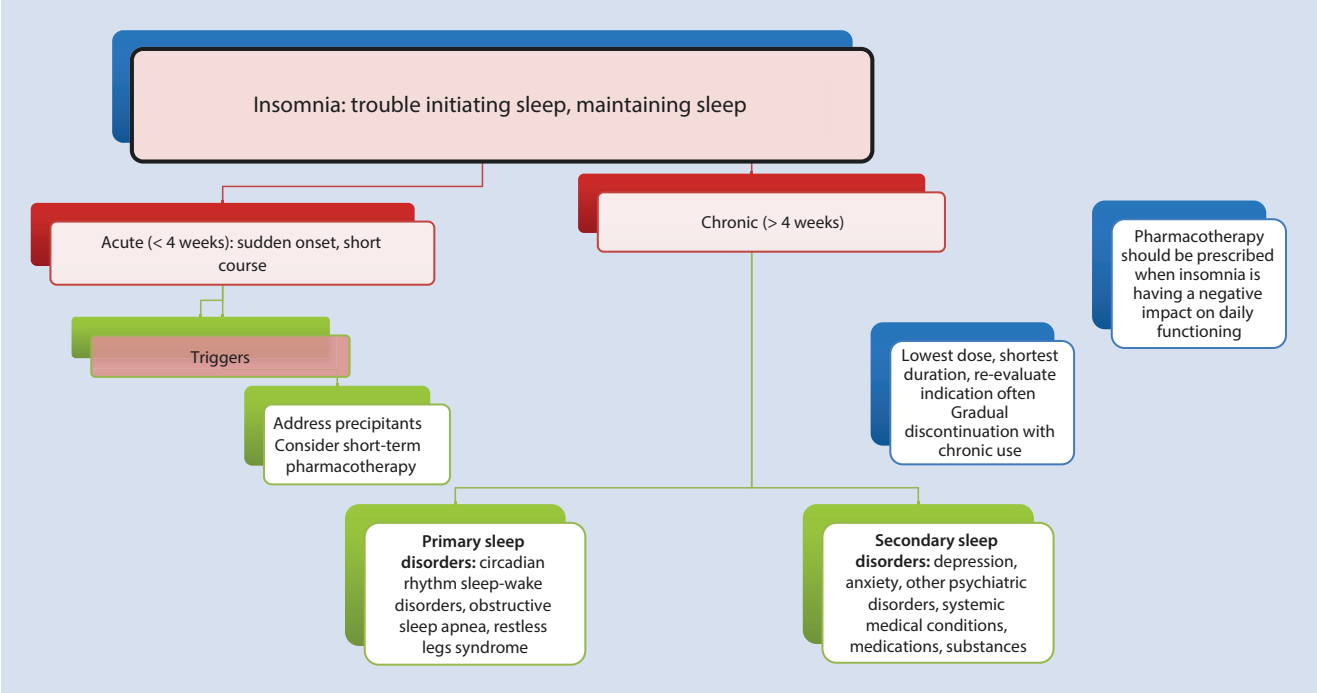

Fig. 24.2 Decision tree approach to assessment and treatment of insomnia

Hypersomnia is common in patients with Lewy body neurocognitive disorder and affects both patients and caregivers. The core features of Lewy body neurocognitive disorder, including visual hallucinations and parkinsonism, as well as overnight sleep disturbances (e.g., REM sleep behavior disorder and periodic limb movements), have been postulated to contribute to the hypersomnia. However, a recent study by Ferman et al. [43] suggests that daytime sleepiness is a distinct feature of this neurocognitive disorder, irrespective of disease stage or contributions from the four core features of Lewy body neurocognitive disorder. (See ▶ Chap. 20.) They proposed that the mechanism causing hypersomnia may be related to neuronal loss from the ascending reticular activating system known to regulate wakefulness [43]. The cells in these areas, particularly the locus ceruleus, raphe nucleus, tuberomammillary nucleus of the hypothalamus, and the basal forebrain, are particularly vulnerable in Lewy body neurocognitive disorder. Additionally, there may be some contribution of hypocretin cell loss, perhaps related directly to Lewy body pathology, leading to hypersomnia [43].

Psychiatric Disorders

Depressive Disorder

Insomnia historically has been seen as a symptom of mood dysregulation, a sign of anxiety, bipolar, or major depressive disorder [44]. More recently, insomnia has been viewed as its own distinct diagnosis, independent of a specific psychiatric disorder, and there is increasing evidence that insomnia is a risk factor for the development and persistence of major depressive disorder [44].

Clinical outcomes in depressed patients with abnormal sleep profiles are worse with respect to symptoms, remission rates, and response to treatment than those with normal sleep profiles [45]. Even after the resolution of a major depressive episode, residual insomnia symptoms may persist and predict earlier relapse [45], raising the importance of treating comorbid insomnia to augment the effects of depressive disorder treatment and decrease risk of future relapses.

Insomnia Disorder

Some older adults have disordered sleep that is not due to changes in their sleep architecture, an identified sleep disorder, chronic illness, or medications and other substances [2]. According to DSM-5, insomnia is a disorder unto itself, where a patient experiences unsatisfactory sleep quantity or quality, with subjective difficulties in initiating or maintaining sleep, at least 3 nights per week for at least 3 months (See ◘ Table 24.1). The insomnia experienced by the patient is found to cause distress and impact their daily functioning. ◘ Figure 24.2 presents a decision tree approach to the assessment and treatment of insomnia.

Non-pharmacological Treatment of Insomnia

After ruling out or treating systemic medical causes for disturbed sleep, the sleep difficulties that remain require further attention. As with any patient complaining of poor sleep, non-pharmacological interventions should be considered prior to prescribing medications. Sleep hygiene interventions are the first place to start and address environmental and behavioral contributions to poor sleep [46]. ◘ Table 24.5 summarizes sleep hygiene principles, highlighting the importance of a

Table 24.5 Non-pharmacological approaches to chronic insomnia in older adults

Avoid/minimize the use of caffeine, cigarettes, alcohol, and stimulating medication before bedtime
Exercise daily, but not close to bedtime
Avoid frequent napping; limit naps to one per day, less than 30 minutes
During the day, increase exposure to natural and bright light
Maintain bedtime ritual: bedroom is used for sleep (room is comfortable, with minimal light exposure)
Avoid heavy meals and liquids before bedtime
Avoid the use of electronics 1–2 hours before bedtime

stable sleep pattern, developing a sleep ritual, and avoiding behaviors that interfere with sleep.

When basic sleep hygiene principles are not effective, cognitive behavioral therapy for insomnia (CBT-i), which aims to address maladaptive sleep patterns by addressing incorrect sleep cognitions and changing expectations about what "normal" sleep is, should be considered. The CBT-i also employs techniques (e.g., stimulus control therapy, sleep restriction therapy, relaxation techniques) to provide lasting improvement in sleep. It is considered the most effective treatment for insomnia, superior to all pharmacological interventions [47].

Pharmacological Treatment of Insomnia

Pharmacological interventions should only be considered when all non-pharmacological options have been exhausted. There are five general principles to consider when using medication for insomnia in geriatric patients, regardless of the type of medication: (1) use of the lowest effective dose, (2) use of intermittent dosing (two to four times weekly), (3) prescribe the medication for a short term (no more than 4 weeks), (4) gradual medication discontinuation to reduce rebound insomnia, and (5) preferential use of medications with shorter elimination half-lives to minimize daytime sedation [4].

Benzodiazepines and benzodiazepine receptor agonists (the "Z" drugs) are widely prescribed due to their sedative properties and effectiveness in promoting sleep onset. However, the risks of using these drugs far outweigh the benefits, especially in patients over the age of 60. Impaired cognition, motor function, and coordination are common in older adults who are taking these medications and result in falls and motor vehicle accidents, as well as daytime sleepiness which impacts quality of life [48].

These risks combined with evidence of poor long-term efficacy and physical dependence have led the National Institutes of Health to establish guidelines discouraging the use of benzodiazepine hypnotics beyond 4 weeks, regardless of patient age [49].

Antidepressants are frequently prescribed off label to treat disturbed sleep in older adults without depressive disorder, although there are far fewer studies conducted in older versus younger patients [50]. Trazodone and mirtazapine are two of the most clinically useful antidepressants for treating insomnia. However, trazodone may causes daytime drowsiness and dizziness, which can cause falls and daytime impairments [51].

Teaching Point

Patients with insomnia who are prescribed sedating medications, particularly the benzodiazepines and benzodiazepine receptor agonists, require monitoring by clinicians for emergence or worsening side effects of oversedation and cognitive impairment. Clinicians should monitor for rebound discontinuation and withdrawal effects and allow the discontinuation schedule to be slow.

24.2 Case Studies

The following two case-based studies describe clinical presentations of sleep-wake cycle disturbances and adverse outcomes that may occur in geriatric patients.

24.2.1 Case 1

Case 1 History

Mr. A. was a 66-year-old community living, happily married, retired teacher who had been recently diagnosed with major depressive disorder by his primary care physician. His most troublesome complaints were low mood, fatigue, and impaired concentration. After several antidepressant trials, he eventually experienced improvement in mood but continued to have ongoing fatigue with low energy. He was sent for a consultation to a sleep clinic. At that time, his medications were citalopram 20 mg daily for major depressive disorder and rosuvastatin 20 mg daily for hypercholesterolemia.

Case 1 Questions and Answers

Case 1 Questions

Question 1. How would you assess the insomnia in this patient?

Question 2. What are the disorders that present with insomnia, and how are those relevant to this case?

Question 3. How are the disorders in *Case 1-Answer 2* treated?

Question 4. How would you manage Mr. A.'s insomnia at this time? What are your priorities?

Case 1 Answers

Case 1 Answer 1 (Question 1—How would you assess the insomnia in this patient?)

A1.1. A thorough sleep history needs to be obtained from both Mr. A. and his wife, who could provide a helpful collateral if she shared his bed. The history surrounding his sleep specifically should include:

- What time does he get into bed and wake up in the morning?
- How long does it take for him to fall asleep? If not falling asleep, what does he do (e.g., watching TV, reading, or getting up)?
- Are there nocturnal awakenings? If so, how many and how long does it take to fall back asleep once awake?
- Is there early morning awakening?
- Does he feel rested when he wakes up?
- Did the sleep difficulties begin before or after the depressive symptoms began?
- Is there a family history of sleep disorders?
- Has his wife noticed issues while he sleeps (e.g., talking in his sleep, sleep walking, thrashing movements, acting out dreams)?
- Has she noticed snoring or apneic spells?

A1.2. Habits and routines surrounding sleep are also important to elicit, as simple sleep hygiene interventions can be implemented where necessary. These interventions can be found in Table 24.5. Clarifying patterns of using caffeine, nicotine, and alcohol consumption, as well as daily exercise routines, is important. Getting a sense of the patients' routines each day, including when they stop using bright screen electronics, what types of activities they do in bed, and any misconceptions they may have about sleep, is essential.

A1.3. It is important to get a subjective sense of Mr. A.'s daytime functioning:

- Is he tired during the day?
- Does he need to take naps? How long are the naps, and what time do the naps occur?
- Does he avoid certain activities or outings because of fatigue?
- Has he fallen asleep while driving or had any accidents secondary to falling asleep?

In the setting of a primary care physician's office, it is often helpful to use direct lines of questioning, instead of validated questionnaires and sleep scales, as these are often difficult to administer given the frequency of comorbid cognitive and systemic medical conditions in the geriatric population [52]. Questionnaires frequently used in sleep clinics include the Epworth Sleepiness Scale, which subjectively quantifies sleepiness using an eight-item questionnaire; however, its utility and validity has not been tested specifically in older adults [53]. Other validated objective sleep scales used to measure sleepiness and sleep quality in a clinical setting include the Pittsburgh Sleep Quality Index [54] and the Stanford Sleepiness Scale [55]; these are used more frequently in sleep clinics and in sleep research.

A1.4. If a physical examination was not done at the primary care physician's office, a full physical exam should be performed, and a review of medical history would be important. Determining which objective sleep assessments are necessary for Mr. A. is essential.

Polysomnography refers to the simultaneous recording of multiple physiologic parameters during sleep. An electroencephalogram monitors sleep stages by recording brain waves, electromyography records muscle activity, and electrooculography tracks eye movements. Additionally, breathing changes are measured via airflow, respiratory effort, and blood oxygenation [52]. The purpose of polysomnography is to determine if there are any abnormalities (e.g., breathing disorders, abnormalities related to sleep stage, unusual nocturnal behaviors such as myoclonus) [56]. Polysomnography is typically indicated for diagnosing sleep-related breathing disorders (e.g., obstructive sleep apnea), violent or injurious sleep-related behaviors, and atypical or unusual parasomnias [52]. In the geriatric population, the use of polysomnography may be limited by its complexity and intrusiveness and the need for specialized centers [52].

The multiple sleep latency test (MSLT) is the best validated measure of daytime sleepiness and is used to determine if there is excessive daytime sleepiness or an abnormal tendency for REM sleep to occur during daytime naps, suggesting a likelihood of narcolepsy [52]. Sleep latency is the time between getting into bed and falling asleep (reaching any sleep stage), and it is measured during a series of 20-minute periods in a laboratory setting, where patients are given napping opportunities. REM sleep is measured, and validation of REM in two or more periods is highly supportive of a narcolepsy diagnosis [57].

Case 1 (Continued)

Upon assessment in the sleep clinic, Mr. A.'s medical history revealed tonsillectomy at age 5 and current dyslipidemia, being treated with rosuvastatin 20 mg daily. There was no history of alcohol or illicit drug use, and he drank one caffeinated beverage per day prior to noontime. He took no over-the-counter medications. His sleep habits revealed that he went to bed at 10:30 PM and woke up at 7:00 AM, for a total of 8 hours of sleep (he fell asleep within 30 minutes). The sleep history elicited loud snoring, nasal congestion, somniloquy (i.e., sleep talking), and daytime fatigue. He admitted to taking daytime naps because of his fatigue and felt he was not as active as he would like because of his subsequent lack of energy. His wife noticed some movements during his sleep, but stated that Mr. A. would not be bothered by these movements and they did not last very long. There was no history of somnambulism (i.e., sleep walking), falling asleep while driving or nearly causing car accidents. Regarding cognitive changes, Mr. A. complained of some difficulty remembering things during the day, but attributed this to his fatigue and resulting poor concentration. He had no allergies. His family history revealed coronary artery disease and an unspecified anxiety disorder.

Physical examination revealed a body mass index of 27.6 kg/m^2 (overweight). His neck circumference was 19 inches (normal in men, less than 17 inches; normal in

women, less than 15 inches), chest was clear, heart sounds were normal, and abdomen was soft. Blood pressure was 134/88 mmHg, heart rate was 67 beats/minute, and oxygen saturation of 98% on room air. MoCA was 23 out of 30 points (with 4 out of 5 points lost on delayed recall task and 3 points lost on attention task).

Because on history taking his wife commented on some movements during his sleep, Mr. A. was subsequently referred for a polysomnography, which revealed a diagnosis of obstructive sleep apnea, with an apnea-hypopnea index (AHI) of 39 (severe) and desaturations down to 75%. A decreased sleep efficiency and severe periodic limb movements with limb arousals were also evidenced on the sleep study. As a consequence, Mr. A. took a CPAP titration study. On a CPAP of 11 cm H_2O, he achieved optimal results, with no reported snoring, choking, gasping, witnessed apneas, daytime fatigue, or sleepy driving.

Case 1 Answer 2 (Question 2—What are the disorders that present with insomnia, and how are those relevant to this case?)

Looking at Mr. A.'s history, there are a number of factors that may be contributing to his insomnia. Perhaps the most obvious to this case would be his depressive disorder. The insomnia may have preceded the depressive disorder, contributing to its development; it may have been a symptom of the depressive disorder; or it may be unrelated to the depressive disorder altogether. Understanding the course of the insomnia, the impact on daytime functioning and comorbidities that may be contributing to it would help direct further investigations and eventually management.

Insomnia has long been seen as a symptom of depressive disorder, with 90% of patients with major depressive disorder complaining of poor sleep. Sleep-related problems in major depressive disorder include difficulty with sleep initiation, sleep maintenance, early morning awakening, and daytime fatigue [58]. However, it is now being better understood that premorbid insomnia is a risk factor for major depressive disorder, insomnia is an independent risk factor for suicide in depressed patients, and antidepressant treatment alone does not always result in the resolution of insomnia [30]. Given Mr. A.'s history of major depressive disorder, treating his residual insomnia is of greater importance in order to prevent a relapse.

As mentioned previously, restless legs syndrome commonly occurs with periodic limb movements in sleep, with restless legs syndrome being diagnosed by history, but the two can occur independently, as was likely in Mr. A.'s case. This would explain the daytime fatigue and his subjective experience of sleeping well overnight with no issues.

The cause of restless legs syndrome and periodic limb movement disorder is unknown, but potential mechanisms suggest a role for the dopaminergic system, as well as other neurotransmitters. Although the cause is thought to be idiopathic, often restless legs syndrome will run in families. As outlined in ► section Restless Legs Syndrome and Periodic Limb Movement Disorder, screening for medical contributors to restless legs syndrome and periodic limb movement disorder may help narrow down diagnoses and assist in treatment. These include iron deficiency, low ferritin levels, and diabetes mellitus.

Case 1 Answer 3 (Question 3—How are the disorders in *Case 1-Answer 2* treated?)

The treatment for both restless legs syndrome and periodic limb movement disorder is similar, and not all patients will require treatment with pharmacotherapy. Many patients will do well with lifestyle and sleep hygiene measures, including limiting caffeine, nicotine and alcohol several hours before bedtime, having a regular and relaxed bedtime routine, and avoiding physical stimulation 1–2 hours before bed. Pharmacological treatments for these disorders have been more widely studied than lifestyle interventions, with practice parameters established by the American Academy of Sleep Medicine [59].

As with starting any new medication, it is important to weigh the severity and impact of symptoms and the risks and side effects of the medication being considered. In general, dopaminergic agents are first-line treatment for restless legs syndrome and periodic limb movement disorder and considered highly effective. The dopamine agonists pramipexole and ropinirole are the current most effective drugs in the treatment of restless legs syndrome and periodic limb movement disorder. Pramipexole has been shown to be effective in treating symptoms of restless legs syndrome and is well tolerated; its typical side effects of nausea and somnolence generally decrease over time, and augmentation is seen infrequently in patients [59].

Teaching Point

Augmentation is a phenomenon caused strictly by medication used to treat restless legs syndrome where, as the dose of the medication wears off, symptoms return at a greater intensity than baseline, begin earlier in the night, and may spread to other parts of the body [60]. Augmentation mainly occurs with long-term levodopa use but can also occur with dopamine agonists [60].

Ropinirole is most effective for the treatment of moderate to severe restless legs syndrome. Similar to pramipexole, ropinirole is well tolerated; side effects include nausea, vomiting, headache, somnolence, and dizziness, and augmentation is a rare side effect [59]. Pergolide, another dopamine agonist, has been found to be highly effective in the treatment of restless legs syndrome, but due to the high risk of cardiac valvulopathy, it is no longer recommended and has been withdrawn from the US market [59].

Carbidopa-levodopa was previously the most frequently used initial treatment of restless legs syndrome; however, due to the side effects (e.g., rebound, augmentation) and availability of newer agents, it is less commonly used [59].

Opioids are effective for the treatment of restless legs syndrome but are only recommended when other agents are ineffective, as the level of evidence supporting opioid use is low [59]. Caution should be used when prescribing opioids given the potential for abuse in some patients and the potential development of or worsening of sleep apnea [59].

A few other drugs are used for treating restless legs syndrome and will be discussed briefly. Gabapentin enacarbil is useful for treating moderate to severe restless legs syndrome and is well tolerated; however, it is a new drug, with evidence still emerging [59]. Gabapentin has evidence supporting its use in mild to moderate restless legs syndrome and recommended if the patient also suffers from pain [59]. Evidence for the use of clonidine and iron supplementation is minimal in the treatment of restless legs syndrome [59]. Clonazepam lacks clinical data warranting its use as a first-line agent [59].

In Mr. A.'s case, the clinician decided that since there were various issues at play (periodic limb movement disorder and obstructive sleep apnea), employing sleep hygiene measures would be the first line, along with managing the obstructive sleep apnea.

Case 1 Answer 4 (Question 4—How would you manage Mr. A.'s insomnia at this time? What are your priorities?)

The primary diagnoses relevant to his complaint of insomnia are major depressive disorder, periodic limb movement disorder, and obstructive sleep apnea. It is probable that his insomnia is not related to the major depressive disorder, as medication has rectified most symptoms related to mood, and the only remaining symptoms are related to sleep and cognition. The best place to start treatment would be with addressing his obstructive sleep apnea. The bidirectional relationship between depressive disorder and obstructive sleep apnea should be noted. Patients with depressive disorder have an increased prevalence of obstructive sleep apnea, and patients with apnea have higher rates of depressive disorder [61]. Moreover, obstructive sleep apnea is a risk factor for developing depressive disorder, and in those with apnea, depressive disorder contributes to the severity of daytime fatigue. In contrast, treatment of obstructive sleep apnea may lead to improvement in depressive disorder [62]. Therefore, there are a number of reasons for which Mr. A.'s obstructive sleep apnea needs to be effectively treated.

With regard to the new diagnosis of obstructive sleep apnea confirmed on polysomnography, Mr. A. has several risk factors (as discussed in ► section Breathing-Related Sleep Disorders) including premorbid hypercholesterolemia, increased body mass index, and increased neck circumference. A diagnosis of obstructive sleep apnea could explain both the daytime sleepiness as well as the cognitive deficits, as demonstrated by his MoCA score (23 out of 30). Appropriate treatment of obstructive sleep apnea may reverse the cognitive impairment and prevent further cognitive decline [20].

The association of sleepiness and sleep disorders would be discussed with Mr. A., particularly that an increased level of sleepiness could result in inattentiveness and increased accidents, including motor vehicle accidents. He was advised not to drive when sleepy. At a 3-month follow-up, his sleep apnea was stable on treatment with CPAP at a pressure of 11 cm H_2O. Mr. A. had also noticed improvements in daytime functioning, most notably that his energy levels were higher; he did not require daytime naps and felt more alert. A repeat MoCA showed improvements in delayed recall, with a new score of 27 out of 30.

Given that treating periodic limb movement disorder was not a priority at this point, the plan was for Mr. A. to continue with his CPAP treatment and follow-up in 3 months. If symptoms persisted or returned, a trial of a dopamine agonist should be considered, with the risks and benefits of the medication explained prior to initiation.

Case 1 Analysis Mr. A.'s complaint of insomnia indicated a differential diagnosis that included major depressive disorder, periodic limb movement disorder, and obstructive sleep apnea. However, it was improbable that his insomnia was a symptom of a depressive syndrome, because treatment of depressive disorder had improved most symptoms related to mood, except for sleep and cognitive changes. Depressive disorder and sleep apnea have a bidirectional relationship. Mr. A. had a number of risk factors for obstructive sleep apnea, and this diagnosis was eventually confirmed with polysomnography. This case emphasized the impact of obstructive sleep apnea on the sleep-wake cycle, including daytime sleepiness, as well as other health-related concerns (e.g., cognitive impairment). Treatment of obstructive sleep apnea with CPAP could improve sleep, reverse Mr. A.'s cognitive impairment, and prevent further cognitive decline. If symptoms persisted, a trial of a dopamine agonist for treating his periodic limb movement disorder could be considered.

24.2.2 Case 2

Case 2 History

Mr. B. was an 82-year-old man living in an assisted living facility for the previous 3 months. He presented with long-standing difficulties in initiating and maintaining sleep, worsening since the death of his wife 3 months previously, to whom he was the primary caregiver. He also endorsed new onset vivid dreams at night, acting out on them (often getting injured in the process), and, despite having trouble sleeping at night, found himself sleeping excessively during the day. His medical history included Parkinson disease (diagnosed 3 years previously), chronic obstructive pulmonary disease (COPD), hypertension, type 2 diabetes mellitus, osteoarthritis, and recurrent falls in the previous 1 year. He reported visual impairment. He requested that his primary care physician prescribe a bedtime sleep aid for his poor sleep and "a pill to perk up" during the daytime.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What else do you need to know to make a diagnosis?

Question 2. What factors in his history are contributing to his sleep difficulties?

Question 3. How would we address Mr. B.'s sleep disturbances, including recommendations regarding his overall health?

Case 2 Answers

Case 2 Answer 1 (Question 1—What else do you need to know to make a diagnosis?)

The first item to elicit is a thorough medical history, including acquiring a list of Mr. B.'s current and previous medications. As he is in an assisted living facility, it would be important to find if Mr. B. takes his own medication or whether these are administered to him. Regardless of the complaints, a medication review would be warranted, and referrals made to the appropriate specialists if needed (e.g., endocrinologist for diabetes mellitus, respirologist for COPD, neurologist for Parkinson disease). His current list of medications included metformin 500 mg po bid for type 2 diabetes mellitus, sitagliptin 100 mg po daily for type 2 diabetes mellitus, fluticasone inhaler 1–2 puffs bid prn for COPD, hydrochlorothiazide 25 mg po daily for hypertension, carbidopa-levodopa 25/100 mg po tid for Parkinson disease, and acetaminophen 325–650 mg po tid prn for osteoarthritis.

You learned that Mr. B. was also taking some of his wife's medication occasionally, a "sleeping pill" she had been prescribed, which he found helpful for getting to sleep. This medication was lorazepam; he was taking 1–2 mg of lorazepam three to four times per week at bedtime but had run out of her tablets in the last 2 weeks, with no refills of his own.

Similar to Case 1, a sleep history would need to be documented, including the nature of the sleep disturbances. Mr. B. reported difficulties initiating and maintaining sleep, so understanding what is keeping him awake would be important. Since he lives in an assisted living facility, asking the caregivers there about any changes they may have documented or noticed would also be important, especially with respect to Mr. B.'s daytime functioning. Inquiring about nocturia, recent infections, or other illnesses would be important to rule out reasons for nighttime awakenings and trouble with sleep maintenance.

The clinician would also recommend that Mr. B. have visual testing done given his complaints of recent impairment, which may also be affecting his ability to take his own medication. A cognitive screening test (e.g., MoCA) would also be warranted given the diagnosis of Parkinson disease and risk of cognitive decline to get a better sense of what type of assistance Mr. B. may require.

Assessing for depressive symptoms, secondary to either the death of his wife or non-motor sequelae of Parkinson disease, would also be relevant, given that sleep disturbance is common with depressive syndromes.

Case 2 (Continued)

You learned that Mr. B. had been taking his own medication each day, which were dispensed in bottles, not in blister packs. Although he believed himself to be compliant, he was erroneously taking his hydrochlorothiazide twice per day, and his metformin only once per day.

Regarding his sleep, he acknowledged difficulty falling asleep, which had gotten worse since running out of lorazepam, but stated that sleep initiation difficulties predated his use the lorazepam by several months. During the night he complained of waking up because of stiffness in his joints and difficulty moving around in bed. He denied any nocturia. He reported that although he could not recall his dreams, there were a number of times he found himself on the floor or having injured himself in the night. During the day, he suffered from excessive tiredness, requiring multiple naps, especially when engaging in activities such as watching TV or attempting to read. He denied any "sleep attacks". He also described that his vivid dreams did not resemble night terrors, and he could not recall sleep walking or waking up in different rooms. He scored 23 out of 30 on his MoCA test (this was 25 out of 30 one year previously), and his visual complaints were confirmed to be secondary to changes consistent with a diabetic retinopathy, likely exacerbated by poor diabetic control and medication misuse. A Geriatric Depression Scale was also administered at this visit, and Mr. B. scored 3 out of 15, suggesting no major depressive disorder at that time.

Case 2 Answer 2 (Question 2—What factors in his history are contributing to his sleep difficulties?)

The following factors in his history that may be contributing to sleep difficulties include COPD, Parkinson disease, pain from osteoarthritis, and medications. Additionally, the vivid dreams need to be addressed, and various differentials considered in this regard.

Disruption in sleep is frequently noted in patients with significant pain. As with all chronic medical conditions, improving the medical condition itself is a priority, followed by adequate pain control. Understanding the quality and nature of Mr. B.'s pain would be important, especially in distinguishing whether the pain is related to his osteoarthritis, Parkinson disease, or secondary to undetected sequelae of a recent injury or fall. Pain and insomnia may have a bidirectional relationship, whereby trouble sleeping may exacerbate pain, just as pain results in insomnia. Studies have shown that treatment of insomnia can lead to improvements in pain [30]. (See ▶ section Insomnia Disorder on approaches to treating insomnia.) Although Mr. B. has a diagnosis of COPD, the sleep disturbances experienced with COPD are not the same as in patients with sleep apnea. Sleep apnea is no more common in patients with COPD than in the general population [63]. Medications commonly prescribed to treat COPD (e.g., theophylline) may have a disruptive effect on sleep and should be looked out for. Also, alcohol and benzodiazepines should be avoided as they

can worsen hypoxemia. Benzodiazepines, particularly in severe COPD, contribute to hypoxemia by inhibiting ventilatory response [63]. Non-benzodiazepine hypnotics (e.g., zolpidem) and the melatonin receptor antagonist ramelteon, however, have been found to improve sleep in this patient population without adversely affecting respiration [64].

Regarding medication, taking extra hydrochlorothiazide would increase Mr. B.'s risk of hypotension, resulting in unsteadiness and falls, but unlikely to affect his sleep. The use of lorazepam, while initially helpful in promoting sleep, would cause rebound insomnia later in the night and, again, put Mr. B. at risk for falls. Understandably, he would have had increasing difficulty with sleep initiation after running out of this medication, as he likely became dependent on it. Despite this, it would not be recommended to resume lorazepam.

Regarding his vivid dreams, visual hallucinations associated with Parkinson disease must be considered on the differential. Nocturnal hallucinations, which affect almost 20% of patients with Parkinson disease, are often caused by antiparkinsonian medication but can also occur secondary to delirium due to an infection, use of sedating medication, drug toxicity, metabolic imbalance, dehydration, or malnutrition [35]. Hallucinations are more common in advanced Parkinson disease and in patients with underlying cognitive impairment [35].

Given that Mr. B. had complaints of acting out on vivid dreams, daytime sleepiness, and a diagnosis of Parkinson disease, a REM sleep behavior disorder must be considered. Initially, gathering a history is important, but polysomnography is required for a diagnosis to be confirmed. As Mr. B. did not have a bed partner, an accurate depiction of bedtime activities would be difficult, as those with REM sleep disorder are often unaware that they are acting out dreams. Mr. B. would, however, be able to comment on whether he had been injured during sleep while thrashing or falling out of bed or, in some cases, whether there was damage to walls or other nearby structures. Of note, patients with REM sleep behavior disorder rarely engage in sleep walking and rarely use objects in their environment to reenact their dreams (e.g., knives, books) [65].

Differential diagnosis of REM sleep behavior disorder to screen for include sleep apnea, periodic leg movements during sleep, normal dream-enacting behaviors, seizure disorder (specifically nocturnal frontal lobe epilepsy), and non-REM parasomnias (e.g., sleep walking, night terrors, confusional arousals) [65]. Sleep walking and night terrors tend to occur in children and young adults, while confusional arousals can occur in older adults who have taken sedatives, those who have major neurocognitive disorders and those arising from sleep apnea [65]. Because of these similar presentations, REM sleep behavior disorder cannot be diagnosed on history alone, but rather requires polysomnography showing the loss of REM atonia [66]. The motor activity described in REM sleep behavior disorder consists of complex movements (e.g., arm or leg thrusts), punching or kicking, and may be accompanied by vocal emotional outbursts. These often violent movements can result in injury to the patients or their bed partner. Interestingly, there can be restoration of normal motor activity, with disappearance of parkinsonian features during the acting out of REM sleep dreams [21].

Independent of a REM sleep behavior disorder, nearly two-thirds of patients with Parkinson disease will experience some time of sleep disturbance. Clinicians must elicit the type of sleep disturbance Mr. B. was experiencing and elucidate the contribution of the disease process itself, a potential REM sleep behavior disorder, and medication affecting his sleep. His insomnia can be divided into sleep onset insomnia and sleep maintenance insomnia. Patients who have advanced Parkinson disease report that sleep maintenance insomnia is one of the most troubling symptoms they experience [67]. The contribution of restless legs syndrome and REM sleep behavior disorder to insomnia in Parkinson disease has been addressed in other sections of this chapter. Insufficient dopaminergic treatment also exacerbates sleep maintenance insomnia, where there is essentially a wearing off effect overnight, causing nocturnal aggravation of the core motor symptoms, as well as trouble with nocturnal akinesia, difficulties turning over in bed, cramps, and anxiety [21].

In contrast, excessive daytime sleepiness, manifesting as hypersomnia, is common in patients with Parkinson disease, occurring in 50–75% of these patients [68] and manifesting as symptomatic daytime somnolence with frequent sleep periods [69]. Excessive daytime sleepiness has a multitude of causes, including abnormalities in sleep-regulating centers, exhaustion due to the motor symptoms, enhancement of motor symptoms aggravated by wearing off of medication, and in some patients, coexisting depressive disorder or sleep apnea [21]. The Epworth Sleepiness Scale is considered the standard for measuring excessive daytime sleepiness in patients with Parkinson disease [70].

Case 2 (Continued)

Baseline laboratory studies (including a complete blood count and basic metabolic panel) and a urinalysis were ordered, all of which were normal, and could safely rule out an acute infective process. Mr. B. was referred to a sleep clinic where he had polysomnography performed, confirming a diagnosis of REM sleep behavior disorder. He was not found to have an obstructive sleep apnea-hypopnea, confirming that his COPD was likely his only breathing-related problem. An Epworth Sleepiness Scale was administered, and Mr. B. scored 12 out of a maximum 24, suggesting mild excessive daytime sleepiness. Upon reviewing Mr. B.'s carbidopa-levodopa, you found that Mr. B. took his three doses at 8:00 AM, at 12:00 PM, and at 5:00 PM. He usually went to bed around 9:00 PM.

Case 2 Answer 3 (Question 3—How would we address Mr. B.'s sleep disturbances, including recommendations regarding his overall health?)

Given his cognitive impairment and host of medical issues, having a family member or trusted caregiver present for the assessment would be advisable. Reviewing the sleep tests, providing psychoeducation about medication, ensuring

Table 24.6 Clinical characteristics that disrupt sleep and management tips in Case 2

Clinical feature	Sleep disturbance contributors	Management tips
Predisposing factors		
Advanced age, normal aging	Decreased SWS and REM sleep	Physical activity, outdoor light exposure; avoid large meal, caffeine, and alcohol several hours before bedtime
Precipitating factors		
Osteoarthritis	Pain-related insomnia	Pharmacologic and non-pharmacologic therapy for arthritis
Hypertension	Sleep-disordered breathing	Avoid sedatives/hypnotics
Parkinson disease	Depressive disorder, sleep-disordered breathing, RLS, PLMD, REM sleep behavior disorder, nocturia due to illness	Targeted treatment
COPD	Insomnia due to hypoxia	Targeted treatment
Medications	Daytime sleepiness (antiparkinsonian medication, corticosteroid, hypoglycemics), nocturia due to medication	Avoid centrally acting medications
Perpetuating factors		
Bereavement Social isolation Caregiving	Irregular sleep-wake patterns, inadequate sleep hygiene	Non-pharmacological approaches for chronic insomnia, CBT-insomnia, physical activity, social support services

Note: CBT cognitive behavioral therapy, *COPD* chronic obstructive pulmonary disease, *PLMD* periodic limb movement disorder, *REM* rapid eye movement, *RLS* restless legs syndrome, *SWS* slow-wave sleep

taking of medication as prescribed, and ensuring that medication reviews are performed every 6 months by the primary care physician are the first steps. Going forward, medication should be dispensed in a blister pack and administered by staff members at the assisted living facility to ensure medication is taken appropriately and on time.

In terms of the antiparkinsonian medication, he was taking his carbidopa-levodopa three times per day, but it is reasonable to believe that his medication may have begun to wear off by the time he has gone to sleep, resulting in symptom exacerbation overnight, manifested by the cramping and joint pain he has been experiencing. Increasing his dosing to four times per day, with one dose being given at bedtime, is an option. An alternative is the introduction of a dopamine agonist at this time; however, as discussed previously, dopamine agonists place patients at increased risk of sleep attacks and would need to be monitored. A referral to Mr. B.'s neurologist may also be warranted if he experiences side effects due to the increased medication dose or does not benefit from reduced overnight symptoms.

Most importantly, treating Mr. B.'s REM sleep behavior disorder would be a priority. As mentioned in ▶ section REM Sleep Behavior Disorder, the treatment for REM sleep behavior disorder includes clonazepam 0.5–2 mg po at bedtime or melatonin 3–12 mg po at bedtime. It would be reasonable to start Mr. B. on clonazepam 0.5 mg po at bedtime, with the possibility of increasing this dose if necessary. It would be important to educate him on the potential side effect of tolerance to the medication and as well rebound insomnia through the night, which occurs as the medication wears off [48]. If the dose of clonazepam is too high, Mr. B. may also experience daytime sedation, which would make his current complaint worse.

Concurrent with the pharmacotherapy, encouraging Mr. B. to engage in appropriate daytime activities at his assisted care facility that promote good sleep overnight is essential. These include physical activity daily as tolerated, exposure to natural or bright light during the day, and minimizing light exposure overnight, limiting and if possible eliminating naps during the day. Table 24.6 lists a summary of the clinical characteristics that disrupted Mr. B.'s sleep and suggested management tips.

Case 2 Analysis This case illustrates the complex interplay of systemic medical and neuropsychiatric disorders associated with sleep disturbances, medications, and combinations of these. A polysomnography confirmed the diagnosis of REM sleep behavior disorder in Mr. B., and treating REM sleep behavior disorder was a priority in order to improve his sleep difficulties. Patient education regarding the potential side effect of tolerance to the benzodiazepine clonazepam, and as well rebound insomnia through the night, which occurs as

the medication wears off, was necessary. If used, Mr. B.'s physician needed to be cautious with the use of dopamine agonists which would place the patient at increased risk of sleep attacks, which requires close monitoring. Considering a referral to Mr. B.'s neurologist may have been warranted if there was no benefit from reduced overnight symptoms or if side effects occurred due to the increased medication dose. Concomitant implementation of non-pharmacological approaches (e.g., physical activity, natural or bright light exposure in the daytime, nap restriction during the day) is essential for the treatment of insomnia.

24.3 Key Points: Sleep-Wake Disorders in Late Life

- Nearly 40% of individuals over the age of 60 experience sleep difficulties.
- Normal age-related sleep changes include a decrease in slow-wave sleep (stages 3 and 4), REM sleep and sleep efficiency, an increase in stages 1 and 2 sleep, and lighter and more superficial sleep; sleep-wake circadian rhythm cycle becomes less effective at responding to cues, making the sleep-wake cycle less consistent across the 24-hour day, as well as phase advance resulting in earlier sleep and wake times.
- Age-related changes in sleep architecture do not account for most of the disturbed sleep in the older adults, but rather there is a combination of systemic medical and psychiatric comorbidities as well as primary sleep disorders that are typically important to account.
- The most common primary sleep disorders are restless legs syndrome, periodic limb movement disorder, REM sleep behavior disorder, and breathing-related sleep disorders.
- Restless legs syndrome is a clinical diagnosis, while periodic limb movements are not usually noticed by the patient and can only be diagnosed by polysomnography. REM sleep behavior disorder is diagnosed by polysomnography; older adults with REM sleep behavior disorder are at increased risk for and can predict development of future neurodegenerative diseases including Parkinson disease.
- Advanced sleep phase syndrome represents a decrease in the ability to phase-delay the circadian rhythm in response to normal environmental cues, called zeitgebers.
- Sleep-disordered breathing is an abnormal respiratory pattern that can range from significant snoring to episodes of complete airway obstruction where breathing ceases for a period of 10 seconds or more.
- Sleep-disordered breathing is associated with cognitive decline.
- Depressed patients with abnormal sleep profiles have worse clinical outcomes for remission rates and response to treatment than those with normal sleep profiles.
- Premorbid insomnia is a high risk for major depressive disorder and is an independent risk factor for suicide in depressed patients.
- The treatment for restless legs syndrome and periodic limb movement disorder includes dopaminergic agents as first-line treatment, followed by opioid and benzodiazepine agents; caution should be used due to side effects, most notably the development of sleep apnea when on long-term opioid treatment, and confusion associated with benzodiazepine/hypnotic use. Clonazepam and melatonin are common treatment options for REM sleep behavior disorder; however, benzodiazepines lack the clinical data warranting its use as a first-line agent.

24.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following statements is *not* true about periodic limb movements?

A. Periodic limb movements are not usually noticed by the patient.
B. Periodic limb movements are diagnosed by polysomnography.
C. Periodic leg movements in sleep present along with restless legs syndrome support a diagnosis of restless legs syndrome.
D. A frequency of limb movements greater than 15 per hour, accompanied by sleep disturbance or other functional impairment, supports a diagnosis of periodic limb movement disorder.
E. Periodic limb movement disorder is at increased risk for Parkinson disease.

Answer: E

Unlike restless legs syndrome, periodic limb movements are not usually noticed by the patient and can only be diagnosed by polysomnography [17]; therefore, statements A and B are true. Because periodic leg movements in sleep occur in up to 90% of patients with restless legs syndrome, its occurrence along with restless legs syndrome supports a diagnosis of restless legs syndrome [18]. Therefore, statement C is true. Limb movements with a frequency of greater than 15 per hour, accompanied by sleep disturbance or other functional impairment, support a diagnosis of periodic limb movement disorder [19], and statement D is true. There is no evidence that older adults with periodic limb movement disorder are at increased risk for Parkinson disease or other neurodegenerative synucleinopathies, unlike REM sleep behavior disorder [35], and thus statement E is not true.

MCQ 2. REM sleep behavior disorder is *not* characterized by:

A. Loss of normal atonia during REM sleep and reenactment of dreams.

B. Walking, thrashing, flailing limbs, or engaging in complex movements while sleeping.
C. Dream acting out caused by benzodiazepines.
D. Linkage to neurodegenerative and non-neurodegenerative disorders, including Parkinson disease, multiple sclerosis, and amyotrophic lateral sclerosis.
E. Prediction for the development of future Parkinson disease.

Answer: C

REM sleep behavior disorder is characterized by loss of normal atonia during REM sleep and reenactment of dreams by the patient. The patients may walk, thrash or flail their limbs, or even engage in complex movements [5]. Therefore, statements A and B are true. REM sleep behavior disorder may occur comorbidly with synuclein-mediated neurodegenerative diseases (including Parkinson disease) and non-neurodegenerative disorders (e.g., multiple sclerosis, amyotrophic lateral sclerosis, narcolepsy, Guillain-Barre syndrome) [20]; therefore, statement D is true. REM sleep behavior disorder often occurs in patients with Parkinson disease, and it can predict the development of future Parkinson disease; therefore, statement E is true. Benzodiazepines such as clonazepam administered at bedtime are a common treatment option for REM sleep behavior disorder, and not a cause for it [22], although a trial of a dopamine agonist can be considered if symptoms are still not improving. Therefore, statement C is not a true characterization of REM sleep behavior disorder.

MCQ 3. Which of the following statements is correct regarding treatment of sleep-wake disturbance?

A. In patients with REM sleep behavior disorder, clonazepam 0.5–2 mg at bedtime and melatonin 3–12 mg at bedtime are common treatment options.
B. In patients with Parkinson disease, restless legs syndrome, and periodic limb movement disorder, levodopa is a first-line treatment.
C. In patients with Parkinson disease, restless legs syndrome, and periodic limb movement disorder, dopamine agonists, ropinirole and pramipexole, should be avoided.
D. In patients with restless legs syndrome alone, pramipexole is ineffective.
E. In patients with moderate to severe REM sleep behavior disorder, ropinirole is the most effective treatment.

Answer: A

In patients with Parkinson disease, restless legs syndrome, and periodic limb movement disorder, dopamine agonists, ropinirole and pramipexole, should be considered first line [35], whereas levodopa should be avoided to prevent further rebound and augmentation during the night, which are common experiences in Parkinson disease patients [35]; thus, statements B and C are incorrect. Pramipexole has been shown to be effective in treating symptoms of restless legs syndrome and is well tolerated; therefore, statement D is incorrect. Ropinirole is most effective for the treatment of moderate to severe restless legs syndrome, not REM sleep behavior disorder as in statement E, which is incorrect. Clonazepam 0.5–2 mg at bedtime and melatonin 3–12 mg at bedtime are common treatment options for REM sleep behavior disorder; thus, statement A is correct. Table 24.7 lists pharmacological treatment options of insomnia in older adults [71–76].

Table 24.7 Pharmacological treatment of insomnia in older adults [71–76]

Drug class	Medication/dosage[a] (at bedtime)	Adverse effects	Drug interactions	Comments
Benzodiazepines[b, c]	Lorazepam 0.5–1 mg (insomnia not official indication but widely used)	Sedation, depression, irritability, delirium risk, memory impairment, dizziness, headache, weakness, dose-dependent ataxia, falls/fracture risk, behavioral changes, rebound insomnia, daytime anxiety	Additive sedation with CNS depressants CYP3A4 substrates	2015 Beers Criteria: *all benzodiazepines* should be used with caution or avoided as potentially inappropriate in older adults. Benzodiazepines should be used in older adults only with specific approved indications; monitor for cognitive status. Risk of tolerance and dependence. More rebound insomnia with lorazepam *Flurazepam*: not recommended (potential for accumulation leading to delirium risk and cognitive impairment) *Triazolam*: should be avoided in older adults, especially doses > 0.125 mg *Clonazepam*: given in REM sleep behavior disorder
	Temazepam 15–30 mg (max dose 7.5 mg for older adults)			
	Nitrazepam 5–20 mg (max dose 5 mg for older adults)			
	Flurazepam 15–30 mg (max dose 15 mg for older adults)			
	Triazolam 0.125–0.25 mg (max dose 0.125 mg for older adults)			
	Clonazepam 0.25–2 mg			

Table 24.7 (continued)

Drug class	Medication/dosage[a] (at bedtime)	Adverse effects	Drug interactions	Comments
Melatonin[d]	Melatonin 0.3–12 mg (max dose 5 mg for older adults)	Dizziness, headache, nausea, somnolence, tachycardia, pruritus, nightmares	Warfarin, nifedipine, fluvoxamine	To be given 30–90 minutes pre-bedtime. Appears to be safe when used for ≤ 3 months. Used in REM sleep behavior disorder. Not well studied in older adults
Ramelteon[b] (melatonin agonist)	Ramelteon 8 mg (available in USA and Japan)	Headache, somnolence, sore throat		No behavioral impairment; no abuse potential; no restriction on duration of use. Contraindicated in patients taking fluvoxamine, liver disease
Z-drugs[b, c]	Zaleplon 10–20 mg (max dose 10 mg for older adults) (discontinued in Canada)	Dizziness, somnolence, gastrointestinal disturbances, ataxia, falls/fracture risk, rebound insomnia, morning hangover effect, transient global amnesia, anterograde amnesia, delirium risk, nighttime acting out, sleepwalking, bitter/metallic taste	CYP3A4 substrate	*All Z-drugs* should be used with caution and for < 90 days in older adults *All Z-drugs* interact with CNS depressants and CNS active drugs. Caution to be exercised when used
	Zolpidem 5 mg SL (available in USA) Zolpidem ER 6.25–12.5 mg (max dose 6.25 mg for older adults) (available in USA)		CYP3A4, 1A2, 2C9 substrate; erythromycin, ketoconazole, rifampin	Should be avoided in patients with cognitive impairment
	Eszopiclone 1–3 mg (max dose 2 mg for older adults) (available in USA)		CYP3A4, 2C1 substrate	Less chance of morning hangover effect, rapid onset, allow 8 hours sleep, complex sleep-related behaviors induced, risk of tolerance/dependence
	Zopiclone 3.75–7.5 mg (max dose 5 mg for older adults) (available in Canada)		CYP3A4, 2C8 substrate	Does not accumulate, less rebound with discontinuation
Tryptophan[d]	Tryptophan 500 mg–2 g	Weight loss, dizziness, xerostomia, headache, nausea, improper sexual behavior, serotonin syndrome (alone and with serotonergic agents)		Given 20 minutes before bedtime. Erratic response
Sedating antidepressants (use when comorbid depression, anxiety, other comorbid indication)	Trazodone 25–100 mg	Orthostatic hypotension, cardiac conduction problems, dizziness, somnolence, xerostomia, dry eyes, weight gain, priapism		Does not depress respiration (safe in obstructive sleep apnea); less risk of morning hangover, tolerance/dependence. Used in agitated behavior affecting sleep in major neurocognitive disorder—"sundowning"
	Mirtazapine 7.5–15 mg	Sedation, constipation, xerostomia, increased appetite, weight gain		Used with comorbid condition; not approved for insomnia
	Doxepin 3–6 mg Nortriptyline 10–50 mg	Sedation, weight gain, urinary retention, constipation, orthostatic hypotension, QTc prolongation, delirium, lethal in overdose		Sedating tricyclic antidepressants (TCAs) can moderately reduce sleep latency and increase total sleep time. Use only low dose; avoid tertiary TCAs in older adults (e.g., amitriptyline, imipramine, doxepin > 6 mg/day) as highly anticholinergic. Contraindicated in those with glaucoma, urinary retention. Use requires ECG monitoring *Doxepin:* only FDA-approved antidepressant for insomnia *Nortriptyline*: used with chronic pain

(continued)

Table 24.7 (continued)

Drug class	Medication/dosage[a] (at bedtime)	Adverse effects	Drug interactions	Comments
Antipsychotics	Quetiapine 12.5–100 mg Olanzapine 2.5–10 mg Risperidone 0.25–1 mg Ziprasidone 20–80 mg	Orthostatic hypotension, QTc prolongation, increased appetite, hyperglycemia, hyperprolactinemia, dyslipidemia, hematologic effects, rash		Use primarily when comorbid psychotic disorders, psychotic symptoms associated with other illnesses (e.g., bipolar disorder, depressive disorder, neurocognitive disorders) that do not respond to other treatments. Use with caution in older adults, especially when comorbid major neurocognitive disorders are not associated with psychotic symptoms. Increased risk of stroke, sudden cardiac death. Use requires metabolic and ECG monitoring
Suvorexant[b] (oral dual orexin receptor antagonist)	Suvorexant 10–20 mg (no doses available for older adults) (not available in Canada)	Somnolence, sedation, muscle weakness, abnormal dreams, headache	CNS depressants; CYP3A4 substrates	Given 30 minutes before bedtime. Caution in obstructive sleep apnea
Dopamine agonists	Ropinirole 0.25–4 mg Pramipexole 0.125–0.75 mg Rotigotine (transdermal patch) 1–3 mg/24 hours	Nausea, somnolence, symptomatic hypotension, syncope, hallucinations; augmentation and rebound are rare; application site reaction with transdermal patch	Interact with dopamine antagonists	First-line treatment in restless legs syndrome and periodic limb movement disorder disrupting sleep; effective and well tolerated
Antihistamines (over-the-counter)	Dimenhydrinate 25–50 mg Diphenhydramine 25–50 mg Hydroxyzine 25–100 mg Doxylamine 25–50 mg	Daytime somnolence, xerostomia, blurred vision, urinary retention		Use not recommended in older adults due to lack of efficacy and safety data. Highly anticholinergic; clearance reduced with advanced age; tolerance develops rapidly (i.e., within a few days)
Valerian[d]	Valerian 450 mg (no doses available for older adults)	Morning somnolence, headache, gastrointestinal effects, anxiety, hepatotoxicity		Not well studied in older adults

Note: [a]Older adult doses where available; [b]FDA-approved for the treatment of insomnia in older adults; [c] Health Canada approved for the treatment of insomnia in older adults; [d]evidence supporting efficacy variable and insufficient

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Personality Disorders in Late Life

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25.1 Background

25.1.1 Generalities and Definitions

For millennia, storytellers have been transmitting legends and myths to describe and depict human experience. Rock art, papyrus, and reenactment of epic battles are examples of vehicles of communication. Later on, novelists, playwrights, and cartoonists blossomed, and they, too, became masters at conveying personality facets translated into emotional expressions, postures, behaviors, amplified idiosyncrasies, or aversions. Amad et al. gave Delay and Pichot's definition and wrote that personality results from the integration of three components: (i) intellectual, (ii) impulse-related, and (iii) emotional. The way such components are related constitute the personality traits, hence the way to relate to, perceive, and think about the world [1].

The so-called normal personality is defined as flexible and adaptable, as opposed to the pathological personality, in which rigidity engenders pathological attitudes and behaviors. Personality disorders can be understood as maladaptive variants of general personality traits [2]. Recurrent psychological distress and chronic suffering are frequent outcomes.

In the study of personality (both normal and pathological), two approaches have been used: dimensional and categorical. The *dimensional* approach examines the quantitative description of various personality dimensions. The pathological dimensions are considered extreme variants of the dimensions from a normal personality. In summary, this concept encompasses a continuum between normal and pathological [1]. A trait-oriented approach is supported by the evidence suggesting that genetic factors do not reflect specific personality disorder clusters in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), but, rather, more general qualities, such as impulsivity, agreeableness, and introversion [3]. The *categorical* approach, on the other hand, stems from a medical vision of the pathological personality. A diagnosis of personality disorder is made when the number of criteria meets a threshold. The DSM-5 has used primarily this approach (see ◘ Table 25.1) [4]. For a complete review of the DSM-5 diagnostic criteria for personality disorders, the reader is referred to the DSM-5 manual [4].

Teaching Point

The patterns of thinking, feeling, and behaving associated with personality disorders are inflexible and pervasive across many situations because they are ego-syntonic, meaning that the patterns are consistent with the ego of the individual and perceived to be appropriate by that individual [5]. People with personality disorders often lack insight into their difficulties and tend to blame others for their problems.

◘ **Table 25.1** Classification of personality disorders based on current DSM-5 model, with general definition and each 10 personality disorders, with the minimum number criteria that must be met for each and their specific patterns of dysfunction [4]

Personality disorders	
General definition: An enduring pattern of inner experience and behavior that deviates markedly from the expectations of the individual's culture. The pattern is manifested in two or more of the following: (1) cognition, (2) affectivity, (3) interpersonal functioning, (4) impulse control	
Cluster A:	*Cluster C:*
Paranoid (4/7): distrust (others' motives are interpreted as malevolent)	Avoidant (4/7): social inhibition and hypersensitivity to negative evaluation
Schizoid (4/7): social and emotional detachment	Dependent (5/8): excessive need to be taken care of leading to submissiveness
Schizotypal (5/9): discomfort in close relations, distortions, eccentricities	Obsessive-compulsive (4/8): preoccupation with perfection and control
Cluster B:	*Other personality disorders:*
Antisocial (3/7): disregard for rights of others; empathy deficits	Personality change due to another medical condition: for instance, secondary to a frontal lobe lesion (specifiers: labile, disinhibited, aggressive, apathetic, paranoid, other, combined, unspecified)
Borderline (5/9): instability in relationships and affects	Other specified personality disorder: the general criteria are met, and: 1) traits from several personality disorders are present, but criteria for any specific personality disorder do not meet the threshold (also formerly called "mixed" or "personality disorder NOS" in DSM-IV), or 2) the individual has a personality disorder that is not included in the DSM-5 classification (e.g., passive-aggressive)
Histrionic (5/8): excessive emotionality, attention-seeking	Unspecified personality disorder: clinical situation not meeting criteria for any of the above categories (also formerly "personality disorder NOS" in DSM-IV)
Narcissistic (5/9): grandiosity, need for admiration, vulnerability to shame	

van Alphen et al. [6], in their editorial, suggest that personality disorder or trait disorder diagnostic criteria for older adults may be more accurate if greater weight is given to the less observable but more stable internal psychological factors of personality disorder and less emphasis on dramatic behavioral expression. It makes sense to focus more on those features which are relatively stable across all age groups, emphasizing factors such as unintegrated and undifferentiated affects and poorly developed representations of self and others. Getting to the core issue in the personality disordered patient (e.g., shame, envy, incomplete individuation) is more important and useful than focusing only on external manifestations (which tend to be less extreme in old age).

The risk of neurocognitive disorders increases dramatically in late life. A common feature of major neurocognitive disorder (formerly dementia) is a *change* in personality (as in major frontotemporal neurocognitive disorder) or an *exacerbation* of preexisting characteristics (like in major neurocognitive disorder due to Alzheimer disease); determining without a careful longitudinal history whether such presentations are manifestations of a personality disorder, major neurocognitive disorder, or both is challenging [7].

Classification of Personality Disorders

Besides the DSM-5, some authors have described three unhealthy patterns in an overview of personality disorders in late life: (a) *fearful*, having a negative view of self and others; (b) *preoccupied*, having a negative view of self and a positive view of others; and (c) *dismissive*, having a positive view of self and a negative view of others. Another angle from which to examine the specific personality style is the preferred source of self-confirmation, that is to say, internal or external feedback. Persons preferring internal feedback tend to disregard or resist input from others. Persons preferring external feedback may have disproportionately high need for direction and support [5].

The DSM-5 groups the various personality disorders in clusters (see Table 25.2). Cluster A personality types (paranoid, schizoid, and schizotypal) tend towards impoverished social integration. Cluster B types (antisocial, borderline, histrionic, and narcissistic) demonstrate a relative lack of concern for others, and cluster C types (avoidant, dependent, and obsessive-compulsive) are prone to negative affect.

Table 25.2 Comparison of clusters based on affect regulation and relationship dysfunction

Cluster A	Cluster B	Cluster C
Affect high (paranoid) or low (schizoid)	Affect high	Affect low (obsessive-compulsive, avoidant)
Relationship low	Relationship dysfunction (high, intense)	Relationship ineffective (low in avoidant and obsessive-compulsive, clingy in dependent)

Table 25.3 Examples of maladaptive variants for each item from the five-factor model

Five-factor model	Maladaptive variants
Neuroticism	Negative affect
Extraversion: low→introversion	Detachment (avoidant)
Agreeableness→ high vs. low	Dependent versus antagonism
Conscientiousness→high vs. low	Paranoid, obsessive-compulsive vs. disinhibition
Openness to experience→ high vs. low	Thrill seeking vs. inhibition/ withdrawal
Neuroticism + extraversion	Impulsivity

Others have divided the personality disorders based on their level of maturity. "Mature" personality disorders (obsessive-compulsive, paranoid, schizotypal, and schizoid) have less primitive defense mechanisms (e.g., perfectionism) than the "immature" disorders (antisocial, borderline, histrionic, narcissistic, and passive-aggressive), who resort to splitting or acting out.

Among dimensional trait models of personality, the five-factor model (see Table 25.3) has been most frequently applied to study the relations between personality disorder constructs and general personality functioning. The five-factor model is a normative approach and probes characteristics present in the general population [8]. It includes five broad domains of personality (neuroticism, extraversion, openness to experiences, agreeableness, and conscientiousness) that are recoverable across age groups throughout the lifespan. It might present the advantage of being more resistant to state effects. High neuroticism appears to be characteristic of most personality disorders [9] and may include:

- Anxiety, fear, worry
- Moodiness, envy, jealousy
- Loneliness, timidity, self-consciousness
- Frustration and difficulty delaying gratification

Openness to experience (which is correlated with level of education) and agreeableness can mitigate some of the less adaptive manifestations. Studies have correlated certain factors to specific disorders; in older age, neuroticism is associated with the recurrence of depression, agreeableness is associated with dependent personality disorder, and conscientiousness is associated with obsessive-compulsive personality disorder. In a sample of older women, it was found that elevated neuroticism, decreased openness to experience, and decreased agreeableness appeared as valuable traits in the description of personality disorders [9].

There seems to be a significant overlap among certain personality entities, regardless of the cluster (e.g., borderline personality disorder with histrionic features, borderline with antisocial traits), and at times the patients end up being diagnosed with other specified personality disorder or unspecified

personality disorder (see ▶ Sect. 25.2, Case Studies). Moreover, malignant narcissism, consisting of a narcissistic core with associated antisocial and paranoid manifestations, is a useful concept introduced by Kernberg in 1984 and often grasps with a greater accuracy some highly pathological personality dynamics (see ▶ Sects. 25.1.4 and 25.1.5 on etiology and phenomenology).

We cannot approach this subject without mentioning construct validity. There is a substantial research base only for antisocial and borderline personality disorders. Narcissistic personality disorder deserves consideration. It was initially removed in the DSM-5 proposals but then (controversially) was reinstated. Paris [10] wrote that reinstatement was the right decision. Narcissistic personality disorder is a good example of a pure trait disorder with few symptoms [10]. The other personality disorders are essentially not validated by research in terms of consistent features, treatment, outcome, or prognosis. Even the epidemiology that uses the full range of personality disorder diagnoses (uncommon) finds that half of the cases identified on the basis of "long standing and very slow to change" are those diagnosed as other specified personality disorder and unspecified personality disorder according to the DSM-5 categories (see ◘ Table 25.1).

Challenges in the Realm of Personality Disorders in Late Life

Upon consulting this chapter, it is important to keep in mind the following limitations: (i) the general effects of aging on personality functioning are still obscure, (ii) the relationships among personality disorders and other psychiatric disorders remain unclear, (iii) problems in definitive diagnosis and assessment have not been solved, and (iv) the various psychopharmacological and psychological therapies have not received systematic studies [11].

Because older patients with personality disorders commonly show symptoms of more than one personality disorder, diagnosis of a specific disorder is likely to be more difficult than in younger adults; thus DSM-5 diagnosis of other specified personality disorder and unspecified personality disorder (formerly personality disorder NOS (not otherwise specified)) is a more common descriptive diagnosis for older patients [7]. What has good support is the observation that all personality disorders can improve with time and as those who have them might see certain features (like impulsivity) "burn out."

Societal Considerations

Traditional societies protect against personality disorder because social networks buffer for psychological risks. Modern Western societies value autonomy, achievement, external admiration, and individualism, and they reward narcissism. A family is a "mini-society" in and of itself. Family dysfunction is commonly associated with community dysfunction, fragility of social networks, and lack of internalized social norms [12]. In fact, some authors talk about "the relentless rise of narcissism in our culture" [3]. There are studies showing that narcissistic self-absorption is indeed on the increase, and there seems to be a "new parenting culture that has fueled the narcissism epidemic."

25.1.2 Adult Development: Attachment, Mentalization, and Individuation

Personality is the interaction between temperament, or genetic predispositions, and character, or the individual's traits from interacting with the environment. Temperament is defined as the automatic, associated responses to basic emotional stimuli that determine habits and skills. Temperament accounts for roughly 50% of personality structure and alters the style of attachment.

Attachment is the first regulator of emotional experience and arousal [12]. During the first 2 years of life, there is a prominent sensory interchange between the mother and her child. Their right brains (dominant in early life) are in constant unconscious communication. Emotional attunement derives from this intersubjectivity (see ▶ Chap. 8). If early attachment is the foundation of personality development, it is also true that unhealthy, insecure (i.e., neglectful, chaotic, disorganized) attachment can contribute to the crystallization of maladaptive personality features and even a personality disorder. The essential ingredients for a healthy attachment with caretakers and ultimately healthy personality are mirroring (i.e., reflecting the child's emotional states) and holding (i.e., emotional and sensorial). Such "good-enough" parenting methods will set the stage for mentalization abilities later in life. A consistent, reliable, and flexible presence (e.g., by responding promptly to a child's distress) helps instill a sense of trust and safety in the infant that he/she will carry within his/her whole life. Goldner-Vukov and Moore quote Schore, who stated that "the mother co-regulates the infant's developing autonomous nervous system and this process over time leads to the child developing a self-regulating system" [12].

Teaching Point

Attachment creates a foundation for mentalization, the reflective function or process of interpreting actions of the self and others as meaningful. Mentalization is a process whereby the child realizes that having a mind mediates his/her experience in the world. It is linked to the development of the self and is the core of social human functioning. Individuals with personality disorders often have difficulty in mentalization [12].

In terms of normal development, Erikson's eight stages of development constitute a useful framework to situate someone in a life trajectory based on the specific developmental challenges he/she is facing or at what stage he/she is "stuck." It is useful for guiding both the diagnosis and the treatment goals.

Based on Erik Erikson's theory of late-life development, the major developmental task of older age is to look back and seek meaning across the life span. The goal is to maintain more *ego integrity* than *despair* about one's life. In this process, each earlier life stage conflict must be reconciled and integrated with the current stage. See ◘ Table 25.4 for examples of clinical situations arising from each unresolved

Table 25.4 Eight psychosocial crises according to Erikson and with associated features or personality disorders that would emerge and manifestations in old age when non-resolved

Stages of development	Associated features if stage was interfered with
Basic trust vs. mistrust	Antisocial, paranoid, borderline
Autonomy vs. shame and doubt	Narcissistic, dependent
Initiative vs. guilt	Obsessive-compulsive
Industry vs. inferiority	Obsessive-compulsive, avoidant, narcissistic
Identity vs. role confusion	Borderline, narcissistic
Intimacy vs. isolation	Borderline, dependent
Generativity vs. stagnation	Depression in narcissistic type
Ego integrity vs. despair	All personality disorders could face challenges Exacerbation of anxiety (generalized anxiety, panic, posttraumatic stress disorder, unresolved grief)

stage. Identifying unresolved developmental issues can lead to a clearer picture in terms of personality structure. For instance, trust might not have been achieved because of insecure or chaotic attachment in childhood. Hence, paranoid or borderline personality traits could develop as a result and then be exacerbated during other life stages (like intimacy versus isolation) (see Table 25.4).

Erikson's conceptualization of life development can also help the clinician to understand why certain personality disorders tend to emerge or decompensate at very specific periods (e.g., the individual's coping mechanisms can be overwhelmed during life transition such as marriage, parenthood, or employment). Jung named *individuation* the lifelong development of personality [13]. "Negative individuation" describes psychic development which is hindered and may then become destructive.

25.1.3 Epidemiology

The mean prevalence of personality disorders is 13.5% in the general adult population and 60.4% in those seeking psychiatric care [6]. The DSM-5 categories of other specified personality disorder and unspecified personality disorder, or situations in which the patients have clear signs of a personality disorder but do not fit into one of the ten specific personality disorders (formerly known as personality disorder not otherwise specified), are the most frequently diagnosed personality disorder [6]. Approximately 1% of the general population has been found to have narcissistic personality disorder, and narcissistic personality disorder is found in 10% of people with other psychiatric disorders (depressive disorders, alcoholism, and other personality disorders, such as borderline and antisocial). Antisocial personality disorder has a lifetime prevalence of 3.5%; males are seven times more likely to have this condition than females [12].

The prevalence of personality disorders among older people in the general population is about 3–13% [6, 14]. For older patients treated in an outpatient mental health setting, percentages between 5% and 33% have been reported [6]. According to other authors, this range is even higher at 33–50% [5]. The prevalence of comorbid personality disorder in older inpatients who receive psychiatric treatment has been reported as between 7% and 80%. The mean prevalence of personality disorders for older adults is 20% [6]. Certain meta-analyses reveal prevalence rates between 10% and 20% in the older adults [1]. In one of them, obsessive and dependent personalities were more frequent. In the second, paranoid and schizoid were more prevalent. Approximately 8% of older Americans have at least one personality disorder [15]. A study looked at the rates of personality disorders in an outpatient sample [16]. The authors found that half of the sample presented with more than one personality disorder. Among these patients aged 60 years or older, there were practically no cluster B diagnoses. High percentages of clusters A and C were instead observed.

In old age, cluster C is the most frequent, followed by cluster A, then B. In some studies of geriatric patients with major depressive disorder and persistent depressive disorder (dysthymia), avoidant, dependent, and other cluster C personality disorders have been the most frequent, followed by cluster A personality disorders [11]. One factor that could explain this is the selective mortality for cluster B personality disorders. Also, risky behaviors often associated with these personality disorders such as substance use or reckless driving also lead to increased mortality earlier in life. On the other hand, these numbers could be a distortion of reality as personality disorders can manifest differently in later life as a result of cognitive deterioration, somatic comorbidity, medications, and psychosocial challenges. For instance, older adults with cluster B personality disorders show less impulsive behavior but more hypochondriacal and depressive complaints, passive-aggressive behavior, and medication abuse.

Older patients with personality disorders and who are hospitalized are more likely to be single, separated, or divorced, have a more complex clinical presentation when depressed, and have a higher prevalence of suicidal behavior [17]. Personality disorder is an important risk factor for suicide in late life. A case-control study quoted by Jahn et al. [18] revealed that personality disorders were more common among older adults who died by suicide than among older adults who died of other causes.

Teaching Point

The prevalence figures of personality disorders in older patients could give a distorted image since personality disorders can manifest differently in later life as a result of cognitive deterioration, somatic comorbidity, medication effects, and psychosocial challenges [6].

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25.1.4 Etiology

Brain changes from early relational trauma are more prominent in the development of narcissistic personality disorder than other biological factors such as temperament and genetic influences. Narcissistic personality disorder runs in families, but this does not mean there is genetic transmission per se [12]. Being raised in a "narcissistic family," where parents value achievement, success, or beauty, can lead to narcissistic personality disorder through the relational trauma of poor emotional attunement or invalidation. The child is not accepted for who he/she is but must rather endeavor to meet parental expectations, becoming their parents "narcissistic fuel" or "narcissistic extension."

Generally, two parameters become problematic in people with personality disorders: affect regulation and interpersonal relationships. Early attachment experiences with primary caretaking figures play a significant role in the ability of a person to regulate difficult emotions and develop healthy and fair relationships with others. Emotional attunement is essential for a child to develop a secure attachment. If caretaking figures were unpredictable, abusive, and/or absent, insecure attachment continues throughout life and is manifested by either intense or constricted affect and chaotic/destructive or decreased interactions (interpersonal deficits).

Adult victims of childhood adversity (see ▶ Chap. 14) have elevated risk of personality disorders, in addition to risky sexual behavior, suicide attempts, and depressive, anxiety, and substance use disorders. Emotional abuse, the least reported type of childhood adversity, consistently had the strongest associations with depressive, anxiety, and personality disorders compared with the other types of adversity (e.g., physical abuse, sexual abuse, neglect) [15]. Families that produce offspring with paranoid personality disorder often have rigid rules, irrational beliefs, mistrust, hatred towards others, and restricted expression of emotions, believing that being "emotional" is a sign of weakness.

There might be a declining resiliency of the hypothalamic-pituitary-adrenal axis later in life. Therefore, chronic alterations in the stress response system can affect symptomatology and the ability to cope with overwhelming situations.

Teaching Point

Early childhood experiences such as unhealthy attachment can significantly interfere with the development of harmonious personality structures to the extent of contributing to maladaptive personality styles and functional impairment.

25.1.5 Phenomenology

The diagnosis of personality disorder among older patients is challenging. The complexity of this entity is accentuated by the heterogeneity of the geriatric population. There may be important differences between the youngest old (65–74 years) and oldest old (85 years and over) [19]. Moreover, biases and misconceptions can be barriers to a valid diagnostic process (see ◘ Table 25.5).

◘ **Table 25.5** Misconceptions constituting barriers to diagnose personality disorder in older adults

Potential bias to the evaluation of personality disorder in older adults
Older people spend little money
Older people do not have sex
Older people are dependent
Older people are less active
Older people have a depressed mood that is "normal"

Current personality disorder diagnostic criteria (there were no changes from DSM-IV to DSM-5) are not adequately attuned to the living situations and experiences of older people. The literature shows that 29% of the DSM-IV criteria for personality disorder led to measurement errors in older people [6, 19]. For instance, antisocial personality disorder criteria are not fully applicable to older people; only three out of seven criteria proved useful [6]. Misdiagnosis is therefore likely. Because older patients with personality disorders commonly show symptoms of more than one personality disorder, the diagnosis of other specified personality disorder and unspecified personality disorder (formerly referred as personality disorder not otherwise specified) is more common [7].

Pathological personalities are deviation of lived and behavioral experience, with consistent and pervasive modalities, bringing a suffering that is clinically significant. The first manifestations are usually detectable, at the latest, at the end of adolescence, or at the beginning of adulthood. In certain situations, it is observed that personality disorders can "appear" de novo. In other words, a personality disorder might have been latent and well compensated for many years and then suddenly become manifest once the stabilizing structure, like a relationship, disappears. Many studies emphasized personality disorder that emerged during a decompensation of another disorder, such as major depressive disorder or anxiety disorder. The clinical picture is either from the evolution of a disorder over decades or a resurgence of previously stabilized pathological personality. Older adults who have endured childhood adversity are more likely to have poor physical and mental health, depressive symptoms, internalizing disorders, and high levels of neuroticism [15].

A cluster A personality disorder can evolve as more social isolation, delusional decompensation (such as persecutory delusion), and depressive disorder occur and exacerbate interpersonal/social difficulties. Such complications might become more apparent later in life because intimate contact is inevitable (e.g., in institutional settings).

The cluster B personality disorders (also known as troubles of emotional maturity) seem rare among the geriatric

population [1]. In this group of people, the duration of depressive episodes seems to be longer and the social difficulties are more significant. More specifically, there might be a decrease of sociopathy in midlife, maybe due to a diminution of impulsivity. On the other hand, substance-related disorders and homelessness could increase with age. Sociopathy, also known as psychopathy (both are synonyms of antisocial personality disorder) is characterized by egocentricity and impulsivity, shallow and labile affects, violation of social norms, and lack of remorse and empathy. The prevalence of antisocial personality disorder has been shown to decline with age [20]. There is an overlap between antisocial and borderline personality disorder.

People with borderline personality disorder present a better global functioning than those with antisocial personality disorder despite a vulnerability to losses. As opposed to antisocial personality disorder, which tends to show a deeper impairment in empathy (deficits in recognition of basic emotions), those with borderline personality disorder tend to mentalize "normally" except in the context of attachment relationships, in which emotional arousal occludes the ability to accurately interpret mind states, particularly when fear of abandonment arises [21]. Even though a decrease in aggression and impulsivity over time has been noted in this population, these patients still engage in self-destructive activities. Different expressions of self-injurious behavior in borderline personality disorder include self-starvation, abuse of medications, and noncompliance with medical treatment [7]. There is also an increase in hypochondriacal preoccupations, depressive complaints, and passive-aggressive behaviors [6]. Additionally, there is a difficulty tolerating being alone: medical staff or family can thereby report anxious clinging behavior, frequent telephone calls, messages of desperation, and heightened somatic complaints. Affective instability remains common, with marked mood shifts from baseline to depression, anxiety, and irritability. Impulsivity might be more common than suggested by some who have observed that older people have less opportunities to be impulsive and/or less drive to engage in destructive behaviors. This might mean that impulsivity is manifested differently with age. For instance, dramatic features may be more subtle or expressed through proxy behaviors, e.g., abuse of prescription medications/illicit drugs/alcohol, chaotic help-seeking such as "firing" caregivers, withholding important facts from them, impulsively switching clinicians, signing out of hospital against medical advice, and/or violating or ignoring prescribed diet and exercise regimens [6, 22].

As reported by Goldner-Vukov and Moore, Cloninger remarked that people with narcissistic personality disorder are excitable, quick-tempered, extravagant, attention seeking, self-indulgent, passionate, insecurely vain, imaginative, and ambitious [12]. The clinical literature describes a paradoxical combination of grandiosity and vulnerability [23]. Grandiose and vulnerable facets of pathological narcissism are hypothesized to derive from self-esteem dysregulation, the attempt to maintain high self-representations (to prevent low implicit self-esteem from becoming explicit) [23].The development of high standards seems to occur as a way to prevent upcoming failures that could elicit shame. In fact, the authors of this chapter observed in their clinical settings that some people with obsessive-compulsive personality traits have a significant narcissistic "core" or difficulty coping with shame. A metaphor encompassing the narcissistic core that underlies various defenses is the "peanut with a candy shell" (i.e., the candy coating could represent the obsessive-compulsive "shell" around the narcissistic peanut "core"). In essence, the "core" is narcissistic (basic insecurity leading to compensatory grandiosity), but the "shell" represents another set of defenses (as the world sees it), like an obsessive-compulsive structure or paranoia; sometimes, at first glance, the person socializes and conforms well (the coating is discrete when defenses are obsessive-compulsive). It is a presentation similar to the "covert" subtype (see Fig. 25.1). But the so-called "pure" narcissist ("overt" subtype or narcissistic personality disorder as defined by the DSM-5) has a different coating, more exuberant (flavorful, red, mauve, or turquoise, for instance). The common denominator of all these variations of narcissism is the need to break down the defenses (or "bite" the coating) to access the core or the inner self (peanut).

People with narcissistic personality disorder also have impaired *emotional* empathy, but *cognitive* aspects of empathy can be intact, which means they present a deficit in their

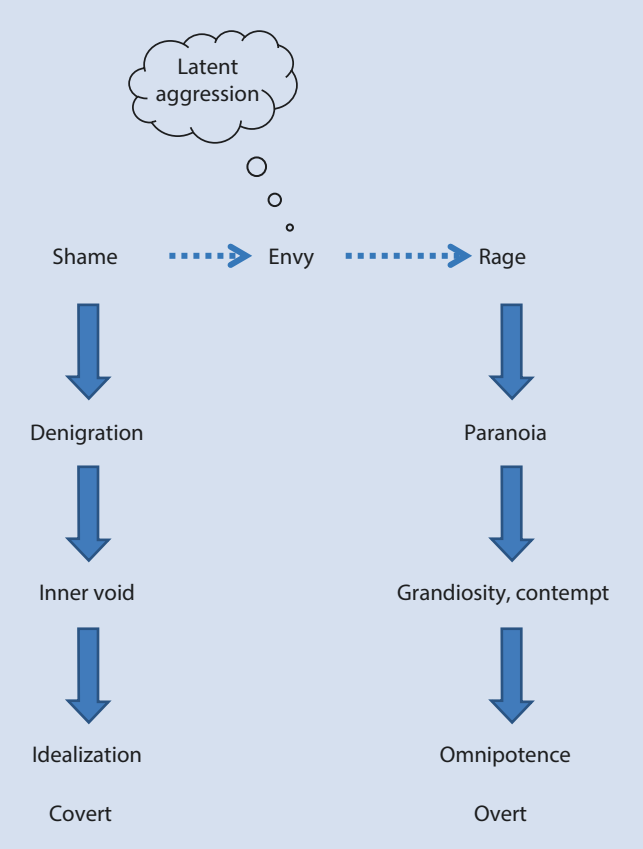

Fig. 25.1 Painful primitive affects and corresponding affective/attitudinal defenses in narcissistic personality disorders (both covert and overt subtypes)

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ability to *emotionally* respond to the *observed* emotional state of another [24]. Abnormal functioning of the anterior insula might be a neurophysiological correlate of decreased capacity for empathy. Smaller gray matter volume in the dorsolateral prefrontal and anterior cingulate cortex might be related to impaired emotion regulation processes, which are especially evident under conditions of threatened self-esteem. Borderline and narcissistic personality disorder have a high comorbidity rate as well and overlap in symptoms such as affect dysregulation [23]. People with malignant narcissism are often prominent individuals who are high achievers and who do not believe they need anyone's help. Others around them may recognize that they have a problem but are most likely afraid to suggest that they seek help.

Histrionic personality disorder evolves in a heterogeneous fashion. Within such a personality structure, people seem to adjust their relationships with the world from the changes in self-image and from the change in their health or living conditions. Seductive behavior could evolve towards hostility and anger outbursts. Somatic complaints (e.g., sexual) are frequent, and the overemphasis on such symptoms results in a poverty of speech [1].

The cluster C personality disorders are apparently the most frequent in old age. The avoidant type is often unmarried, without children, isolated, and lonely. Major depressive and anxiety disorders are the most frequent complications. Older adults have to increasingly cope with health-related problems and are often dependent on others for their care, which throws the person with personality disorder into unavoidable, intense interactions.

During periods of transition, underlying (mal)adaptive personality traits and coping mechanisms of an individual are challenged, and this can result in exaggerated behavioral and affective expressions. Since the core of the difficulties that those with most personality disorders encounter are in the interpersonal sphere, management of personality disorders in late life poses specific and important challenges for caregivers and therapists.

Teaching Point

In summary, the complexity of this diagnostic entity and the absence of specific criteria for older people explain why studies of this theme are rare [1].

Individuals with personality disorders tend to have [14]:

- Lower self-perceived quality of life and general health
- Decreased physical, social, and cognitive functioning
- Lower self-esteem
- Less life satisfaction
- Decreased well-being
- A lower number of, and satisfaction with, social supports
- Increased predisposition to other psychiatric disorders

Interpersonal relationships could mediate suicide risk. The interpersonal theory of suicide posits that there are two critical and proximal risk factors for suicidal ideation: (i) thwarted belongingness (defined as lack of reciprocal care in valued relationships and feeling like one does not belong in social groups) and (ii) perceived burdensomeness (defined as the belief that one is so incompetent that he/she is a liability to others and that others would be better off if he/she were gone) [18].

Table 25.6 Defense mechanisms and examples of personality disorders in which those defenses become the preferred coping

Defense mechanisms	Associated personality disorders
Denial	Avoidant
Projection	Paranoid
Projective identification	Borderline, narcissistic
Acting out	Borderline, narcissistic
Undoing	Obsessive-compulsive
Rationalization	Narcissistic, antisocial
Grandiosity	Narcissistic, paranoid

Based on specific examples provided earlier, we can see that a lot of personality disorder subtypes overlap or present in various combinations. For instance, dependent personality traits can co-occur with borderline personality traits, and narcissistic personality can present with antisocial personality manifestations. It might be more useful to identify the presence of a personality disorder by determining if there are affective dysregulation, interpersonal deficits, and rigid defense mechanisms. Those with personality disorders typically lack insight into their personal presentation to others, think and behave in ways that distance them from necessary relationships, and create restricted social worlds [5]. What will determine which cluster or personality disorder a patient has is the type of defenses that are most prominent (e.g., acting out in cluster B, avoidance in cluster C). See Table 25.6 for examples of personality disorders associated with maladaptive defenses.

Psychodynamic Understanding

Hatred is always a core element of severe personality disorders [13]. In people with malignant narcissism, destructive aspects of the self and expression of aggression become idealized. Failure to succeed results in mood swings (e.g., irritability, rage) and feelings of emptiness. Their intellect is shallow and they are often materialistic. They are prone to pathological lying. They can be charming but are unable to develop deep relationships. Antisocial manifestations of malignant narcissism include burglary, assault, and murder. They may even become leaders of sadistic or terrorist groups.

Narcissistic wounding underlies and drives various personality disorders. Disturbing feelings of inferiority, self-doubt, boredom, alienation, emptiness, and aimlessness underlie their persona. Malignant narcissism is situated between narcissistic and antisocial personality disorder and

is separated from the latter by the capacity for selected loyalties. People with antisocial personality disorder drown depressive feelings in addictive excitement from law-breaking and violence [13]. They also have a paranoid stance. They see others as bad objects who are potential threats. They have disorganized superegos and lack the capacity for remorse, sadness, or self-exploration. They are preoccupied with conspiracy theories. Their pathological grandiosity is a defense against paranoid anxiety (see ◘ Fig. 25.1). The ego-dystonic sadism can be apparent when they destroy, symbolically castrate, and dehumanize others. They can become suicidal during crises and see suicide as something triumphant, or it can be a way to cope with unbearable shame [12]. Envy is also a defense against aggression. Shame goes hand in hand with envy. Since both are usually intolerable for fragile personality structures, rage becomes a defense against them, and denigration versus idealization or paranoia and grandiosity are external manifestations (see ◘ Fig. 25.1). Contempt and omnipotence are other salient characteristics of narcissistic configurations.

Course

Stability is no longer considered an immutable personality characteristic [11]. Certain dimensions (e.g., agreeableness, conscience, harm-avoidance) increase with age, whereas others (e.g., extraversion, openness to experience/novelty-seeking) decrease [1]. Cluster A personality structure could even represent a *forme fruste* or a risk factor for late-life psychotic disorder [11].

As reported by Bernstein et al., Zanarini concluded that most cases of borderline personality disorder seem to come to professional attention first during the late teens or early 20s [25]. Typically though, such a personality configuration usually starts to develop gradually during the preceding years. Some children have self-injurious behaviors or dissociative tendencies, for instance. The number of criteria for borderline personality disorder was found to diminish gradually with advancing age. It could be due to age-related changes in brain structures (e.g., medial prefrontal cortex) responsible for emotional processing [26]. Also, older people have less opportunity to be impulsive. There is also less identity disturbance in older people with borderline personality disorder. There is a possibility that any surviving sample of older adults consists of less severely impaired and/or more resilient patients. But older adults are more likely to report chronic emptiness. Zanarini, quoted by Morgan et al., remarked that dependency and anger are more stable over time [27].

Upon assessing the quantitative aspects of a condition (like the number of diagnostic criteria), one should not overlook its qualitative aspects. Some studies report that functional impairment persists even when full criteria for a personality disorder are no longer met [27]. Interpersonal impairment often continues throughout the lifespan. According to Kernberg, narcissistic personality traits decrease with time, and psychotherapy is not effective before a certain age, younger subjects being reinforced by the social valorization of grandiosity (see ▶ Chap. 8). One might assume that the maladaptive personality categories dissolve as people get older, therefore rendering the general definition of a personality disorder (or the diagnostic categories of other specified personality disorder and unspecified personality disorder, formerly referred as personality disorder not otherwise specified) more useful for that population. In fact, obsessive-compulsive, dependent, and (former) personality disorder not otherwise specified (or other specified personality disorder and unspecified personality disorder) were found to be the most prevalent type in certain studies [28]. Obsessive-compulsive personality disorder is one of the most stable personality disorders over time. The diagnostic criteria that present the most stability are rigidity, perfectionism, and the inability to delegate. There are not enough data on the evolution of dependent personality. There are three scenarios possible: personality disorder can either become attenuated, accentuated, or appear de novo depending on the cluster and social context.

Teaching Point

Longitudinal studies show a decline of impulsive behaviors associated with aging. It seems that immature or flamboyant personality disorders tend to improve with time, possibly as a result of the decrease in impulsive behaviors. Older individuals have fewer opportunities to manifest recklessness or impulsivity [2, 6]. More "mature" personalities (avoiding or dependent) display a more chronic evolution with relative stability, like cluster A [1].

In the study by Raposo et al., age did not moderate the effect of childhood adversity on mental health. In other words, the negative effects of childhood adversity do not become significantly weaker in later life [15]. Some wounds just will not heal completely with time. Neuroticism (the tendency towards pessimism, distress, anxiety, sadness), which is predominant among cluster C personality disorders, was associated with premature death among older men [1].

In older adults with paranoid, schizoid, schizotypal, or obsessive-compulsive personality disorder, the behaviors seem more likely to remain unchanged, although specific traits like rigid behavior or suspicion may increase. These "mature" disorders have later onset and little variation over time, while the "immature" ones are more evident in younger individuals and tend to moderate by mid-adulthood. Following dormancy in mid-adulthood, the distinctive disturbances of borderline personality disorder may reappear in later life [29].

Per Supiano and Carroll, it seems that all personality disorders (except for antisocial personality disorder) worsen with age [5]. But the DSM-5 criteria for antisocial personality disorder are not fully applicable to older people; as mentioned earlier, only three of the seven criteria proved useful [6]. Antisocial behaviors might also shift towards a more narcissistic presentation (e.g., subtle actions like manipulation)

as the person approaches later life. The concept of heterotypic continuity refers to the idea that the manifestation of personality can change while the underlying traits remain stable [2].

Some features could become even more ego-syntonic with advancing age, simply a function of the personality disorder symptoms being present for a longer duration [19]. Impulsivity and entitlement resolved relatively quickly with age, but other symptoms (e.g., anger, loneliness, emptiness) were more stable [7]. In general, personality disorder features increase risk for suicidal thinking, suicide attempts, and death by suicide among older people [9]. Theory and research support an association between narcissism and late-life suicidal ideation and behavior. Suicide risk has been associated with shame in narcissistic personality disorder [23]. Suicide risk has also been associated with lack of openness and flexibility and with difficulty adapting to losses [17].

Differential Diagnosis and Comorbidities

The differential diagnosis is important and should be thorough to ensure the validity of the personality disorder diagnosis. Other potential explanations should be sought after. For instance, a widow who has a decrease in social interactions could meet diagnostic criteria for avoidant or schizoid personality disorder but her manifestations could be transient and in response to her change in marital status and social functions. Similarly, a patient who is hypervigilant from a decrease in visual acuity could appear paranoid. It is therefore important to obtain longitudinal information regarding the evolution of symptoms and put them into context.

Maladaptive personality traits are manifest in early adulthood, sometimes in late adolescence. A late-onset personality disorder might in fact be the unmasking of maladaptive personality features that were already present, but well compensated for by the previous social milieu. Once the latter changes and the coping abilities are overwhelmed, some personality traits may emerge. A medical or iatrogenic cause should always be ruled out, especially in old age, when neurocognitive changes take place and when the aging brain is more sensitive to the effects of illnesses or medications. Neuropsychiatric symptoms of major neurocognitive disorder should be in the differential diagnosis. Moreover, substance-related disorders can co-occur and exacerbate maladaptive personality styles. In narcissistic personality disorder, addictions are driven by shame, lack of connectedness, and suppressed emotions [30].

In mixed-age patients with depressive disorders, comorbid personality disorders have been linked to an earlier onset of depressive disorder, multiple depressive episodes, longer duration, and greater severity of depression [11]. Depressive disorders with increasing severity of episodes or chronicity may conclude with a personality disorder dénouement.

Neuroticism, an enduring disposition characterized by high negative affect, has been shown to increase the likelihood of encountering negative and traumatic events as well as posttraumatic stress disorder symptom severity. Neuroticism increases the availability of memory for stressful events and the tendency to interpret neutral or ambiguous stimuli in a negative or threatening manner, which in turn may increase posttraumatic stress disorder symptoms [31]. Since neuroticism decreases with age, posttraumatic stress disorder symptoms could in fact be under-expressed in older patients.

Table 25.7 Challenges associated with the diagnostic process of personality disorders in old age

General challenges with diagnosis	Self-report can be limited by
Complex entity at any age	Lower accuracy/reliability of recall covering 40 or 50 years
How to distinguish a functional difficulty from age versus personality disorder	Cognitive and memory deficits
DSM does not take into account changes associated with aging	Social stigma
False positives	Lack of insight
	Depression (can distort account of previous functioning)

Teaching Point

In old age and also as far as personality disorders are concerned, co-occurring disorders is the rule. Therefore, the diagnostic process of personality disorder in old age can be extra-challenging. (See Table 25.7 for examples of factors that could increase the degree of challenge in such a process.)

25.1.6 Treatment Approaches

General Principles

Just like for any other psychiatric disorders, a thorough assessment is key. This will allow the identification of difficult attachment aspects through understanding and constructing a coherent life story with patients. The Adult Attachment Interview says that the highest correlated item (in the entire inventory) with security is narrative. Improving narrative coherence improves security, which in turn can lead to the extinction of narcissistic overcompensation and many other features of personality disorders. During the clinical interview, while listening to the person's narrative in his/her own words, some elements should be explored (see Table 25.8). It is important to screen for early traumatic experiences. Severe abuse is typically well remembered and false reports of abuse are rare [15]. A multidisciplinary team setting, where various sources of information converge, can also be precious and informative.

Table 25.8 Elements of the clinical interview to identify a personality disorder

Biographical domains	Example of aspects
Developmental history	Adverse childhood experiences
Relationship history	Milestones
Employment history	Circumstances of job changes
Coping	Stress management, emotional reactions to separations, losses, illnesses
Negotiation of life transitions	Marriage, parenting
Other people's perception	Have they been labeled "eccentric" or "loner"
Experiences with psychotherapy	Circumstances of termination
Sociocultural	Cultural expectations and level of identification/adherence to cultural norms Cohort-specific elements
Background check	Substance use, legal/incarceration

A dimensional approach using the five-factor model might be considered too ambiguous. Some advocate for a mixed approach, combining categorical and dimensional elements. When it comes to psychotherapy, it is important to keep in mind that we treat an individual. The categorical approach might prevent the therapist from "seeing" the person with all her/his complexities. The engagement is more linked to the patient's inner desire to change rather than the clinical subtype of the personality. We treat a person with symptoms, not a specific diagnostic entity. Plus, most people do not think of themselves as "narcissistic" or "dependent" but might identify better with more descriptive terms such as "a strong need for admiration" or "wanting to please others at all costs."

When older adults are assessed in their own environment, clinicians should place special attention to personal objects; e.g., pictures could give clues in regard to past relationships, and books or other items could indicate fields of interest. Such elements can be convenient icebreakers and set the foundations of the therapeutic alliance.

Informants can be highly valuable. In one study, when selected by the patient, the informants tended to report lower levels of narcissism, paranoia, and antisocial personality disorder in the patient, maybe as a result of positive evaluation from a form of selection bias. Also, older substance abusers showed lower levels of crime and drug use compared to when they were younger [7]. Thus, it is not inconsistent for older patients with personality disorders to exhibit fewer "high-energy" diagnostic criteria (law-breaking, identity disturbance, promiscuity). Does this mean that a maturational change has occurred or merely that the symptom displays are more subtle because of physical and institutional restrictions? Informants must fill the questionnaire with the older patient in mind *before* suffering from other psychiatric disorder such as major neurocognitive disorder or depressive disorder in order to make the distinction between what has been a more consistent personality pattern throughout life versus recent change from medical condition, for instance [6]. Informant data minimize the cognitive and somatic load associated with frailty in older adults [14].

Psychotherapeutic Interventions

Because of the nature and etiology of personality disorders, psychotherapy is usually the first-line treatment modality. The healing from earlier relational trauma or neglect can take place through the reenactment of attachment struggles within the therapist-patient relationship. (See ▶ Chap. 8) It will help the psychotherapist to keep in mind that personality traits serve different functions in different life roles across the life span [5]. Learning about etiology involves understanding the reasons for the "young learning" version of the patient not having gained fairness and good mentalizing skills many years earlier, which is part of the narrative. Psychotherapy can include specific adaptation (grieving) activities to help leave old patterns behind and move to new, more healthy replacement habits.

Shame has been acknowledged as a central emotion in pathological narcissism and narcissistic personality disorder across different models of psychotherapy. Interventions to treat pathological shame have been developed, such as self psychology, transference-focused psychotherapy, schema-therapy, and cognitive behavioral therapy. Therapists should be aware of the patient's susceptibility to shame and avoid shaming the patient. For instance, shame might be elicited by clarifying comments or interpretations. It might be helpful to provide patients with a causal model of shame. Dose-by-dose desensitization to build affect tolerance of shame might be an overarching goal [23].

In psychotherapy, the goal is not to "cure" but move incrementally maladaptive elements of thinking and behavior from the level of the disorder to one of "personality style" by helping the patient to increase function, emotional stability, and a sense of mastery and responsibility [5]. The trend has been in favor of directive techniques such as dialectical behavior therapy (DBT), interpersonal therapy (IPT), cognitive behavioral therapy (CBT), and problem-solving therapy (PST) [11]. Moreover, mindfulness is a modality that is widely recommended to cope with distress and increase general well-being (see ▶ Chap. 8). To explain to a patient what mindfulness is, the clinician might say that it consists of being aware of *what* you are doing, feeling, or thinking *as* you are doing, feeling, or thinking it. Although it exists in a more formal approach called mindfulness-based therapy and can benefit everyone (there are no known contra-indications), mindfulness alone can be practiced and integrated as part of a healthy behavioral coping and can thus evolve into a general way to approach life, to be "in the moment." This form of intrapersonal attunement is a prerequisite to mentalization skills.

An individualized approach, usually combining individual and group formats, is optimal. Helping the patient identify not only the dysfunctional aspects of the self but also inner strengths is necessary. Reflecting the specific skills to the patient will help him/her stay connected or return to the redemptory thread in his/her life, whether it is music, sports, or other cultural activities. Being able to see the good in each patient also helps the clinician deal with powerful and negative countertransference feelings.

A mixed approach like DBT uses the dimensional and the categorical perspectives, which allows a work on the four major dimensions of borderline personality: affect, interpersonal relationships, impulsivity, and cognition. A strong therapeutic alliance is the most powerful contingency in therapy. The therapeutic alliance is a challenge for narcissistic behavior and a "container" for functional behavior. Skills training include mindfulness, distress tolerance and radical acceptance, emotion regulation, and interpersonal effectiveness using mentalization. DBT has been adapted for older people with depressive disorder and personality disorder. A systemic approach might be indicated; the children of older adults with personality disorder may have had their own psychiatric illnesses which could affect their ability to negotiate an effective care plan with their parent [5].

Changes in behavior or in interpersonal relationships are realistic therapeutic goals for old people. There is proven efficacy of CBT (including schema-focused therapy) and brief dynamic therapy in the treatment of anxiety and depressive disorders. More specifically, CBT could help address the perceived burdensomeness (see ▶ Sect. 25.1.5, Phenomenology) and other cognitive distortions, and DBT in group settings can help dispel the thwarted sense of belongingness by enhancing self-efficacy and socialization. Hence, psychotherapeutic interventions can be useful in preventing suicide. For people with malignant narcissism, the principles of effective treatment include requiring patients to accept responsibility for their antisocial behavior, maintain rational actions, insisting on the development of consequential thinking, social reinforcement of respectful boundaries and respect for the needs of others, strong confrontation of unjust behaviors, recognition of manipulation with immediate confrontation, and consequences for every transgression. Because an individual approach is insufficient to meet such requirements, the most effective treatment for personality disorders is a therapeutic community where an intensive holding and corrective environment is part of the foundation of treatment [12]. Peer pressure breaks down resistance and promotes personal growth. The community also promotes creativity and offers a sense of belonging.

During the evaluation process, it might help to ensure that the conversations are perceived as social exchanges rather than "examination" (see ◘ Table 25.9). Open-ended questions are usually more engaging and trust eliciting than a checklist approach, and it is preferable to allocate the patient plenty of room to express his/her experiences of himself/herself and the world in his/her own words. Such a style is similar to what Allen describes as "unstructured talk therapy" [32]. A strength-based focus permits reframing the patient from "a difficult person" to someone with challenging aspects of personality style [5]. Hence, we would recommend for the clinician to do one's own cognitive restructuring and change the language used to describe the challenging personality styles to address potentially counterproductive countertransference regarding such patients. Also, it might be helpful to put aside the categorical terminology or checklist approach and develop a narrative formulation of the patient. A first useful step might be to screen for and identify specific defenses (e.g., isolation of affect, grandiosity) and dig deeper to discover the core issues (e.g., injured narcissism, feelings of shame or rage that are defended against).

◘ **Table 25.9** Examples of questions during the general screening of personality style

Domains	Open-ended questions
Self-perception	What do you like about yourself?
	What are you most proud of?
	In terms of aspects of yourself, what would you like to work on?
	Do you have any regrets?
Relationships	Throughout your lifetime, who or which type of person did you get along the best, and why?
	Conversely, who or which personality style was the most difficult to get along with, and why?
	If your best friend were in the room, how would he/she describe you as a person?

Teaching Point

There are effective therapies for borderline personality disorder but none for antisocial personality disorder or severe narcissistic personality disorder (both of which, by some thinking, are on the same spectrum). But mindfulness-based therapy appears to be a potential treatment of consideration for antisocial personality disorder in terms of relatively high level of acceptability and promising treatment effects [21]. The other disorders do not have research supporting choices or outcomes for therapy.

Obstacles to effective treatment for narcissistic personality include poor motivation, a defensive "invincible armor" of power, sadistic injury, superior IQ, lack of remorse, and lack of capacity for attachment [12]. Stone listed several positive prognostic factors: the capacity for loyalty, remnants of genuine concern for others, a sense of remorse, being gifted or talented in some life skills, being attractive, and having self-discipline [12].

Pharmacotherapy

When other psychiatric illnesses are comorbid with personality disorder(s), the treatment is initially directed to the other psychiatric illness(es). However, the comorbid personality disorder may complicate medication treatment.

Since personality disorders represent a range of phenomena, the pharmacological approach is generally symptom-driven. Depending on the prominent manifestations and comorbidities (e.g., depressive, anxiety, substance use disorders), one class of medication may be preferred over the other. For instance, atypical antipsychotics can be prescribed when there is paranoid thinking or frail contact with reality, mood stabilizers can address mood fluctuations, and selective serotonin reuptake inhibitors (SSRIs) can help depressed mood, suicidality, aggression, or obsessionality. SSRIs act like a "brake" modulating limbic irritability and hyperarousal as well as improving frontal lobe function [12]. Naltrexone and clonidine have been used to relieve self-mutilation. Beta-blockers and central norepinephrine blockers help reduce norepinephrine levels that are shown to be elevated in aggression. Goldner-Vukov and Moore [12] wrote that atypical antipsychotics are the preferred treatment for certain personality disorders. They improve anger and impulsivity and the cognitive-perceptual abnormalities that underlie psychotic symptoms. Some of these symptoms can be found mostly among people with personality disorders falling into clusters A and B.

Patients with personality disorders have higher rates of attrition with pharmacological treatments. The interventions can also be foiled by exaggeration of drug side effects or litigiousness, and the personality psychopathology itself can undermine the therapeutic alliance [11].

Teaching Point

The guidelines for pharmacological treatment of older populations should be adjusted and take into account various medical comorbidities and address symptoms that cause the most functional impairment.

Hospitalization

Hospitalization becomes necessary only when there is an immediate threat to the patient, or others (because of the patient's symptoms), and usually when the risk factors for suicide are modifiable (e.g., by medication adjustment). Grave disability from a severe loss of contact with reality (psychotic decompensation in patients with borderline personality disorder, for instance) is another indication for psychiatric admission. We have to be careful in not prolonging hospital stays to avoid regression (especially with patients displaying dependent or borderline personality features). A more suitable compromise might be a very short-term admission (24–48 hours) in a crisis stabilization unit that acts as some form of "transitional space" or holding environment. Gradually, as the patient develops self-regulatory skills, such higher level of care measures are not necessary. Ultimately, the patient should be taught that he/she is responsible for his/her life and choices [25].

25.1.7 Special Considerations

Psychiatrists and mental health professionals are in a privileged position to promote the evolution of social consciousness by educating the population and the institutions about personality development and the importance of "good-enough" parenting. Because of the damaging impact of severe personality disorders on individuals and societies at large, the need for increasing awareness of the maladaptive personality styles to protect the younger generations is obvious. Sometimes, healing a person with personality disorder at the end of life will mean accompanying the person in an unresolved generativity versus stagnation stage, where the person might need to make amends with younger generations. This, in turn, can be healing for the abused child now grown up and can subsequently prevent further transgenerational relational trauma with the person's own children and grandchildren. It is everyone's responsibility to protect our children. This is a lesson that older people who suffered their whole lives from poor attachment experiences can teach us. We owe it to them and all their descendants to break the cycle of child abuse. Repentance translated into concrete efforts to make this world a better place makes a person graduate from the generativity stage to achieve integrity and die in peace.

25.2 Case Studies

The following case scenarios will illustrate the process of identifying the manifestations of some personality features in old age and their corresponding approaches to promote treatment and healing.

25.2.1 Case 1

Case 1 History

Ms. P. is a 67-year-old Caucasian divorced woman who lives alone. She is referred to you for "anxiety and insomnia" by her primary care physician who just inherited her case. She takes an angiotensin-converting enzyme inhibitor for essential hypertension, calcium supplements, and lorazepam on occasion (leftover from an old prescription). She has never been assessed by a psychiatrist and was never admitted to a psychiatric facility. She has never attempted suicide, although decades ago endorsed passive morbid thoughts in the context of stress from single motherhood. She describes herself as a "worrier" and has completed psychotherapy many years ago for a few months, saying "it felt good to talk to someone." She is religiously following the primary care physician's recommendations, and her most recent mammogram and colonoscopy are normal. Her Pap smear done 7 years ago was

negative. Her liver-associated enzymes and renal function were within normal range. Her cholesterol was slightly elevated but not enough to start a medication. She promised she would walk every day, "Did Dr. Romberg tell you I was a good . . . good patient?" she adds, with a nervous smile.

Apparently, as you are glancing through faxed records (some notes are handwritten and not very legible), you read that she never smoked based on the "zero pack-year" reported on a recent health screening sheet, but there was a discrepancy in the chart: she described herself as a "social smoker" in her late thirties. She reports drinking alcohol "on occasion," and she denies being tipsy or passing out, but her primary care physician noted ethylic breath during a recent exam. The other progress notes are not very informative and contain minor medical problems such as "dry cough," "fever," "high systolic pressure," or "concerned over a 2-kg (4.4 lb) weight loss after viral illness." But you are struck by the increased number of medical visits over the years.

She noticed that her insomnia worsened upon coming back from a trip to visit her daughter, who lives abroad. Her primary care physician mentions to you that she was noticeably nervous when he asked her to do a Montreal Cognitive Assessment (MoCA), she was rather hesitant, stuttering a lot, and admitted being fearful of giving the wrong answer. At the end, she asked if her score was good and whether there was something abnormal going on. Her voice trembled as she realized she had a score of 25 out of 30, "I used to take tests, no problem, I was a school teacher, you know." Normally, her younger daughter was accompanying her during those visits, but she had to cancel at the last minute because she was experiencing marital problems and had to meet with her lawyer. Upon saying this, the primary care physician noted that she started crying profusely, wondering what would happen to her daughter. He would like you to take over her psychiatric care because he suspects that some of her symptoms have a "psychosomatic" origin.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What is your next step?

? Question 2. What is your differential diagnosis?

? Question 3. What will be your approach with this patient?

Case 1 Answers

Case 1 Answer 1 (Question1—What is your next step?)

You are the psychiatrist who was consulted by the primary care physician. Verifying the patient's understanding of the referral process by asking: "What brings you here today? What questions do you think your primary care doctor was hoping to get answers for?" might be a good way to reassure the patient while obtaining a general sense of the perceived issues. A full assessment including the family history (a genogram might be helpful), birth history, and the patient's developmental milestones should be done. Other medical illnesses, like head trauma, seizure disorders, major car accidents, and endocrine problems should be screened for. Exploring her upbringing to identify family dysfunction and unhealthy attachment is crucial, especially if you want to assess for maladaptive personality traits. School functioning, socialization, employment and relationship history, context of ruptures, and coping mechanisms are additional elements that are helpful (see ◘ Table 25.8). Screening for past and current depressive and anxiety disorders is also an essential step. If there are dysphoric affects, how are they typically handled? Exploring any history of addictive behaviors in the past or currently is important.

Obtaining the patient's authorization to access collateral information from a person who knows the patient well (spouse, or in this case, an adult child) should also be done because people with personality disorders generally have low insight and self-awareness. Moreover, it can provide a precious window into significant interpersonal dynamics.

It is useful to ask the patient directly how would he/she describe him/herself. "What do you like about yourself? What are you most proud of? Do you have any regrets? Throughout your lifetime, who or which type of person did you get along the best, and why? Conversely, who or which personality style was the most difficult to get along with, and why?" Sometimes it helps to ask "if your best friend were in the room, how would he/she describe you as a person?" See ◘ Table 25.9 for examples of such questions. Getting the informant's perception is equally important, and a strong mismatch could alert us to the possibility of a challenging relationship.

The goal of this step is to get acquainted with the person, their narrative, and to get a sense of how the self was shaped throughout the decades. The more detailed this process is, the wider the range of experiences reported; hence the greater validity because it is important to gather as many data about the individual's ways to cope and relate to the world as possible before drawing conclusions about personality style. A phenomenological approach rather than a "checklist" or categorical approach is more appropriate. Formulating a narrative that summarizes the person's temperament and character and then trying to determine if it matches one or more personality disorders is more optimal than starting with the criteria and have the person's symptoms "fit" in those boxes. One method that helps the scaffolding of a representative narrative is starting with specific quotations that can reveal cognitive distortions about the self and the world. Maybe the person will end up meeting criteria for one personality disorder in particular, but how about other potential traits? Can it be a "mixed" personality disorder? Is there a core structure associated with features from another personality cluster, for instance?

The moderating effect of other psychiatric disorders should not be underestimated. Screening for depressive, anxiety, or substance-related disorders is important. Ruling out a systemic medical condition, or a neurocognitive disorder, is necessary because such diagnoses could mimic a specific personality structure and redirect the treatment approaches.

Case 1 (Continued)

"My-my new doctor wanted me to come, maybe it is because of the . . . the test he did, with all these questions, repeating words, trying to remember things . . . Or is it because he has no experience? But I have nothing, nothing against him . . . He is young, he-he must have graduated recently. My other doctor, who re-retired, was very nice. I could call him whenever I had a question about my . . . about my health. He looked very much like my father, tall and calm."

She informs you that her father passed away at age 67 from colon cancer. Her mother was a harsh disciplinarian, "very severe," with a recurrent alcohol problem, and she would "not spare the rod." The patient, who was the oldest child, was punished a lot. She says that she gets along well with her siblings, they all are close and help each other, especially since her divorce, which she described as the most difficult event of her life. Her husband was cheating on her and "angry a lot." "But maybe I deserved it, when my youngest was born, I was not paying as much attention to him . . ." She has two grown daughters, the older, an architect, lives in Europe and the younger is a social worker "who, unlike her sister, preferred to stay close to me." She calls her every day, "she is so supportive, when I'm worried, she finds the right words to tell me that everything is going to be OK. But now she is going through some . . . some stuff. I pray every day for her not to divorce, that's terrible, what will she do?"

She always wanted to be a nurse and care for sick people but did not think she could go through the studies. She became an elementary school teacher. She was well liked by her students, many of them stayed in touch with her. At age 58, she decided to retire because "the principal said I was not firm enough with these kids . . ." She was teaching in an elementary school in a poor neighborhood and the children had significant behavioral problems. She says she had no problem adjusting to retirement, and she kept busy volunteering at a nursing home and also taking care of aging relatives, bringing them food or giving them rides to their medical appointments. She was raised as Catholic and goes to church weekly.

She endorses insomnia since coming back from her trip to Europe to visit her older daughter a few weeks ago. She said she had a good time, she visited a lot, but now she tosses and turns in bed even though she feels tired. She admits that her mind is "racing" about various people in her life. After falling asleep, she wakes up sometimes in the middle of the night, sweaty, her heart pounding, sometimes "skipping a beat." She went to her doctor because she thought she would have a heart attack but her electrocardiogram was always negative. She endorses unpleasant dreams during the few weeks before her trip (e.g., she would take the wrong flight), but has no nightmares. She says drinking an extra beer with her glass of wine every evening used to help, but not now. She denies changes in appetite, weight loss, sad mood, or anhedonia. She does not have thoughts of hurting herself, "I am happy, I want to live a long life." Recently, she experienced bouts of sadness with crying spells while thinking about her younger daughter. She likes to socialize, she has friends over almost every day ("they help me make decisions when I remodel the house, or we just sit and talk"), and she enjoys the presence of her dog and two cats. She likes to knit socks and travel to visit her grandchildren. She usually goes with a friend who also takes care of travel bookings for her because she is fearful of traveling alone, especially so far away.

On mental status exam, you see a woman who is pleasant and polite. She is mildly overweight. Her expression is candid. She maintains good eye contact. There are some stereotypical gestures, she rubs her fingers a lot, or touches her hair repeatedly but no tremor or dyskinesia are noted. She is generally very expressive and smiles a lot, but at the same time seems on the verge of tears. There is a stutter of mild severity. Her affect is not distressed, except when she mentions her divorce (she becomes tearful) and when you ask her about suicidal ideation and insomnia. Her speech is conversational, with some hesitancy from nervousness and stuttering. Her vocabulary is a little limited, and she tends to echo what you say when she cannot find the words and when you try to suggest some answers. The main themes consist of her concerns of others, her anxiety, and what you suspect is a fear of death or serious illness. You detect some avoidance of new situations and episodic clingy behavior. Alcohol use might be minimized. No evidence of disturbed perceptions and evidence of mania or suicidal ideation. Her abstract thinking is limited; she interprets statements literally. Her intellectual level does not seem consistent with her educational achievement. She is alert and oriented, with a MoCA score now of 26. She can read the short paragraph about the instructions for the genogram, but follows each line with her finger and moves her lips as she murmurs the content. Instructions must be repeated; she forgets some pieces of information about recommendations. She struggles to make the genogram, not understanding how to link the relatives within the structure. Maybe some level of anxiety and distractibility are contributing to a seeming difficulty in processing certain information.

Then, she allows you to meet alone with her daughter. She hints to the fact that she is hoping you can give the daughter some advice because of the marital crisis. She also fully trusts her daughter to reveal anything she thinks might help you understand the situation, "I might have forgotten some important information." Her daughter says that everyone likes her mother, and she hopes that you can help her. She never really had any concerns about her, "but my older sister does, she always used to describe her as a frightened deer. She was also very upset with my mom when we were teenagers, because my mom would hang around with other divorced women and they would smoke like chimneys during those dinners. But my mom never bought cigarettes for herself." Both became concerned when they thought their mother was taking care of too many pets (she apparently takes care of a dozen of feral cats in addition of her own pets). "If it makes her happy . . . You know, she was very lonely when she raised us." She says her sister often complained of how "panicky" she was when they grew up. "It's true that my mom tend to be jumpy when there is too much going on around her . . . She

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was also crying easily and very vulnerable to criticism. But I make sure people in her life are kind to her, and she listened to me when I suggested an early retirement, this school principal was very mean and bitchy with her." Her fragility became obvious the years that preceded the divorce. You learn that her ex-husband was emotionally abusive, and after the separation, she had at least four relationships within a few years. "All of these men, my mom loved them and gave them everything, but they were such losers . . ." She never remarried. She had difficulty assisting her daughters in their high school homework or school projects. She seemed easily anxious and overwhelmed by such cognitive tasks, excusing herself by saying, "I teach elementary school kids, you know," asking her own siblings to assist her daughters. If she sticks to her routine, she is fine, but she gets momentarily anxious when she must change an itinerary or even try a different recipe. The daughter agrees to fill out some questionnaires. You ask her to do so with her mother's status (before suffering from her current anxiety and possible cognitive decline) in mind.

Case 1 Answer 2 (Question2—What is your differential diagnosis?)

She presents with prominent anxiety features and executive dysfunction. It is important to rule out a systemic medical cause. Thyroid function tests should be ordered since hyperthyroidism could present with panic symptoms and hypothyroidism could present with a depressive episode and/or a neurocognitive disorder. Quantifying her alcohol use and determining its impact is also important. Using the CAGE questionnaire or asking questions such as "does drinking alcohol take a lot of room in your life? Do you feel like alcohol controls your routine? Does your life revolve around alcohol?" is a good first step. A sleep study could help identify sleep apnea. The recent jetlag could be contributing to current insomnia, but should improve with time. Monitoring blood pressure is also indicated. Anxiety or depressive disorders, sleep deprivation, and alcohol use disorder could all contribute to cognitive dysfunction.

If her baseline intellectual functioning appeared below average, we could consider learning disability or borderline intellectual functioning. Mild neurocognitive disorder should also be considered if there is evidence of decline over time. Neurocognitive disorder secondary to substance use disorder like chronic alcohol use disorder is also a possibility. Some additional neuropsychological testing and brain imaging could be warranted.

Based on her relationship history, dependent personality disorder should be ruled out. She displays poor affect regulation, interpersonal issues, and cognitive distortions. As a result, she developed chronic, maladaptive attitudes and behaviors that cause significant distress. She seems to have difficulty tolerating solitude and making decisions without others' input. Plus, she has low self-confidence and she seems easily intimidated by authority figures. She needs to be reassured and wants to avoid displeasing others. She seems to oscillate between dependency and being extra available to others; her apparent good functioning in situations where she cares for others highlight potential co-dependent dynamics (see ▶ Chap. 8). People with cluster C personality disorders tend to be anxious, and excessive anxiety levels can interfere with optimal cognitive functioning. Borderline personality traits (mood dysregulation, multiple relationships after her divorce, self-destructive behavior such as binge-smoking and chronic alcohol use, and externalized split as evidence by polarization of daughters) are also possible. Avoidant personality traits should be screened for. Regardless of the specific name for the diagnosis, there seems to be a strong personality component to her difficulties, and it could be due in part to traumatic childhood experiences. In summary, she seems to be arrested developmentally. Since she presents some traits from various personality disorders, the most appropriate diagnosis at this time would be other specified personality disorder (see ◘ Table 25.1).

Psychodynamically, a few factors might account for the manifestations of anxiety; she has reached the age her father was when he died. Her numerous visits to her previous doctor, who acted like a father and reassuring figure, might be an indication of hypochondriacal preoccupations, the latter being fed by possible subconscious (or conscious) fear of death, reactivated in the context of anniversary age. Moreover, there was a recent change of primary care physicians, which could have exacerbated anxiety and dependency needs. Her daughter is going through a separation and this might reactivate painful feelings about her own divorce. She might also be unconsciously concerned that her younger daughter, who is her most consistent source of support, is becoming less available to her as she is going through her marital crisis.

Since she worries excessively about her health and also about her daughter, generalized anxiety disorder should be in the differential. This is a pervasive pattern of worrying about various topics and usually starts in childhood. A specific phobia, like fear of flying, can also be part of the differential. Finally, panic disorder or posttraumatic stress disorder should be ruled out. If experienced as traumatic, as is often the case, her abusive relationships with her mother and (later in life) with her husband could contribute to such syndromes.

Case 1 (Continued)

To complete the assessment, you discuss her case with her older daughter over the telephone. The patient had given you the authorization to talk to her. This daughter voices her concerns about her mother's dependency needs. She seems anxious whenever she travels away from her siblings. They all live within a short driving distance and see one another every week. She thinks her mother deteriorated significantly after the divorce and was "falling apart" every time she had a major decision to make; e.g., changing jobs, moving, or buying a new home. "Her universe has shrunk." She thinks that her mother also "suffered from depression" during many years; she cried a lot, drank alcohol, and spent a lot of time wonder-

ing what could have been done differently in her marriage. At the same time, she was fearful of her daughters' father and settled for less than what she was entitled to in court, just to keep the peace. They suffered from her emotional unavailability and later on from her "180-degree shift" as she became intrusive when they started dating. The sisters ended up in psychotherapy themselves as young adults for anxiety and depression. Regarding further medical investigations, a computed tomography (CT) of brain scan was ordered and was within normal limits.

Case 1 Answer 3 (Question3—What will be your approach with this patient?)

You reassess for the possibility of major depressive disorder. She is not currently depressed but admits, "now that you are bringing this up," to have been very "down" decades ago when her marriage disintegrated. With the father of her daughters gone, she suddenly felt that she was "a nobody." She felt unlovable and worthless. She also became overwhelmed with all the responsibilities, believing she could not do it all on her own, that she needed a companion.

Once the diagnosis is clarified, the first step overlaps with the assessment, where psychoeducation should be provided about most likely conditions, using a language that is not technical and not overly pathologizing, and instill hope by listing the recommendations, including self-care, having a healthy lifestyle and sense of purpose. Presenting the problem using the perspective of developmental pause instead of "personality disorder" is less intimidating and reflects more accurately the challenge at the core of the person's functional impairment while implying the treatment philosophy, which is continue to support the person's own development. Also, reflecting the specific vulnerabilities by saying something like "some people become anxious when they face a difficult situation, others feel sad and have low self-esteem" can help identifying potential triggers and prepare more optimally for stressors.

With each patient, this one in particular, it is important to foster growth and empowerment by encouraging self-efficacy in determining specific goals. Which areas would the patient like to improve? This patient seems generally adherent but needs some initial direction. A more structured approach like CBT, PST, or DBT could teach useful tools initially; coaching her in developing strategies to address overwhelming affects (via mindfulness) or managing dysfunctional cognitions and anxiety symptoms like avoidance or hypochondriasis through Socratic reasoning could help. If there is a specific relationship issue, IPT should be recommended. A twelve-step program could address the substance misuse and/or co-dependency issues. Brief psychodynamic psychotherapy could also guide exploration of the past and how it affects the present, if she is motivated and receptive enough. Some level of an existential approach could be incorporated once the alliance is established, and her attitudes towards death could highlight unresolved conflicts. Her history of hypochondriacal anxiety and fear of exploration illustrates that the fear of death might, in fact, stem from a fear of living. An emphasis on living in the present (through mindfulness practices) can help alleviate anxiety about the unknown and facilitate the acceptance of what is, and in turn, increase general well-being.

The healing of past traumatic attachments can take place in the setting of a safe, structured, professional relationship with a consistent therapist. Regardless of the approach, the common factors can be beneficial for the patient's growth. (See ► Chap. 8)

If the anxiety symptoms are disabling, a low dose of an SSRI antidepressant could help with the panic manifestations. Benzodiazepines like lorazepam should be avoided due to the risk of cognitive symptoms (which could be part of the problem in Ms. P.'s case), exacerbating depression, or causing falls. A beta-adrenergic-blocker or clonidine could help with specific phobia (e.g., fear of flying).

Case 1 Analysis Ms. P. is currently struggling to make sense of her life and why certain events happened to her, and you reflect to her that chronologically she is at the phase that Erikson called "ego integrity versus despair." On a psychological level, she has also some unresolved developmental stages, e.g., "autonomy versus shame and doubt" and "intimacy versus isolation." She agrees to start psychotherapy and she says she is interested in a group format. She is open to going to Alcoholics Anonymous because she admits that there was a time in her life when she drank more. She did not want to admit it at the time, but now she wants to address this problem to not end up like her mother, who went to substance abuse rehabilitation many times and died of liver failure. Since she likes watching TV more than reading, you suggest some CBT and mindfulness modules on video formats. You do exposure psychotherapy with her to deal with avoidance of stressful situations and past trauma and challenge the dysfunctional thought patterns such as ruminations and negative thinking. You refer her to a CBT group as well. Once her self-confidence increases, you tell her about narrative psychotherapy, and she agrees to try this after she became more comfortable in group settings (she did not participate much at first but became more engaged after a few weeks). She is interested in doing family psychotherapy with her daughters as well and maybe having a few sessions with her older one when she visits. She wants to try a low dose of an SSRI antidepressant. You introduce sertraline at 25 mg daily for 2 weeks and increase it to 50 mg daily, which she tolerates well. She stops using her lorazepam and decreases her drinking to twice weekly, no more than two glasses in one sitting, saying "I want to see my grandchildren graduate." With time, her physical preoccupations decreased, she became gradually more comfortable in new situations (she now travels long distances by car to go to her grandson's recital) and developed a positive outlook on her life and the person she is evolving into. She sleeps better as she found ways to stop "sweating the small stuff." She tells you that you made her realize that she was still capable of learning skills and discover her inner strengths, "even at my age."

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25.2.2 Case 2

Case 2 History

You are a fellow resident in forensic psychiatry and asked to evaluate Mr. E.'s (who wants to be called "X"), a 72-year-old man who is under custody after law enforcement seized juvenile pornographic material at his home. A female forensic psychiatrist supervisor who is currently pregnant refused to assess him and assigned him to a male colleague and you. Several charges are listed, namely, possession and sale of juvenile pornography. He was mute during the preliminary hearing, and the court requested an assessment to determine if he is fit to stand trial and if he was criminally responsible for his actions. You consult the medical chart, and it reveals that he lives alone, he has children who are alienated from him, and he has a history of incarcerations in his twenties and thirties. He also has various aliases and lived in 17 different locations. He had a small business at some point but mostly worked as a butcher until he was deemed "permanently disabled" on obscure grounds 15 years ago. A background check listed previous felony charges, namely, statutory rape when he was in his twenties, sexual harassment charges (dismissed) when he had his business, various assaults ("bar fights"), and, in his sixties, disturbance of the peace while intoxicated. More recently, the police was called after a neighbor complained that he was going on the balcony naked sometimes.

He has no history of hospitalizations but had repeated emergency room visits for "severe pain." He would often leave against medical advice. No CT scan was ever done despite suspicion of traumatic brain injury. He is not very forthcoming during the interview. He falls asleep after a few minutes. He answered only when you asked his name. You suspect that he is simulating at first but decide to verify his urine toxicological screen done recently upon admission. It was positive for alcohol, opiates and cannabis. His liver enzymes were elevated, and his hemoglobin was low at 115 g/L. Serum albumin and 25-hydroxyvitamin D levels were also decreased. All other laboratory results (metabolic panel, renal function) were within the normal range. In the emergency department, the physical exam revealed constricted pupils, emaciation, and mild resting tremor. The blood pressure was 141/95 mm Hg.

Case 2 Questions and Answers

Case 2 Questions

- Question 1. What are the criteria determining if someone is fit to stand trial, and in this particular case, what are the elements for and against it?
- Question 2. What is your differential? What is the conclusion you will write in your report for the court regarding criminal responsibility?
- Question 3. List the indicated approaches taking into account the prognostic factors for this man.

Case 2 Answers

Case 2 Answer 1 (Question1—What are the criteria determining if someone has the capacity to stand trial, and in this particular case, what are the elements for and against it?)

As discussed elsewhere in this textbook, fitness to stand trial and criminal responsibility are the most common types of assessment performed by a forensic psychiatrist. It should be noted that even when assessing an individual's capacity in the context of a fitness assessment, the person is presumed to be capable until proven otherwise, usually on a balance of probabilities [33].

In order to determine if Mr. E.'s is fit to stand trial, we have to evaluate if Mr. E.'s has the ability to understand and appreciate the following (see ▶ Chap. 29, *Geriatric Forensic Psychiatry*):

- The charges against him (what he is accused of)
- The possible consequences
- The legal proceedings
- Who are the participants (judge, jury, attorney, witness)?
- Does he want to be represented by an attorney, and if not, why not?

Currently, because of his mental state, there is no evidence that he meets criteria for fitness to stand trial. In fact, he might be intoxicated (he had mind-altering substances in his urine). He might be malingering as well but there are objective results potentially going against that (the influence of the drugs on his mental state is prominent).

Therefore, you talk with your supervisor and together request a treatment or detainment order to restore his capacity. The goal is to let the effects of the drugs subside and reassess once he is no longer intoxicated. Since you cannot conduct an optimal assessment at this time, you would not recommend any standing medication orders beyond some as-needed antipsychotics in case of agitation.

Case 2 (Continued)

After a few days, Mr. E.'s is more alert but was noted to be solitary on the unit during meals. He was described as flirtatious by the nurses, making inappropriate comments on their hairstyle, outfits, or make-up.

He refuses to discuss the charges with you, saying that he has an attorney that will take care of this "misunderstanding." He expresses contempt, wondering what the big fuss is about; somebody obviously is trying to lock him up. "I am sure it was a set up, should've never trusted that new neighbor!" He mentions a young man with whom he watches movies and smokes marijuana. "He's after my money, I'm sure." You stay neutral when you inquire about the movies, but his answers are vague, "mostly old westerns." You learn that the young man is 22 years old.

He denies any trouble sleeping recently or depression and claims to not recall much about his childhood. He was the last of seven children and their mother had to work two jobs after their father abandoned them (he found out later that his dad had been murdered). He learned to "survive" and had to defend himself against older siblings while his mother was

working (they were jealous of him, "I was her favorite"). He was beaten up severely in school by peers and also expelled due to aggressive behaviors but at some point an older gangster took care of him. He learned that people could not be trusted. He married four times but had more romantic partners in between. "I never slept with a legitimate prostitute, never had to . . . The ladies were usually fist fighting to have me." Two of them had pressed charges against him, "they must have felt intimidated by my superior intelligence." He says that it was a good riddance anyway. "The children they gave me were such losers." He says he has "many kids," but has not heard from them in a while. "They refuse to let me see my grandchildren. What kind of family spirit is that?" He says that later in life he studied economics at Harvard University and had a successful business in cosmetics and he currently owns three mansions, one in Europe and another in South America. "Once I get the hell out of here, I will invite the whole unit and we will throw a decadent party." You bring up the topic of recent charges again, asking "what is your understanding of what happened?" Again, he says he should not have let his guard down with this neighbor, and maybe he had too much to drink. "I don't remember having shared the materials. Plus, they are just videos, who cares? I have not actually touched those kids." When you ask if he ever has touched minors, he pauses then says, "No, the sexiest are the 11-year old girls and I have not seen any in a while." You ask him if he gets aroused when seeing minors or thinking about them, and he replies, "how about you?"

On mental status exam, he is a tall man, slightly balding on the temporal areas, with dyed-blond hair that is fixed with gel. You are struck by the heavy cologne in contrast with relatively poor hygiene. His nails are long and dirty. Some teeth are missing. He wears worn-out polo shirt, jeans, and cowboy boots. You see various tattoos (a knife with dripping blood, a naked woman on a motorcycle, a crying skull) and some scars on his forehead but also on his hands. He has an intense stare that expresses disappointment, "I thought they would send me a young person, preferably a woman."

His attitude is intimidating, intrusive, asking you direct and personal questions (at the sight of your colorful socks: "so . . . which pronouns do you use?"). His affect is constricted, guarded, and detached upon talking about loaded subjects (e.g., his father), and he smiles mostly when he uses sarcastic humor or makes intimidating comments. He becomes irritated when you try to explore past relationships and early attachment experiences and how they affected him. His mood is described as "fine, OK," although you suspect some dysregulation. His speech is conversational, not pressured, with some hesitancy, especially while you wrote down observations. Thought process was a bit vague, mostly linear, no evidence of difficulty expressing himself. Thought content was notable for difficult childhood experiences, grandiose elements (inflated sense of self), and low capacity for empathy, with poor ability to mentalize. He endorses hearing the voice of his mother sometimes. He denied suicidal or homicidal ideation, although a recent attempt to die by overdose is not excluded. There is no evidence of perceptual disturbances during the interview. Insight is poor. Judgment is fair. Cognition is intact, and he is alert and oriented. Intelligence seems slightly above average. He scored 29 out of 30 on the MoCA.

After this emotionally difficult and draining encounter (you actually felt nauseated when he talked about the videos and the victims and disgusted about his attitude towards women in general), you review the police report and it describes that the materials were mostly pictures and videos of 11-year old girls performing sexual acts. Mr. E.'s does not appear on any of those videos. However, his apartment is under investigation to determine if some of the scenes took place at his address.

One of his sons (from his first wife) contacted you to provide collateral information. He says his father was in trouble with the law a lot. He was incarcerated on multiple occasions and would come home almost triumphant whenever he was released. His mother, his siblings, and he were scared of him because he was drinking excessively. His mother divorced him after he was suspected of having sexually assaulted their teenage babysitter. He says he hopes his father gets a prison sentence, "so many people suffered because of him. It's terrible to say this of one's dad, but I think he is evil."

Case 2 Answer 2 (Question2—What is your differential? What is the conclusion you will write in your report for the court regarding criminal responsibility?)

He implied a sexual preference for minors (11-year old girls), so pedophilia must be ruled out, based on the recent charges, seeming predatory behavior and recidivism (statutory rape, sexual promiscuity and harassment, and use of juvenile pornographic materials). One can also wonder about the nature of his relationship with his young neighbor. Even though he is chronologically an adult, he could have a lower developmental age (from a mental disability) which could make his intellectual functioning equivalent to a 16-year old, for instance.

He reports facts (owning mansions, being a Harvard graduate in economics) that are inconsistent with his presentation (appearance, modest apartment, being on disability for many years). Therefore, we have to rule out grandiose delusions from a manic episode, but his speech is not pressured on exam and he has no sleep disturbance. It could be pathological lying or mythomania. He endorses a chronic mistrust of others. He could therefore be lying deliberately for sensation or because he does not trust the examiner, or because of inflation of the self to compensate from narcissistic wounding in childhood (abandonment by father, neglect, and abuse). A history of victimization from sexual abuse is not excluded, especially in the context of family dysfunction and being "protected" by a gangster. Pedophilia is highly correlated with sexual abuse during childhood. The grandiose sense of self, the pathological lying, and paranoid behavior could be part of a personality configuration called malignant narcissism. He has a long history of law-breaking, disregard for others, with limited ability to learn from his

actions and their consequences. Another comorbid condition to rule out is multiple substance (opioid, cannabis, and alcohol) use disorders. It is possible that his numerous emergency department visits were driven by an addiction to opioids. A neurocognitive disorder or behavioral sequelae from traumatic brain injury (from repeated concussions) should be excluded, but less likely in this case (almost a perfect MoCA score). Malingering is often in the differential in forensic settings. He tends to be deceptive (multiple aliases), and he might have simulated medical symptoms in the past to obtain controlled substances. Also, malingering might be a different expression or conceptualization of malignant narcissism.

In summary, Mr. E.'s has pedophilia, a severe form of narcissistic personality disorder (also conceptualized as malignant narcissism), and possibly various substance use disorders. Regarding criminal responsibility, you cannot identify any comorbid psychiatric disorder that could have interfered with his judgment or capacity to know right from wrong. Even though he might have been intoxicated while being in contact with pornographic materials, he is still responsible because he chose to use substances (therefore, he must be accountable for whatever happens while being intoxicated).

Even though he has a severe personality disorder, it does not qualify as a "severe mental disorder" per se in the sense that people with personality disorders must be held accountable for their actions, unless there is another comorbid psychiatric condition that affects the judgment at the time of committing the crime (such as a psychotic episode or neurocognitive disorder). He is rationalizing or minimizing the impact of the charges most likely to save the face.

Case 2 (Continued)

Your supervisor validates your impression after meeting with the patient. Then, a nurse rushes in to alert you that the patient had stolen the medication tray she was carrying for the evening dose. He had started ingesting some of the antipsychotics and some benzodiazepines. He had to be intercepted by staff and security guards. His vital signs were normal, he was alert, and after doing the pill count and looking at the other patients' chart, it was found that he had time to ingest valproic acid 2000 mg, lorazepam 4 mg, metoprolol 20 mg, and quetiapine 100 mg.

You wonder if he was trying to postpone the court hearing or self-medicate. The next day, upon trying to assess him to discuss what had happened, you find him deeply asleep and for the second time wonder if he was trying to commit suicide. You realize with some discomfort that you forgot to ask him about previous suicide attempts during your assessment.

Case 2 Answer 3 (Question3—List the indicated approaches taking into account the prognostic factors for this man.)

Restorative justice and correctional rehabilitation are the most important elements in the management of these individuals. A therapeutic community should be part of the treatment infrastructure for an optimal distribution of the clinical load and potentially difficult countertransference experiences (see ► section Psychotherapeutic Interventions). Mr. E.'s severity and chronicity of violent and illegal actions and his lack of insight and empathy are indicative of a poor prognosis.

Case 2 Analysis Mr. E.'s was sentenced to 9 years in prison. He was court-ordered to do a drug rehabilitation program as well as dialectical behavioral therapy. The next morning, he was found dead in his cell. He had hanged himself. He had no clothes on and there were messages of hatred written on the wall. Suicide might have represented his only outlet to shame or a "triumphant" gesture by which to avoid incarceration.

25.3 Key Points: Personality Disorders in Late Life

- Personality disorders are usually present in early adulthood; late-onset personality changes should increase the level of suspicion for other central nervous system or systemic medical causes (such as major neurocognitive disorder, cancer, iatrogenic reaction, or Cushing syndrome).
- The prevalence of personality disorders in old age is about 20%.
- Attachment trauma or adverse childhood experiences are etiological factors in the development of personality disorders.
- Poor affect regulation and interpersonal deficits are salient characteristics of personality disorders. Impulsivity, a core feature of borderline and antisocial personality disorders, tends to decrease with age.
- Personality in general evolves throughout time, and specific maladaptive personality traits can also present differently in late life.
- The frequency of strictly diagnosable personality disorders shows at least small declines with aging.
- During the examination phase, the informant who fills questionnaires should do so with the older patient in mind before the patient suffered from depressive disorder or major neurocognitive disorder (due to cognitive impairment, the patient may not be able to self-report).
- Personality disorders in older adults can exacerbate depressive disorders. Personality disorder features increase risk for suicidal thinking, suicide attempts, and death by suicide among older adults.
- It is possible to work on changing maladaptive attitudes and behaviors with therapeutic interventions.
- Psychotherapy and symptomatic pharmacotherapy are the main treatment modalities.
- Malignant narcissism is a form of severe personality disorder with poor prognosis.
- In summary, personality disorders are long-term stable conditions and serious enough to interfere with healthy functioning. The main focus of history taking

must establish that the features associated with diagnosis and categorization have been present and relatively stable through the lifetime (adult at least) of the patient. The assessment process does not have to take excessive time if well focused. Collateral information is often necessary.

25.4 Comprehension Multiple Choice Questions (MCQ) Test and Answers

MCQ 1. Which statement is the most accurate regarding empathy and narcissistic personality disorder?

A. Patients with such a personality have none.
B. They can display emotional empathy only.
C. They can display cognitive empathy only.
D. They can display both emotional and cognitive forms of empathy but only as they grow older.
E. They can display both emotional and cognitive forms of empathy but their emotional empathy is impaired and the cognitive form is unaffected.

Answer: E

Patients with narcissistic personality disorder have difficulty being emotionally attuned to others, so statement B is not accurate. But the cognitive aspects of empathy can be unaffected. Statement C is not true because the emotional empathy is impaired to various degrees, as opposed to totally absent or severely impaired, like in malignant narcissism. Statement A is not true because with mentalization therapy, these patients can eventually learn to develop some empathetic skills. Statement D is not true because aging alone is not sufficient to improve empathy and, generally, therapy or exposure to social situations is necessary to develop mentalization skills. Therefore, the correct answer is E.

MCQ 2. Which personality disorder is the most common in old age?

A. Other specified personality disorder and unspecified personality disorder (formerly personality disorder not otherwise specified)
B. Borderline personality disorder
C. Obsessive-compulsive personality disorder
D. Schizotypal personality disorder
E. Depressive personality disorder

Answer: A

Older adults with personality disorders present a complex clinical picture, and the DSM criteria historically have not been adapted to the realities of aging. Depressive personality has been removed from the DSM-5, but it can still appear in older individuals. Generally, clusters C and A, to which obsessive-compulsive personality disorder (answer C) and schizotypal personality disorder (answer D) belong, respectively, are more frequent, but other specified personality disorder and unspecified personality disorder seems to be the most frequent diagnosis because the complexity of the presentation can come from a combination of attenuated traits belonging to various clusters. Therefore, the correct answer is A.

MCQ 3. It is important to screen for personality disorder in old age for all of these reasons *except*:

A. Having a personality disorder is an important risk factor for suicide in late life.
B. It can affect other health outcomes.
C. If identified and addressed, it can help improve the prognosis of depression.
D. It is essential to repair all damaged relationships.
E. When faced with despair, examining maladaptive personality traits can help develop a coherent narrative.

Answer: D

Personality disorder, especially from cluster B, is a risk factor for suicide in late life; therefore it must be screened for (statement A is true). Because of maladaptive behaviors associated with personality disorder including poor adherence to treatments, a maladaptive personality can affect health outcomes. Early childhood trauma also affects various body systems directly and also through crystallization into a destructive personality style, so statement B is also true. Personality disorders can complicate the course of depression; therefore, if treated, the prognosis of depression improves (statement C is true). It is unrealistic to repair all damaged relationships. It is better to focus on the patient's own responsibility in what went wrong and trying to learn from that. Some relationships have been lost, but it is possible to start a work on the unresolved losses, through a coherent narrative (statement E is true). Statement D is the correct answer because it is the least accurate.

MCQ 4. What is accurate about the differential diagnosis of personality disorders in late life?

A. Paranoid traits are temperamental and therefore exclude the possibility of a neurocognitive disorder.
B. Actual dependency from physical decline must be assessed if the patient presents with clinginess towards caretakers.
C. An old person who was generally withdrawn, and never displayed grandiose behavior, excludes narcissistic personality and is more suggestible of schizotypal traits.
D. Passive-aggressive, depressive, sadistic, and self-defeating styles are useless concepts and should therefore never be on the differential.
E. An abrupt change in personality signals a late onset of severe personality disorder.

Answer: B

25

Paranoia de novo in an older person should always be thoroughly evaluated for other possible causes (e.g., delirium, major neurocognitive disorder). Therefore, statement A is false. Explicit grandiosity is not essential to diagnose narcissistic personality disorder. In fact, a more vigilant, "covert" form of narcissism is highly sensitive to criticism and tends to avoid social contact because of the development of obsessive defenses in coping with shame or other painful affects like envy, as opposed to the more "overt" type who can use arrogance, contempt, and externalized rage (see Fig. 25.1). It is simply a different defense to vulnerability or inadequacy of feelings. Statement C is false. Four personality disorders (passive-aggressive, depressive, sadistic, and self-defeating) have been removed from the DSM-5, but this does not preclude patients from presenting with robust forms of these personality deficits, as these personality patterns have been identified and used clinically for decades [34]. Statement D is also false. Personality disorders usually develop over time and are present in late adolescence or young adulthood. An abrupt change in personality should prompt the clinician to rule out a systemic medical cause, such as an intoxication, or a severe psychosocial stressor. Therefore, statement E is false. The correct answer is B: a person who presents with dependent behavior might have higher dependency needs from physical frailty and is not necessarily dependent in a pathological way.

MCQ 5. For an old patient with cluster B features who is vulnerable to shame, which one is the least useful intervention?

A. Suicide assessment at first visit.
B. Mentalization-based treatment.
C. Elicit feelings of shame to work on them by giving explanations for his mistakes, and then reassure and normalize with statements like "It can happen to anyone."
D. Pay attention to powerful defenses to identify underlying shame and help him build affect tolerance to shame.
E. Techniques borrowed from DBT and CBT.

Answer: C

Shame is a generally unpleasant emotion and is especially powerful and painful in patients with narcissistic personality disorder. As a result, they try to avoid it at all costs (see defenses in Fig. 25.1). Paying attention to the defenses and then helping the patient build tolerance to it with dose-by-dose desensitization is a good idea; therefore, statement D is correct. Given that he has cluster B features (potentially borderline personality traits), he would likely benefit from DBT and/or CBT to develop healthy coping skills when experiencing unpleasant affects and also address unrealistic views or expectations of the self ("I cannot make mistakes"); therefore, statement E is appropriate. A suicide assessment is necessary, especially since older people with unhealthy narcissism are at risk of shame-related suicidal crisis [23]. People with narcissistic personality disorder (and also with antisocial and borderline personality disorder) often have deficits of mentalization and, therefore, can benefit from such an approach. It can indirectly help them with feelings of shame if they are able to develop a theory of the mind that is balanced and therefore might be less likely to misinterpret the therapist's interventions in a paranoid manner or as if trying to shame them. Therefore, statement B is useful. Statement C is the most counterproductive in the sense that the therapist must be careful not to trigger shame feelings by clarifying comments or interpretations. Plus, although well meant, a statement like "it can happen to anyone" is not necessarily reassuring for someone who views himself as special and not being like anyone else.

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Special Topics

Contents

Psychosomatic Medicine/ Consultation-Liaison Psychiatry in Late Life

James A. Bourgeois and Caroline Giroux

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26

26.1 Background

26.1.1 Definition of Psychosomatic Medicine

Psychosomatic medicine or consultation-liaison psychiatry is the subspecialty of psychiatry that focuses on the psychiatric complications and comorbidities of systemic medical/surgical illness (see Fig. 26.1 and Table 26.1). Historically, psychosomatic medicine was primarily based in the general hospital; general hospital-based practice is still the most common and characteristic venue for psychosomatic medicine practice. However, in more recent times, psychosomatic medicine has also evolved an outpatient focus. Examples of outpatient psychosomatic medicine include psychiatric consultation services embedded into general medical (e.g., primary care) clinics, as well as in medical clinics managing illness with a high degree of psychiatric comorbid illness (e.g., neurology, HIV, obstetrics/gynecology). Specific "subsubspecialties" within psychosomatic medicine (where there is a specific knowledge base and clinical practice) include HIV psychiatry, transplant psychiatry, and psychooncology. Psychosomatic medicine functions at the junction of psychiatry (including elements of psychological and behavioral medicine) and other medical or "physical" specialties (see Fig. 26.2).

26.1.2 Clinical Practices Common in Psychosomatic Medicine

Due to the higher prevalence of systemic illness in geriatric patients, the overlap of psychosomatic medicine and geriatric psychiatry is inherently substantial (see Fig. 26.3). The same is true for the frequent overlap of psychosomatic medicine services with chronic pain management and palliative care services. Due to the nature of psychosomatic medicine practice, many illnesses routinely managed in a psychosomatic medicine service (e.g., catatonia, neuroleptic malignant syndrome, serotonin syndrome, delirium, medication toxicity states) are relatively rarely seen in outpatient psychiatry services. The general outpatient psychiatrist may thus not be current in the evaluation and management of these illnesses and may, on occasion, benefit from a consultation with a psychosomatic medicine psychiatrist.

The primary task of the psychosomatic medicine consultant is to understand the medical/surgical illness(es) that generated the hospital admission and to be able to assess the comorbid psychiatric illness in this context. Then, the consultant must be able to accomplish an appropriately thorough psychiatric assessment of the patient and integrate a psychiatric intervention plan for the comorbid psychiatric illness that takes into account the ongoing medical/surgical illness (see Fig. 26.4). It is crucial to meet the patient "where he or she is at" by identifying his or her explanatory model of illness. As the adjustment to the distress of the presenting sys-

Table 26.1 The roles of the psychosomatic medicine specialist

Evaluation situations	Interventions
Psychiatric evaluations Laboratory and imaging Ongoing symptom monitoring Decisional capacity assessments	Pharmacotherapy recommendations Brief in-hospital psychotherapy Arrangements for admission to inpatient psychiatry for some cases Liaison functions to other medical teams and integration of care

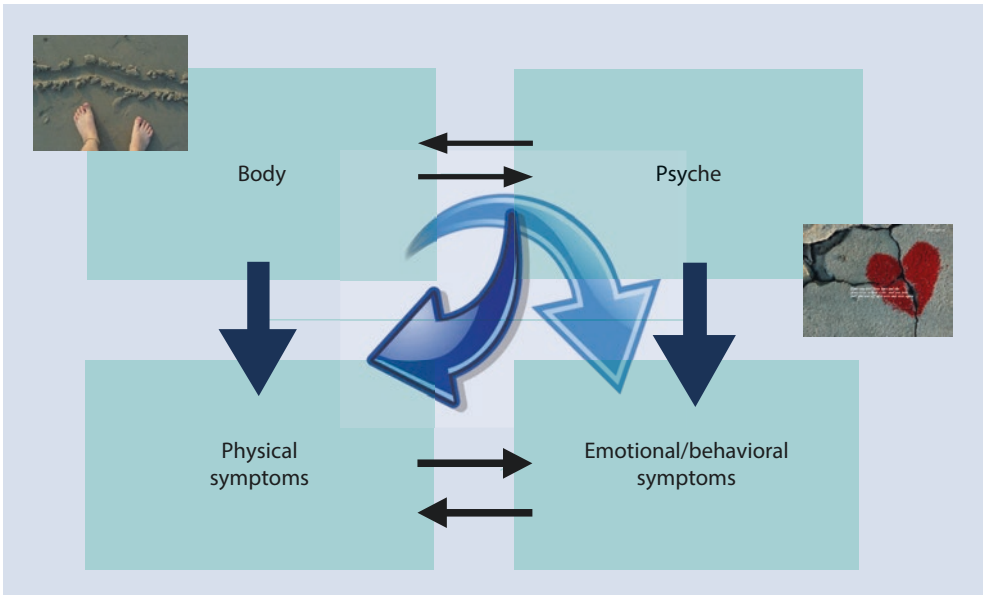

Fig. 26.1 Mind-body integration

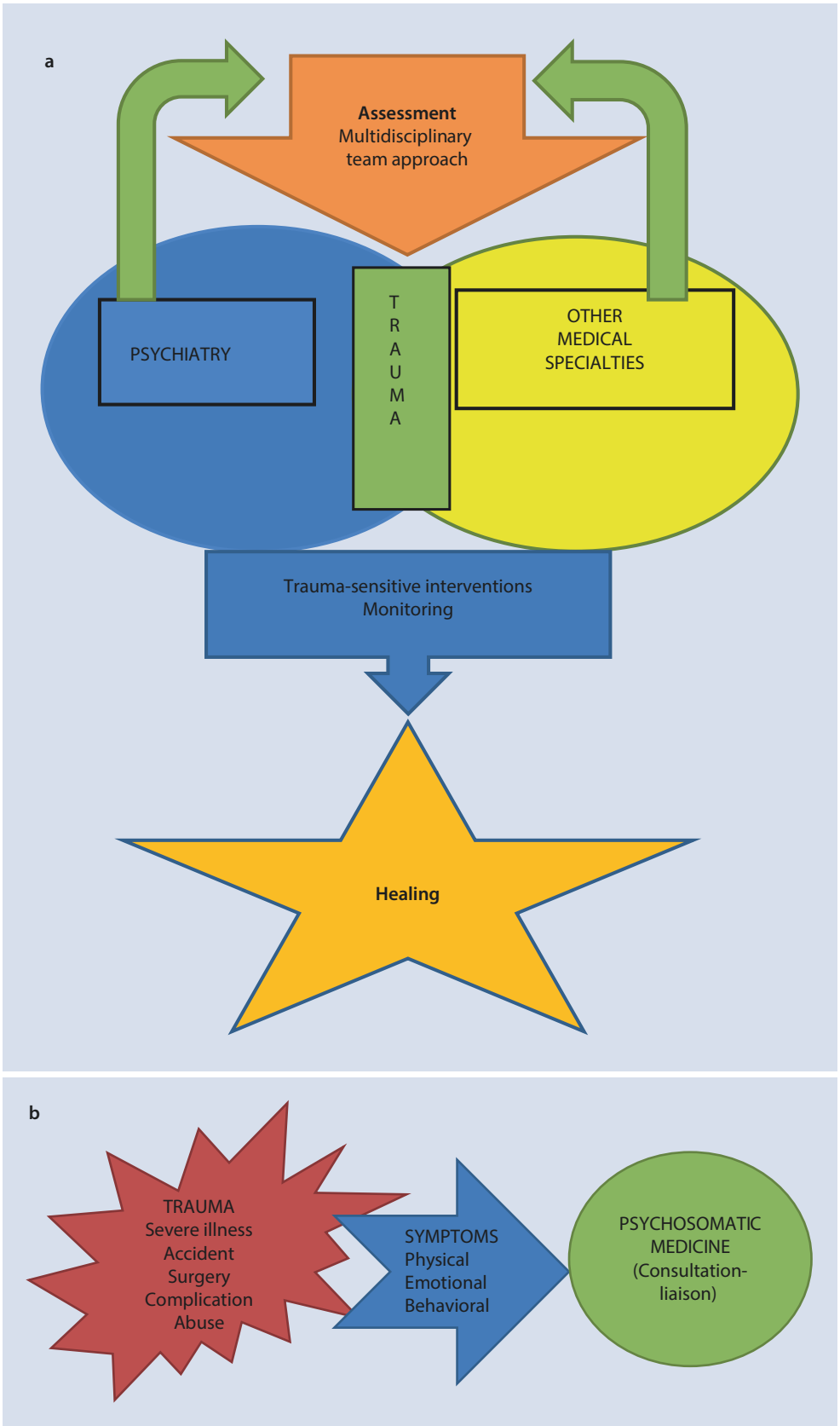

Fig. 26.2 **a** The trauma-informed role of the psychosomatic medicine specialist at the junction of psychiatry and other medical specialties. **b** The holistic role of the psychosomatic medicine specialist

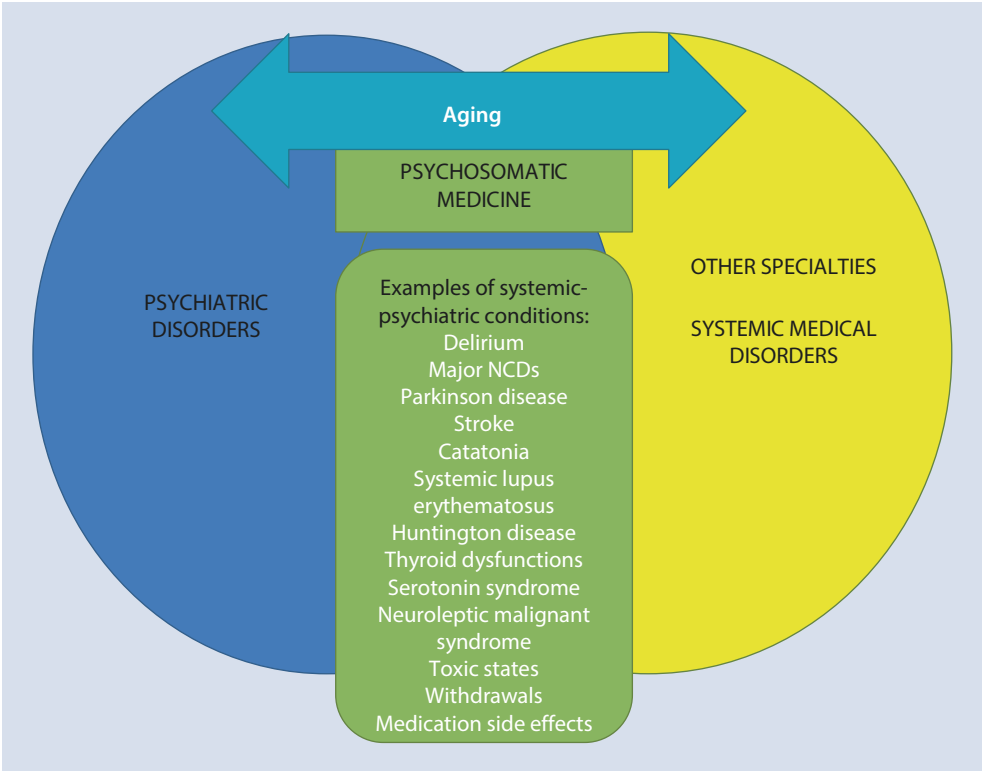

Fig. 26.3 Increased "psychiatry and other specialties" overlap in the older adult

temic medical/surgical illness must always be considered in the encounter with the patient, efforts to understand how much the patient understands about the presenting illness and how he or she is managing to cope with illness and hospitalization may have a profound impact on the illness experience and hence affect the outcome of the consultation encounter.

In the typical inpatient psychosomatic medicine practice model on inpatient services, the patient is admitted to another medical or surgical service (either ward or ICU) for an index medical/surgical illness. Patients who are admitted to inpatient psychiatry are managed by the inpatient psychiatry attending physician and would be seen by a psychosomatic medicine psychiatrist only in those circumstances where a subspecialty opinion was needed. Hospitalized patients remain the primary responsibility of the admitting medical or surgical service. Psychosomatic medicine consultations are requested by the "primary team" as are any other specialty/subspecialty consultation. The psychosomatic medicine psychiatrist sees the patient, integrates existing clinical data sources (e.g., chart notes, diagnostic imaging, laboratory, medication and allergies lists, and vital signs), and writes a consultation note. Typically, medical consultants do not write orders for medications and other interventions, but rather make targeted recommendations to the primary team to then write orders and to integrate the psychosomatic medicine consultant's recommendations along with consultation recommendations from other requested medical specialties.

A common exception to the practice of consultant not themselves writing medical management orders may be in the area of psychiatric commitment documents. Depending on local jurisdiction law and/or institutional practice, the psychosomatic medicine psychiatrist may be expected to write psychiatric commitment orders on admitted medical/surgical patients meeting the legal criteria for civil commitment for safety. In many jurisdictions, these criteria may include the patient manifesting acute dangerousness to self (i.e., suicide risk), dangerousness to others (i.e., homicide risk), and/or grave disability (profound inability to provide for self-care, food, shelter, and/or other basic necessities of life) on the basis of a diagnosable neuropsychiatric illness.

An important and common role for psychosomatic medicine psychiatrists (which represents a significant fraction of psychosomatic medicine consultation requests) is the determination of decisional capacity. Decisional capacity determinations are less frequent in outpatient general psychiatric practice. A common scenario leading to the formal determination of decisional capacity is that of a cognitively impaired patient who needs medical/surgical intervention. While many such patients are not per se suicidal (i.e., not "dangerous to self"), homicidal (i.e., not "dangerous to others"), and able to describe the ability to meet minimal survival and social needs (i.e., not "gravely disabled") under the locally relevant psychiatric commitment statute (see paragraph above), they may not be able to adequately understand the risks, potential benefits, and/or side effects of proposed medical/surgical interventions or, conversely, the risks/benefits of declining such interventions and thus are determined to have diminished decisional capacity specific to the proposed medical/surgical intervention. The majority of patients determined to have impaired decisional capacity suffer from one or more neurocognitive

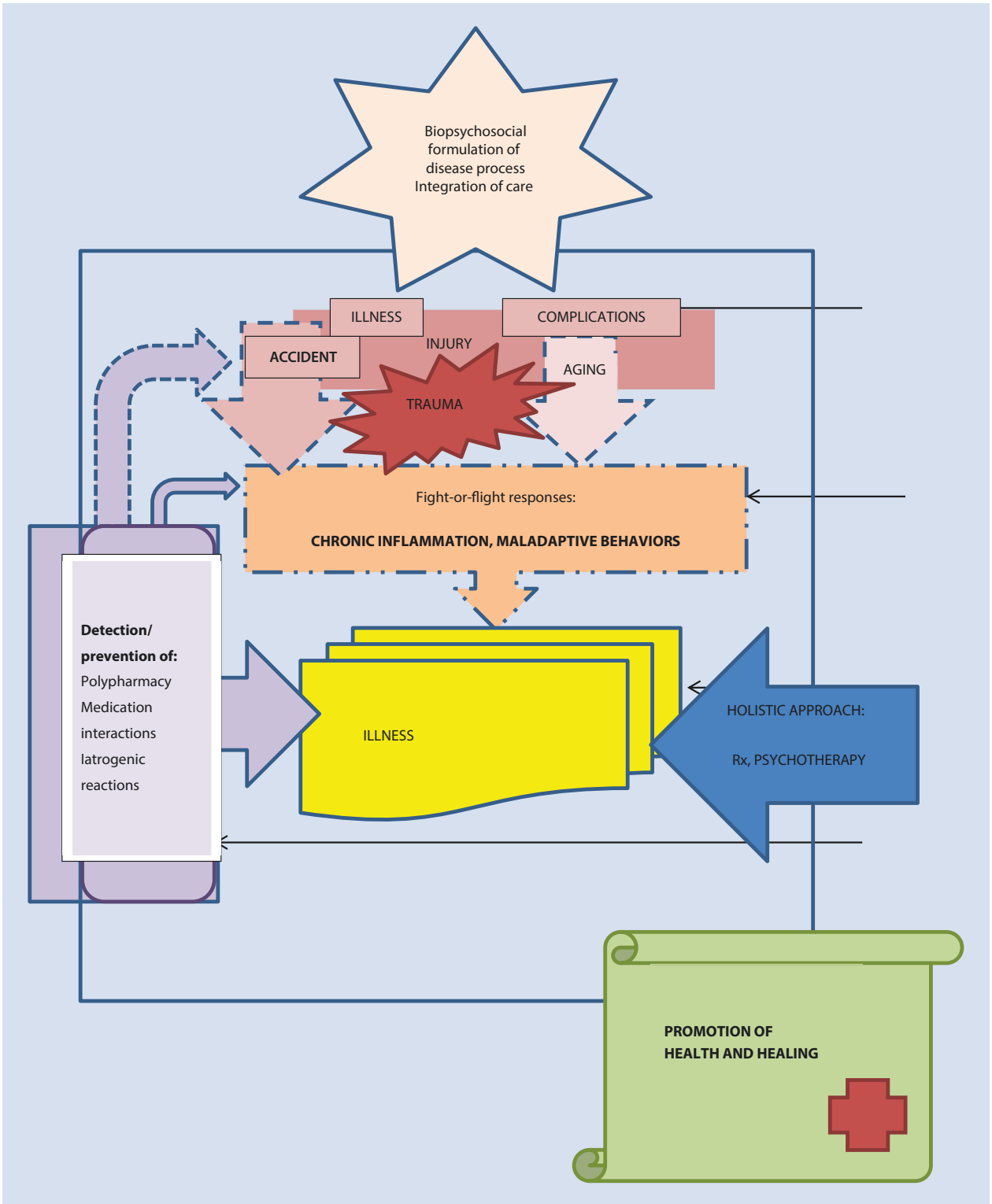

Fig. 26.4 The psychosomatic medicine framework

disorders (i.e., major or mild neurocognitive disorder—formerly dementia), delirium, or both. Other psychiatric illnesses (e.g., psychotic disorders, depressive disorders, bipolar disorders) may impair decisional capacity, but much less often than neurocognitive disorders and usually during an acute exacerbation of symptoms.

A common decisional framework for the determination of decisional capacity is the patient's ability to understand his or her illness, appreciate the clinical circumstances (regarding the risk, benefits, and side effects of the proposed intervention versus the natural history of the illness), demonstrate rationality in the decisional process (e.g., be able to "weigh"

the intervention versus nonintervention options regarding overall life goals and values), and verbalize a clear and consistent choice [1]. (For more details, see ▶ Chap. 9.) Decisional capacity determinations are specific to the clinical issue at hand and cannot be pronounced in an indefinite, "open-ended" way. This is important to emphasize as many decisional capacity determinations are occasioned by an acute episode of delirium. Delirium commonly results in (often transiently) impaired decisional capacity, but, with clearance of the delirium and resolution of the associated systemic disturbance, decisional capacity may improve, thus necessitating a repeat of the decisional capacity determination. It is emphasized that the presence of a psychiatric commitment order does not imply either intact medical decisional capacity or impaired decisional capacity; decisional capacity must be separately determined specific to the proposed medical intervention (although the presence of the commitment order as an index of psychiatric illness severity can be taken into account by the consultant).

Teaching Point

Each decisional capacity determination is *specific* to a warranted intervention for a clinical issue that occurs at a certain point in time; hence, it cannot be pronounced in an indefinite, "open-ended" way.

26.1.3 Psychosomatic Medicine in Geriatric Patients

Psychosomatic medicine consultations on older patients are often more complex than those accomplished on younger patients. In addition to the high rates of psychiatric comorbidity seen in all medical inpatients (the presence of which often renders the management of the comorbid medical/surgical illness more complicated), psychosomatic consultations on older patients need to also include evaluation for the neurocognitive disorders far more common in older patients.

A significant number of inpatient psychosomatic medicine consultations are for the medical complications of psychiatric illness and/or psychotropic medications. Specific conditions infrequently seen in psychiatric outpatient clinics, such as catatonia and delirium, are common in psychosomatic consultations; acute management of the presenting clinical problem in concert with care given by our medical/surgical colleagues in a comanagement approach of care is a model that promotes active consideration of the psychiatric comorbidity in medical/surgical presentations.

Moreover, the experience of delirium itself and the subsequent medical/surgical interventions often experienced as intrusive can reactivate traumatic manifestations in patients with prior history of posttraumatic stress disorder or be associated with the development of acute stress disorder in patients without a history of posttraumatic stress disorder. Post-delirium assessment (after the patient has recovered cognitive function) is recommended to screen for delirium and illness-specific traumatic syndromes. Thorough communication about the management of the patient's systemic medical and psychiatric illness in the general hospital with the patient's outpatient psychiatrist (and other clinicians) is crucial for ongoing aftercare of these patients. Trauma (physical and psychological), even if not clearly codified as acute stress disorder or posttraumatic stress disorder, often affects the whole person (see ▶ Chap. 14) and does not split the body into mind and body as in Cartesian dualism (see ◘ Figs. 26.1, 26.2 and 26.4). Therefore, the psychosomatic psychiatrist has a crucial role in reintegrating those dualities for the benefit of the patient's biopsychosocial healing following serious medical/surgical illness rendered even more complicated by the often painful and frightening experience of delirium. Examples of situations that could potentially reactivate trauma-based symptoms are listed in ◘ Table 26.2 and illustrated in ◘ Fig. 26.5. When these phenomena complicate a case of delirium, it is important to use trauma-informed care techniques (see ◘ Table 26.3) and give the patient and family (and, at times, the hospital staff members) an opportunity to process difficult experiences after the acute phase of delirium has been managed.

In general, comprehensive clinical interviews and diagnostic testing, routine use of cognitive assessment instruments, regular determination of decisional capacity following a systematic assessment protocol, and integration of clinical laboratory and diagnostic imaging data are routine elements in the integrated psychosomatic medicine consultation. Regular collegial interface with referring medical and surgical teams,

◘ **Table 26.2** Types of traumatic experiences that could reactivate trauma-based symptoms

Categories of triggers					
Transference	**Accident**	**Disfigurement**	**Invasive procedures**	**Experience of illness**	**Existential trauma**
Remnants of childhood trauma being reenacted in relationships with hospital staff due to regression in illness (PTSD/borderline-type dynamic)	Physical injury Urgent surgery Amputation	Mutilation due to illness Injury affecting body image	Intubation Arterial line chest tubes Urinary catheter Elective surgery or amputation	Symptoms of delirium itself (agitation, paranoia)	Confronting illness/ disability Impending death

Note: PTSD posttraumatic stress disorder

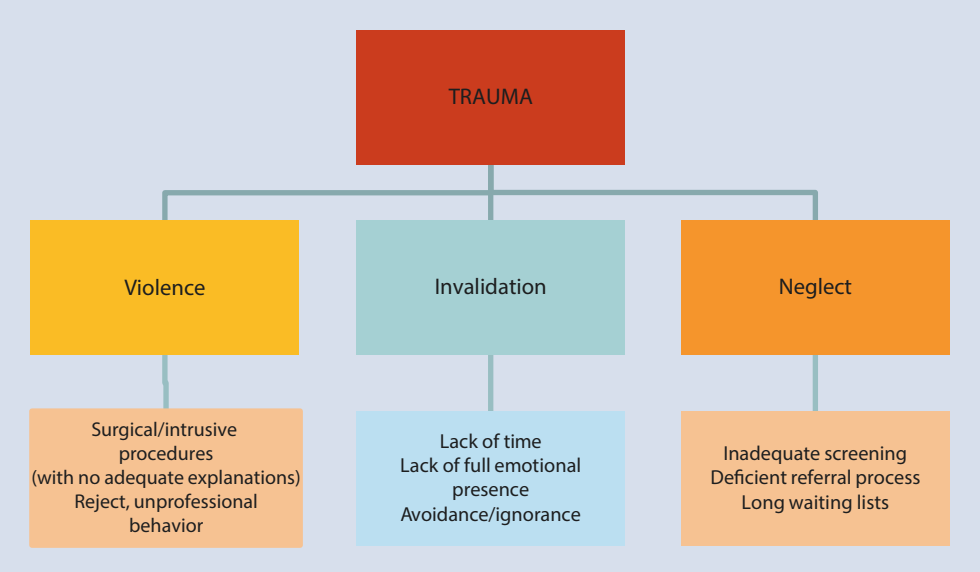

Fig. 26.5 Re-traumatization in medicine

Table 26.3 Examples of trauma-sensitive approaches

Intervention/procedure	Trauma-sensitive approaches
General assessment	Provide explanations (context of consultation, what to expect, how long it would take) Be attentive to signs of PTSD reactivation (e.g., dissociation, fear, autonomic response)
Physical exam	Explain all the steps Address environmental interference (e.g., adjust light and noise to take into account sensory impairment) Let the patient set the pace Monitor how the patient is doing Make necessary adjustments
Fostering sense of safety, trust, and alliance	Ask permission before touching Invite patient's questions Support, validation, reassurance (e.g., about confidentiality) Praise the patient's courage for sharing difficult stories Emphasize strengths (e.g., resilience, motivation to get better)

Note: PTSD posttraumatic stress disorder

frequent communication with nursing staff, and interface with outpatient treating physicians and other clinicians to facilitate proper transitions of care are essential elements of psychosomatic medicine practice. Given the typically greater illness burden and frequently increased social complexity with older patients, these areas are even more important in geriatric psychosomatic medicine practice.

26.2 Case Studies

This section presents two complex cases to illustrate the framework of psychosomatic medicine and various, illness-specific psychiatric interventions. The roles for psychosomatic medicine psychiatrists are also emphasized.

26.2.1 Case 1

Case 1 History

You are the psychosomatic medicine consultant urgently summoned to evaluate a patient in the ICU of a major academic medical center. Mr. G. is a 65-year-old man with a history of hepatitis C, alcohol-associated cirrhosis of the liver and subsequent hepatorenal syndrome. He has had no other major medical illnesses. Over several weeks, he developed life-threatening liver and kidney failure and needed to be managed with lactulose and hemodialysis, while awaiting liver and kidney transplant.

You learned that at a transplant psychiatry preoperative clinic evaluation by the psychosomatic medicine service 1 month preoperatively, he denied depressive, hypomanic or

manic, psychotic, or anxiety symptoms. He had no other psychiatric history except for a remote history of alcohol dependence, since in remission. He asserted insight into his alcoholism and had been abstinent for over 2 years, with regular attendance at a recovery program. He denied any other comorbid psychiatric illness.

His preoperative psychiatric evaluation had been unremarkable. His affect was non-tearful, non-labile, though he was understandably mildly anxious over the prospect of surgery. Thought process was linear and organized, albeit mildly circumstantial. His preoperative Hamilton Depression Inventory score was 10 (indicative of a subsyndromal phase for major depression); his ongoing low energy, poor appetite, and poor concentration (attributed to his progressive liver and kidney disease) accounted for 8 of these points. His preoperative MoCA score was 22 out of 30, with deficits in recall, attention, and concentration. He had some difficulties with reciting the months of the year backward. However, he was able to adequately understand his clinical illnesses, the rationale for the hepatic and kidney transplant, and the risks, benefits, and side effects of the surgical procedures and was able to rationally choose to proceed with surgery. He identified that his wife of 40 years would be his choice for surrogate decision-maker, should his capacity to make health-related decisions become impaired. His wife, who accompanied him to his preoperative transplant evaluations, readily decided to be available as a contingent surrogate decision-maker. He had a continued commitment to recovery and understood the need for lifelong immunosuppression postoperatively. He was able to describe adequate social and logistical support for the postoperative recovery period and had realistic expectations for the postoperative condition. He was thereafter cleared for transplant surgery.

He presented to the hospital for a planned simultaneous liver and kidney transplantation. The surgery was successful, albeit lengthy, and his immediate postoperative laboratory assessment was consistent with adequate graft function. He initially did well, but 2 days postoperatively, he developed symptoms consistent with hyperactive delirium, with altered sleep-wake cycle, fluctuating level of consciousness, motor agitation, and frightening paranoid delusions that the medical center staff members were trying to "eviscerate" him to steal his newly transplanted organs. He refused all medications (including his immunosuppressants) and water, fearing that they were "poisoned." Due to the abrupt change in mental status, a psychosomatic medicine consultation was thus ordered by the ICU team.

Teaching Point

Hyperactive delirium is characterized by restlessness, hypervigilance, rapid speech, irritability, and combativeness, whereas slowed speech and kinetics, apathy, and reduced alertness are manifestations of hypoactive delirium. Hypoactive delirium patients tend to have more severe cognitive disturbances and a poorer medical prognosis. There is a third category: mixed delirium which includes features from both hyperactive and hypoactive types. Delirium is frequent but often missed, especially the hypoactive type (see Table 26.4).

Table 26.4 Delirium subtypes

Hyperactive	Hypoactive
Restlessness/combativeness Hypervigilance Rapid speech Irritability	Psychomotor retardation Reduced alertness Slow speech Apathy
Mixed	

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What other information about this patient do you (as the psychosomatic medicine consultant) immediately need for your working diagnosis?

? Question 2. What other information about this patient do you need to make an accurate final diagnosis? What is your proposed intervention?

? Question 3. Would you allow Mr. G. to leave the hospital at his request at this time?

Case 1 Answers

Case 1 Answer 1 (Question 1—What other information about this patient do you (as the psychosomatic medicine consultant) immediately need for your working diagnosis?)

A thorough review of the patient's medical records, obtaining collateral information, and performing serial assessments are essential components. In this case, upon review of the patient's medical chart and obtaining collateral information from the ICU staff members, you learned that Mr. G. remained extremely agitated, confused, and uncooperative with the medical treatment. However, when the psychosomatic medicine service team sees him now several hours later after the request for consult was made, his behavior has changed significantly. On examination, he is no longer exhibiting agitation or paranoia. His eyes are open but he makes no eye contact and instead manifests a blank "vacant" stare apparently into the distance. He has no spontaneous speech and is largely nonverbal except for echolalia of the examiner's questions, which he would repeat perseveratively in an unemotional, monotone manner. He displays motor posturing in the form of tightly gripping his bedsheets in a non-purposeful manner and resists the examiner's attempts to move his upper extremities. He refuses meaningful interaction with the interviewer and has continued to refuse medications and water. He repeated (only in response to

questions and in a perseverative way) that he was "frightened" and that he had to "leave this place, right away. It is not safe here. They will get me for sure." Due to his fluctuating course of the presentation, a diagnosis of delirium was made. (See further ▶ Sect. 26.4.1, at MCQ 1 regarding diagnostic impressions in this case.)

Teaching Point
The fluctuating course of the presentation is a hallmark of delirium. The level of confusion or agitation can vary throughout the day. Hence, it is important to conduct serial assessments and review the medical records from the inpatient unit. (See ▶ Chap. 17, Delirium in Older Adults.)

Case 1 Answer 2 (Question 2—What other information about this patient do you need to make an accurate final diagnosis? What is your proposed intervention?)

Furthermore, the psychosomatic medicine consultant will need to review documentation of serial vital signs, laboratory and imaging results, as well as the medication list including recent addition or withdrawal of medications. You learned that Mr. G. was afebrile with normal blood pressure and pulse. Repeated laboratory tests of liver and renal function indicated that the grafts were continuing to function well, and serum ammonia level was normal. Complete blood count values showed mild anemia; thyroid function, serum calcium, and B_{12} level were normal. An urgently obtained non-contrast CT of brain was unremarkable. An ECG measurement of QTc was 475 milliseconds. Creatine phosphokinase was normal. For further investigations in this case, see ▶ Sect. 26.4.1 at MCQ 2 for the role of the electroencephalogram (EEG). Upon examination, you learned that Mr. G. could not orient to place or time (although he knew his own name), he could not complete any MoCA items, and he could not recite the months of the year in reverse, stating "December, January, December, January" in a perseverative manner. His presentation was consistent with a score of 14 on the Bush-Francis Catatonia Rating Scale (BFCRS), with findings in the areas of stupor, mutism, staring, posturing, echolalia, rigidity, and withdrawal (typically a score of 2 or more on the first 14 items is consistent with a diagnosis of catatonia).

Teaching Point
The preferred rating instrument for assessment of catatonia is the Bush-Francis Catatonia Rating Scale.

Catatonia is a neuropsychiatric syndrome with multiple signs. Catatonia was first described in 1863 by Karl Kahlbaum as "tension insanity" [2–6]. It was originally primarily (if not solely) regarded as a subtype of schizophrenia [3]. Later studies have shown its association with other antecedent psychiatric illnesses, notably depressive disorders [7, 8]. This appreciation of the diversity of associated psychiatric illness led to a change in nomenclature to where the previous *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV formally classified catatonia as a distinct syndrome, not merely a form of schizophrenia [9]. The DSM-5 has included it back in the section "schizophrenia spectrum and other psychotic disorders" [10].

Clinically, catatonia manifests with many neuromotor signs and symptoms, including mutism (the patient is awake but silent or with very limited speech), echophenomena (the patient repeats the examiner's words (echolalia) or movements (echopraxia)), other speech disorders such as verbigeration, foreign accent or "robotic" speech, stereotypy (the patient exhibits nonsensical, repetitive motor behavior), mannerisms (the patient engages in odd purposeful movements), ambitendency (the patient appears "stuck" in hesitancy to movement), negativism (the patient resists manipulations with strength equal to that applied by the examiner or retains urine or feces), posturing or "catalepsy" (the patient maintains postures for long periods of time, sometimes in strange and painful positions), and "waxy flexibility" (the patient initially resists the examiner's manipulations before gradually allowing reposturing) [9–12]. The patient must present three or more of the above symptoms to meet the DSM-5 criteria. (See further ▶ Sect. 26.4.1 at MCQ 3 for the rating instrument appropriate for more precise classification and monitoring in this case.)

Catatonia typically presents acutely in the setting of a preceding comorbid psychiatric illness (e.g., delirium, schizophrenia, mania, depression), suggesting that it is a final common pathway of severe psychiatric decompensation [13–17]. It is important to recognize the signs of catatonia as phenomenologically distinct from (if occasionally associated with) delirium, neuroleptic malignant syndrome, and schizophrenia, as clinical intervention for catatonia is specific and, if left untreated, the prognosis is poor. Anticonvulsant medications (benzodiazepines and barbiturates) and electroconvulsive therapy (ECT) are reliably effective treatments for catatonia; usually a trial of IV lorazepam is considered first-line empiric treatment [9, 18, 19]. If optimized and sufficiently aggressive lorazepam treatment is unsuccessful, ECT should be considered [9].

Untreated catatonia may become chronic and be associated with many potential complications [20]. Concurrent systemic medical illness may be diagnosed late because of the patient's nonverbal status. Aspiration pneumonia may be associated with a weak cough response and/or poor respiratory effort. Deep venous thrombosis may lead to life-threatening pulmonary emboli in the setting of prolonged immobility and dehydration. Malnutrition, urinary retention, and vaginal infections may follow. Flexion contractures, postural nerve palsies, and rhabdomyolysis may follow prolonged immobility.

In Mr. G.'s case, the interventions of lorazepam for catatonia and olanzapine for the agitation and paranoid delusions (consistent with hyperactive delirium) that preceded the decompensation into a catatonic episode were chosen for different if complementary psychiatric clinical indications.

While there was no clear evidence of a delirium-provocative metabolic disturbance, antipsychotic treatment for postoperative delirium antedating the onset of catatonia was indicated on empiric grounds. Due to the postoperative presentation, a full workup for delirium in parallel with delirium management is clearly indicated, even if there remains some doubt whether delirium was clearly causative of the catatonic episode, or if the patient was "just" acutely psychotic due to the stress of illness and surgery, because delirium is a serious (and potentially fatal) medical complication. If diagnostic clarity is needed to rule in delirium, then an EEG showing bilateral diffuse slowing would be confirmatory of delirium. The proposed interventions and treatment response in Case 1 are reemphasized and briefly summarized in the ▶ Sect. 26.4.1 at MCQ 4, MCQ 5, and MCQ 6.

Case 1 Answer 3 (Question 3—Would you allow Mr. G. to leave the hospital at his request at this time?)

Because of the impaired cognitive state and inability to accurately understand and appreciate his current medical situation, Mr. G. was determined to be of impaired decisional capacity to leave the hospital against medical advice (AMA).

Neurocognitive disorders (including delirium) are the most common psychiatric illness associated with impaired medical decisional capacity (the cognitive incapacity to accomplish medical informed consent) and impaired dispositional capacity (the cognitive incapacity to be safely discharged and self-manage outside of the hospital). In light of this, the psychosomatic medicine consultant is particularly likely to be called on to assess decisional capacity on an older medical/surgical inpatient. Often this issue will surface in the context of delirium management, when acute onset cognitive impairment may lead to patients having poor judgment about their needing to stay in the hospital for the very medical management that is necessary to improve the episode of delirium.

Case 1 Analysis Mr. G. was diagnosed with catatonia (temporally associated with initial postoperative delirium) and was treated with lorazepam 1 mg IV every 6 hours for catatonia and olanzapine 2.5 mg po at bedtime for underlying, associated delirium. Other routine delirium precautions (including avoidance of anticholinergics and opioids, monitoring of sleep-wake cycle, and promotion of sleep) were instituted. On postoperative day 3, he showed some improvement, with some fleeting eye contact, but he had no further motor posturing; he had some spontaneous speech and less frequent echolalia. His BFCRS was now positive on 4 items and improved from baseline. Lorazepam was cautiously increased to 2 mg IV every 6 hours.

By postoperative day 4, he answered "yes" and "no" appropriately and was now cooperative with taking medications, including his immunosuppressants. The following day, the catatonia had resolved; he was oriented and interactive without echolalia, posturing, agitation, or paranoia. His BFCRS was now 0. He now remembered having had the operation and recalled having felt "confused" afterward. He now had a normal sleep-wake cycle and no longer endorsed paranoid delusions. Lorazepam was tapered to 1 mg every 6 hours. On postoperative day 6, the patient continued to engage well and scored a 19 out of 30 on the MoCA. The MoCA was used to assess his cognitive function as part of the evaluation for possible residual delirium, as the catatonia had clearly resolved. Lorazepam was then discontinued. His laboratory studies continued to be consistent with intact graft function, and no other laboratory abnormalities were discerned. He was followed daily and eventually scored a 21 on the MoCA. He was debriefed about the symptoms of catatonia and delirium that he had experienced and counseled to the effect that, if in the future, he ever experienced such symptoms again, he should promptly seek care in the emergency department.

By postoperative day 9, there had been no further evidence of delirium, so the bedtime olanzapine was stopped with continued monitoring of motor and cognitive status. When he was discharged several days later in stable condition, the inpatient surgical team coded "Catatonia, resolved" and "Delirium, resolved" in the inpatient electronic medical record and arranged for direct communication with the patient's outpatient primary care physician for aftercare and continued surveillance of cognitive status.

Psychosomatic medicine psychiatrists treating organ transplant cases should be aware of the possibility of post-transplant catatonia, which may follow delirium or could possibly present discretely. Lorazepam may effect prompt relief of acute catatonia in the posttransplant patient. Patients need not have a history of premorbid psychiatric illness to be at risk. Whether this phenomenon is clearly associated with delirium or not is a matter of some speculation; in any case, surveillance for delirium needs to be considered in the context of catatonia presenting in the postoperative period or any other clinical context which places the patient at a high risk of delirium.

26.2.2 Case 2

Case 2 History

You are the psychosomatic medicine consultant who was asked to see Mr. X. on a medical ward for medical review of his lithium carbonate treatment. Mr. X. is a 67-year-old married white male, retired architectural engineer, with history of bipolar disorder, onset in his 20s, with several subsequent hospitalizations for manic and major depressive episodes. Early in the course of illness, he had comorbid alcohol use disorder and some periods of treatment nonadherence due to poor judgment and poor compliance. He was initially tried on courses of antipsychotic and antidepressant medications, but only had a partial response to this treatment. He had eventually stabilized on a trial of lithium carbonate and was thereafter managed with lithium carbonate monotherapy for 35 years, with monitoring of his lithium level every 6 months. He had no prior episodes of lithium toxicity. His lithium dose at time of this presentation is 1200 mg per day. He has been doing well without recent mood episodes for several years

and regular engagement in psychiatric care including medication management and supportive psychotherapy, emphasizing illness acceptance, relapse prevention, and medication adherence.

You learned that earlier today, he presented acutely to the emergency room with subacute onset of tremors, ataxia, and confusion. He was unable to give full details of his clinical history and had to rely on family members to render collateral history. There was no evidence to support medication misuse or toxic ingestions. He has not been using drugs or alcohol. He has recently been started on hydrochlorothiazide and a nonsteroidal anti-inflammatory drug (NSAID) for mild hypertension and osteoarthritis. Since these new medications were started, he has noted more frequent urination and greater thirst. He also had a history of coronary artery disease, smoking, and hyperlipidemia (managed with atorvastatin).

On evaluation, he denied mood symptoms suggesting a depressive or manic episode. He denied suicidal ideation, homicidal ideation, or hallucinations. Physical examination revealed low-amplitude coarse tremor of the hands, mild bilateral nystagmus, and mild vocal tremor. Vital signs were normal. He had mild ataxia and required assistance with ambulation. Mental status examination revealed anxious, non-tearful, non-melancholic, but mildly perplexed affect. His level of consciousness was full. He had minor motor restlessness without agitation (Richmond Agitation-Sedation Scale—RASS, +1). His thought process was mildly tangential with perseveration, but without disorganization. MoCA score was 16 out of 30 with notable deficits in attention, concentration, memory, and elements of orientation. He stated that he had to "leave this hotel right away, this is not the place for me, I want to go home." He was unable to appreciate that he was in a hospital and denied that there was anything wrong with him, saying repeatedly "I need to take more lithium, it always chills me out and calms me down."

His MRI of the brain revealed ventriculomegaly, diffuse cortical atrophy, and mild white matter vascular disease, without acute bleed or mass lesion. Laboratory studies revealed all elevated levels for creatinine of 1.6 mg/dL (141 μmol/L), lithium level of 2 mEq/L (2 mmol/L), sodium of 150 mEq/L (150 mmol/L), thyroid stimulating hormone (TSH) of 6 mIU/L, parathyroid hormone (PTH) of 103.7 pg/mL (11 pmol/L), and serum calcium of 10.4 mg/dL (2.6 mmol/L).

Case 2 Questions and Answers

Case 2 Questions

Question 1. What is the current psychiatric diagnosis?

Question 2. What is the recommended immediate clinical management in such cases?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is the current psychiatric diagnosis?)

For a list of differential diagnoses, please see discussion at ▶ Sect. 26.4.2, MCQ1. Mr. X. manifested symptoms of delirium, due to multiple etiologies, including hypernatremia (caused by diabetes insipidus), hypothyroidism, and hyperparathyroidism, all secondary to lithium toxicity. New exposure to diuretic and an NSAID, possibly on an underlying chronic renal insufficiency due to chronic use of lithium, were likely proximate causes of the apparent subacute to acute lithium toxicity in this case.

Acute lithium toxicity can present at any time during lithium treatment [21–23]. While purposeful lithium overdose (as a suicide attempt) must always be actively considered, acute toxicity can be due to the addition of new, renally active medications (e.g., NSAIDs, diuretics) and/or environmental considerations (e.g., dehydration due to climate/exertion, failure to maintain adequate oral hydration). Acute lithium toxicity can present "atop" chronic lithium toxicity, with a gradual increase in serum creatinine over time due to long-term exposure to lithium [21–23]. Lithium toxicity often presents with psychiatric (delirium), neurologic (tremor/ataxia), cardiac (conduction system disease), and endocrinologic (hyperparathyroidism and/or hypothyroidism) manifestations [21–24].

Case 2 Answer 2 (Question 2—What is the recommended immediate clinical management in such cases?)

Mild degrees of lithium toxicity can be managed safely by discontinuing lithium and instituting aggressive fluid and electrolyte management with regular monitoring of lithium level, renal panel, and volume status. For lithium levels significantly above 2 mEq/L, especially if the patient has neurologic and cardiac complications, hemodialysis is often indicated. For this determination, a prompt consultation with a nephrologist is needed. Cases of lithium toxicity with delirium but without other significant neurologic signs and without cardiac conduction disease may not necessarily need hemodialysis, if the lithium level can be promptly decreased with medical management [21–24].

Older patients with long lifetime exposure to lithium who present with lithium toxicity should be actively considered for alternative therapy for bipolar disorder. Even after the acute management of lithium toxicity is accomplished, and the patient has validated lithium level of 0 mEq/L with normal range of serum creatinine and sodium, continued vigilance for the syndrome of lithium-effectuated neurotoxicity (SILENT) is needed. Such patients have persistent (sometimes irreversible) motor symptoms (primarily reflecting cerebellar impairment and central pontine myelinosis with ataxia, dysarthria, extrapyramidal symptoms, and major neurocognitive disorder) even in the absence of ongoing acute lithium toxic states [25]. Risk for SILENT is unclear, as is prognosis; at the very least, any patient presenting with symptoms at all suggestive of SILENT should never be exposed to lithium again, irrespective of the status of their bipolar disorder or recovery of intact renal function.

Valproate is the usual first alternative medication for acute and chronic management of bipolar disorder. In

patients with normal liver and hematologic function, it is usually well tolerated. However, in some patients, more likely in patients with (often subtle) disorders of urea cycle enzyme function, it is associated with hyperammonemia, which may present as delirium, typically without hepatotoxicity [26–29]. The risk of valproate-associated hyperammonemia is not sufficiently high such that routine pretreatment screening of serum ammonia levels is routinely accomplished. However, due to the risk of hyperammonemic delirium presenting in this context, valproate-treated patients should have ammonia routinely assessed and monitored when presenting with delirium. Patients presenting with delirium in this context need to have valproate discontinued immediately and alternative therapy for delirium and bipolar disorder initiated (typically with atypical antipsychotics), while recovery of normal serum ammonia levels is documented.

Delirium in the context of valproate may also reflect hematologic (thrombocytopenia) and pancreatic (medication-induced pancreatitis) effects of valproate; any patient on valproate therapy who presents with unexplained thrombocytopenia, abdominal pain or a gastrointestinal complaint, and/or delirium should have these possibilities evaluated.

With geriatric presentations of patients with long-term chronic psychiatric illness, physiological changes associated with aging may have the consequence of rendering previously well-tolerated psychotropic medications to become unsafe. The example of an older patient managed with chronic lithium therapy illustrates this well. There may come a time when the patient's chronic psychotropic medication management needs to be modified in the face of age-related changes in medication metabolism, as opposed to any change in the therapeutic efficacy. See ▶ Sect. 26.4.2, MCQ 2 and MCQ 3 which describe the recommended immediate course of action for the patient in Case 2.

Case 2 Analysis Mr. X. was diagnosed with delirium, due to hypernatremia (caused by diabetes insipidus), hypothyroidism, and hyperparathyroidism, all secondary to lithium toxicity. Proximate causes of apparent subacute to acute lithium toxicity in this case included new exposure to diuretic, NSAID, and rule out chronic renal insufficiency due to chronic use of lithium.

He was admitted to intensive care unit. Lithium was held and he was treated with fluid management, empiric valproic acid 10 mg/kg/24 hour (both to manage acute delirium and to serve as loading dose of an alternative therapy for bipolar disorder). Serum lithium levels and renal panels were assessed every 6 hours for the first 72 hours of hospitalization. Within 3 days, lithium level had reached 0 mEq/L, sodium level had renormalized, creatinine had decreased to 1.3 mg/dL (114.9 μmol/L), calcium had normalized, and TSH had decreased to 5 mIU/L, still mildly elevated. His tremor and ataxia had improved significantly and he was no longer agitated.

However, now he experienced lethargy and continued confusion. RASS had changed to −1 (drowsy). MoCA was still in the impaired range, at 18, and was effortfully completed due to his lethargy. Additional laboratory evaluation at this time revealed an elevated blood ammonia of 98 mcg/dL (69.9 μmol/L), liver function tests were normal, platelets were normal, and serum valproate level was 52 mcg/mL (360 μmol/L) (within the therapeutic range). He was now diagnosed with hypoactive delirium and hyperammonemia due to valproate. He was then immediately switched from valproate to risperidone 1 mg po bid. Within 7 additional days, he was no longer lethargic and his level of consciousness was full during the day. He by that time had a normal sleep-wake cycle. Repeated laboratory studies showed that the ammonia was improved to 39 mcg/dL (27.8 μmol/L) and MoCA had improved to 24. Renal and hepatic function remained stable. He was discharged in stable condition on risperidone maintenance for outpatient care of this bipolar disorder.

26.3 Key Points: Psychosomatic Medicine/ Consultation-Liaison Psychiatry in Late Life

- Psychosomatic medicine consultations on older patients are often more complex than those accomplished on younger patients.
- Inpatient psychosomatic medicine consultations represent a significant number of the referrals for the medical complications of psychiatric illness and/or psychotropic medications.
- Specific conditions infrequently seen in psychiatric outpatient clinics, such as catatonia and delirium, are common in psychosomatic consultations; acute management of the presenting clinical problem in concert with care given by medical/surgical specialist is the comanagement approach of care model.
- In addition to the high rates of psychiatric comorbidity seen in all medical inpatients, psychosomatic consultations on older patients need to also include evaluation for the neurocognitive disorders far more common in older patients.
- Neurocognitive disorders, particularly delirium, are the most common neuropsychiatric illness associated with impaired medical decisional capacity and impaired dispositional capacity. In light of this, the psychosomatic medicine consultant is particularly likely to be called on to assess decisional capacity on an older medical/surgical inpatient.
- Often decisional capacity and impaired dispositional capacity questions will occur in the context of delirium management, when acute onset cognitive impairment may lead to patients having poor judgment about their needing to stay in the hospital for the medical management that is necessary to improve the episode of delirium.
- The experience of delirium itself and the subsequent medical/surgical interventions often experienced as intrusive can reactivate traumatic manifestations in

patients with prior history of posttraumatic stress disorder or be associated with the development of acute stress disorder in patients without a history of posttraumatic stress disorder. Post-delirium assessment is recommended to screen for delirium and illness-specific traumatic syndromes.

26.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

26.4.1 For the Following MCQs, Consider the Patient in Case 1 Presentation

MCQ 1. What is the likely diagnosis of this presentation?
A. Catatonia
B. Delirium and catatonia
C. Acute onset psychotic disorder
D. Acute stress disorder
E. Major depression with melancholic, psychotic, and catatonic features

Answer: B

Sequence of events most suggests initial delirium complicated by catatonia; therefore, the correct answer is B.

MCQ 2. What laboratory and other investigations would confirm a diagnosis of delirium?
A. Blood and urine cultures
B. Wound cultures
C. Magnetic resonance imaging (MRI) of brain
D. Electroencephalogram (EEG)
E. Lumbar puncture

Answer: D

While not essential for diagnosis, EEG revealing bilateral diffuse slowing without seizure focus would rule in delirium, while catatonia per se does not have a characteristic EEG. If it is problematic to obtain an EEG, empiric medication treatment of catatonic delirium (see MCQ 3 below) should commence without delay; therefore, answer D is correct.

MCQ 3. What rating instruments are appropriate for more precise classification and monitoring of this case?
A. Bush-Francis Catatonia Rating Scale (BFCRS)
B. Delirium Rating Scale (DRS)
C. Richmond Agitation-Sedation Scale (RASS)
D. Montreal Cognitive Assessment (MoCA)
E. Hamilton Depression Inventory (Ham-D)

Answer: A

The BFCRS is most specific for the catatonia; however, the DRS and RASS may also be helpful. He could not complete the MoCA (which has limited specificity and value at extremely low levels of cognitive function), and Ham-D requires a fully verbal patient. Therefore, the correct statement is A.

MCQ 4. What is your initial proposed intervention? (May choose more than one answer.)
A. Continued delirium precautions
B. Continued delirium workup
C. Trial of antipsychotic medication
D. Trial of lorazepam
E. Electroconvulsive therapy (ECT)

Answer: A, B, C, D

Several things need to happen in concert. Empiric trial of lorazepam (details at MCQ 5 and MCQ 6) is indicated for any catatonia presentation, irrespective of likely mechanism. Given post-op setting, severe antecedent illness and initial mental status presentation before onset of catatonia, delirium precautions (e.g., avoidance of anticholinergics and opioids, monitoring of sleep-wake cycle), and delirium intervention (judicious use of antipsychotic) are indicated along with catatonia management. While sometimes proposed as an initial intervention for catatonia, ECT is more customarily reserved for cases unresponsive to initial trials of lorazepam. Therefore, the correct statements are A, B, C, and D.

MCQ 5. How will you judge initial treatment response? (May choose more than one answer.)
A. Change in catatonic behavior
B. Improved Bush-Francis Catatonia Rating Scale (BFCRS) score
C. Ability to complete MoCA
D. Ability to complete other bedside cognitive tests

Answer: A, B

First likely changes in response to trial of lorazepam would be a change in overt catatonic behavior, sometimes from the first few doses, especially in cases with acute onset of catatonia which are promptly evaluated. Following such response to the lorazepam, with resolution of the catatonia episode, the patient in Case 1 may well still be delirious, so improvement in actual cognitive status may be delayed as the delirium more gradually resolves with management. Therefore, the correct answer is A and B.

MCQ 6. In the following options, what is the most likely recommended starting dose for lorazepam in the treatment of catatonia?
A. 1 mg PO q6h
B. 1 mg SC q6h
C. 1 mg IM q6h
D. 1 mg IV q6h
E. 0.25 mg IV q6h

Answer: D

Benzodiazepines are the first-line of treatment for catatonia. Efficacy of benzodiazepines in catatonia is dose dependent. Lorazepam is generally accepted to be the first-choice agent. Most clinicians recommend starting lorazepam at 1–2 mg IV at least every 4–6 hours, with daily incremental dosages in order to improve catatonia without sedating the patient. Lower initial and subsequent dosages may be necessary for older patients. Patients should be monitored carefully for excessive sedation, respiratory depression, and risk for falls especially if high doses of lorazepam are used. With an adequate dose, response is usually seen within 3–7 days; however, in some cases response can be gradual and slow. Chronic catatonia may respond over days or months, rather than hours. Benzodiazepines are generally discontinued once the underlying illness has remitted. In a number of cases, catatonic symptoms can reemerge each time lorazepam is tapered off, suggesting the need for continuation of benzodiazepines for an extended period of time. Because the dose in statement E is not nearly enough, whereas the route of administration in statements A, B, and C is non-intravenously, the correct answer is statement D.

26.4.2 For the Following MCQs, Consider the Patient in Case 2 Presentation

MCQ 1. What is the current psychiatric diagnosis?

A. Vascular major neurocognitive disorder due to multiple vascular risk factors
B. Bipolar disorder, current episode manic
C. Bipolar disorder, current episode depressed
D. Delirium due to hypothyroidism
E. Depressive episode due to hypothyroidism
F. Delirium due to lithium toxicity

Answer: F

Combined altered attention, psychotic symptoms, and diminished cognitive status in the face of clearly explanatory metabolic disturbances are classic features for delirium. Recall that any mood symptom can present in delirium. While alterations in thyroid and parathyroid status may themselves cause delirium, the acute lithium toxicity and its direct central nervous system (CNS) effects are most likely explanatory. Therefore, the correct answer is F.

MCQ 2. What is the recommended immediate clinical management?

A. Taper lithium, see him in psychiatry clinic to manage on a lower lithium dose.
B. Discontinue NSAID, recheck lithium level in 1 week, readjust lithium dose as needed.
C. Discontinue hydrochlorothiazide, recheck lithium level in 1 week, readjust lithium dose as needed.
D. Perform MRI, carotid Doppler, lipid profile to more fully evaluate vascular major neurocognitive disorder.
E. Admit to hospital to manage lithium toxicity and delirium.

Answer: E

Due to the high lithium level, which may increase further before down-trending, he needs admission for aggressive fluid and delirium management. The decision to consider hemodialysis will be based on the degree of CNS and/or cardiac impairment in most cases. Therefore, the correct answer is E.

MCQ 3. What is the cause of his tremor and ataxia?

A. Subcortical vascular major neurocognitive disorder
B. Cerebellar vascular major neurocognitive disorder
C. Peripheral neuropathy
D. Hypothyroidism
E. Hyperparathyroidism
F. Lithium toxicity

Answer: F

Since these motor symptoms are due to cerebellar effects of lithium, they are likely proportional to the degree of lithium toxicity affecting neural tissue directly. Delirium from other causes does not specifically affect cerebellar function this way, although there are other examples of this effect in specific delirium syndromes (e.g., phenytoin toxicity). Serial assessment of these motor findings may reveal improvement in tremor and ataxia as serum lithium level decreases. Thus, the correct statement is F.

26.4.3 Additional Comprehension Multiple Choice Questions

MCQ 1. What are the most common endocrinologic abnormalities in lithium therapy?

A. Hyperthyroidism and hyperparathyroidism
B. Hypothyroidism and hypoparathyroidism
C. Hypothyroidism and hyperparathyroidism
D. Hyperthyroidism and pseudohyperparathyroidism
E. Hypothyroidism and pseudohyperparathyroidism

Answer: C

MCQ 2. What is the acute management of lithium toxicity presenting with delirium and ataxia?

A. Taper lithium and monitor psychiatric and neurologic status.
B. Immediately hold lithium, admit to hospital, fluid management, monitoring of electrolyte, psychiatric, and neurologic status.
C. Remove comorbid medications (e.g., NSAIDs, diuretics) while maintaining lithium therapy.
D. Continue lithium, and add antipsychotic for delirium and beta blocker for tremor.
E. Do not change medications initially but actively hydrate and reassess.

Answer: B

MCQ 3. What is the recommended next step for management of bipolar disorder in an older patient who has recovered from an episode of lithium toxicity but still has impaired renal function?

A. Lithium therapy at a lower dose
B. Resumption of full dose lithium with more frequent monitoring
C. Antipsychotic or anticonvulsant
D. Electroconvulsive therapy
E. Transcranial magnetic stimulation

Answer: C

MCQ 4. What is the recommended routine monitoring in an uncomplicated case for valproate therapy in bipolar disorder?

A. Liver-associated enzymes, complete blood count, serum valproate level
B. Pancreatic enzymes, liver-associated enzymes, complete blood count
C. Ammonia, serum valproate level, and complete blood count
D. Abdominal ultrasound, liver-associated enzymes, valproate level

Answer: A

MCQ 5. If a patient maintained on valproate presents with apparent delirium, what laboratory studies need to be prioritized in the delirium workup?

A. Liver-associated enzymes
B. Complete blood count
C. Ammonia level
D. Serum valproate level
E. All of the above

Answer: E

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Aging with Intellectual and Developmental Disabilities

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27.1 Background

27.1.1 Intellectual and Developmental Disabilities

27

Terms and trends are ever-changing in the field of what is now referred to as intellectual and developmental disabilities (IDD). IDD is an internationally recognized term to describe conditions of cognitive and/or physical disability, with significant impairments in adaptive functioning and onset in the developmental period (generally prior to age 18, though DSM-5 does not specify). Those who live with IDD have typically been through assessment processes to provide diagnoses based on specified criteria. Two of the most widely used classification systems of psychiatric disorders are the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) [1], and the *International Classification of Diseases*, 10th revision (ICD-10) [2]. Both serve as classification and diagnostic tools to facilitate more standard and reliable descriptions of psychiatric disorders. Diagnostic criteria have been generated by expert committees to provide not only more consistency with identification but also improved international communication about conditions and clarity in research. Diagnostic systems and manuals for psychiatric conditions have limitations. Syndromes are defined by diagnostic criteria based on signs/behavioral descriptors and symptoms; the diagnostic categories are not etiologically driven; there is overlap among syndromes with features shared by non-disordered individuals. Diagnostic categories and criteria may also change over time. The DSM-5 is most widely used in North America. There is acknowledgment of the importance of underlying biological, psychological, developmental, and social contextual variables in the assessment and care of the individual with a psychiatric disorder. Indeed, a biopsychosocial model is required to assess and address biological-psychological-social domains that can affect well-being. The DSM-5 provides specifiers in recognition that individuals will vary in severity or complexity of features, though not specifically describing relationship to aging or stages of development.

The DSM-5 uses neurodevelopmental disorders as an overarching category, with subtypes including [1]:

- Global developmental delay
- Intellectual disability (ID)
- Communication disorders
- Autism spectrum disorder (ASD)
- Attention-deficit/hyperactivity disorder
- Specific learning disorder
- Motor disorders
- Other neurodevelopmental disorders

Neurodevelopmental disorders are characterized by the onset of symptoms during the early developmental/growth period and are considered lifelong disabilities. These disorders can affect a variety of realms of functioning (e.g., learning ability, executive functioning, self-control, memory, emotion regulation, social skills), which unfold throughout development. This chapter will review neurodevelopmental disorder subtypes of ID and ASD focusing on aging issues and practical assessment approaches for medical and allied health clinicians. The DSM-5 neurocognitive disorders (formerly dementias) will also be referenced with special considerations for those with ID associated with the genetic phenotype of trisomy 21 (Down syndrome).

Intellectual Disability

Intellectual disability (ID) has been preceded by nomenclature that has been abandoned because of improved understanding of conditions or pejorative use of terms (i.e., idiocy, feeblemindedness, imbecility, mental retardation, handicapped). In the eighteenth and nineteenth centuries, institutionalization was presented as a medicalized treatment solution. During the institutional era, habilitative aims were often compromised by overcrowding, various forms of neglect or abuse, and inadequate or overuse of medication. Furthermore, individuals with disabilities had shorter life expectancy [3].

ID is characterized in DSM-5 by significantly below-average intelligence and significant impairments in skills necessary for day-to-day living (adaptive skills). With the DSM-5, intellectual quotient (IQ) is no longer central to the severity levels (mild, moderate, severe, and profound). According to the DSM-5, diagnosis of ID rests on identification of deficits in general mental abilities (intellectual functioning) with impairments in adaptive skills. Intelligence encompasses cognitive abilities to learn, reason, make decisions, plan, solve problems, and think abstractly. Adaptive skills in three domains are considered necessary for day-to-day functioning: conceptual (communication, self-direction, planning, organizing), social (self-regulation, interpersonal communication, social judgment), and practical (community use, home living, self-care, health, and safety). It is recognized that those with ID can and do learn; however, the mode, rate, and types of learning vary. Formal assessments are used to elucidate the pattern of strengths and weaknesses in order to optimize autonomy and match appropriate supports and services. In some cases individuals with ID present with a "cloak of competence": those with sufficient expressive skills present with a façade suggesting capacity beyond their cognitive and adaptive skills. Although ID is considered a lifelong disability, functioning can be helped by individualized supports or hindered by unsuitable expectations at any given stage of life. Diagnostic criteria must be met for DSM-5 diagnosis of ID (see Table 27.1).

Autism Spectrum Disorder

As with ID, terms for autism spectrum disorder (ASD) have evolved: autistic disorder of affective contact [4], childhood-onset schizophrenia [5], pervasive developmental disorder with subcategories of autistic disorder, and Asperger syndrome [6]. In the DMS-5 [1], diagnoses previously under the umbrella term pervasive developmental disorder fall under the heading of ASD. The term ASD and current DSM-5 criteria are the latest attempts to describe syndromic impairments. DSM-5 eliminated subcategories and collapsed the previous triad of social, communication, and behavioral

Table 27.1 DSM-5 diagnostic criteria for intellectual disability [1]

Intellectual disability (intellectual developmental disorder)	
Diagnostic criteria	
Intellectual disability (intellectual developmental disorder) is a disorder with onset during the developmental period that includes both intellectual and adaptive functioning deficits in conceptual, social, and practical domains. The following three criteria must be met:	
A. Deficits in intellectual functions, such as reasoning, problem solving, planning, abstract thinking, judgment, academic learning, and learning from experience, confirmed by both clinical assessment and individualized, standardized intelligence testing	
B. Deficits in adaptive functioning that result in failure to meet developmental and sociocultural standards for personal independence and social responsibility. Without ongoing support, the adaptive deficits limit functioning in one or more activities of daily life, such as communication, social participation, and independent living, across multiple environments, such as home, school, work, and community	
C. Onset of intellectual and adaptive deficits during the developmental period	
Note: The diagnostic term *intellectual disability* is the equivalent term for the ICD-10 diagnosis of *intellectual developmental disorders*. Although the term *intellectual disability* is used throughout this manual, both terms are used in the title to clarify relationships with other classification systems. Moreover, a federal statute in the United States (Public Law 111–256, Rosa's law) replaces the term *mental retardation* with *intellectual disability*, and research journals use the term *intellectual disability*. Thus, *intellectual disability* is the term in common use by medical, educational, and other professions and by the lay public and advocacy groups.	
Specify current severity:	
317 (F70)	*Mild*
318.0 (F71)	*Moderate*
318.1 (F72)	*Severe*
318.2 (F73)	*Profound*
Specifiers may also be used that enrich the clinical description. In addition to severity ratings, specifiers may include age of onset, associated medical (e.g., seizure disorder) and genetic (e.g., trisomy 21) conditions or environmental factors (e.g,. low birth weight).	

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impairments into two domains (social communication and/or interaction plus restricted and/or repetitive behaviors) (see Table 27.2). This edition of DSM added hyper- or hyporeactivity to sensory input or unusual interests in sensory aspects of the environment. ASD is acknowledged as a spectrum syndrome that encompasses tremendous heterogeneity of the presenting symptoms, etiologies, comorbidities, and developmental trajectories.

Table 27.2 DSM-5 diagnostic criteria for autism spectrum disorder [1]

Autism spectrum disorder
Diagnostic criteria
A. Persistent deficits in social communication and social interaction across multiple contexts, as manifested by the following, currently or by history (examples are illustrative, not exhaustive, see text):
1. Deficits in social-emotional reciprocity, ranging, for example, from abnormal social approach and failure of normal back-and-forth conversation, to reduced sharing of interests, emotions, or affect, to failure to initiate or respond to social interactions
2. Deficits in nonverbal communicative behaviors used for social interaction, ranging, for example, from poorly integrated verbal and nonverbal communication, to abnormalities in eye contact and body language or deficits in understanding and use of gestures, to a total lack of facial expressions and nonverbal communication
3. Deficits in developing, maintaining, and understanding relationships, ranging, for example, from difficulties adjusting behavior to suit various social contexts, to difficulties in sharing imaginative play or in making friends, to absence of interest in peers
Specify current severity:
Severity is based on social communication impairments and restricted, repetitive patterns of behavior
B. Restricted, repetitive patterns of behavior, interests, or activities, as manifested by at least two of the following, currently or by history (examples are illustrative, not exhaustive; see text):
1. Stereotyped or repetitive motor movements, use of objects, or speech (e.g., simple motor stereotypes, lining up toys or flipping objects, echolalia, idiosyncratic phrases)
2. Insistence on sameness, inflexible adherence to routines, or ritualized patterns of verbal or nonverbal behavior (e.g., extreme distress at small changes, difficulties with transitions, rigid thinking patterns, greeting rituals, need to take same route or eat same food every day)
3. Highly restricted, fixated interests that are abnormal in intensity or focus (e.g., strong attachment to or preoccupation with objects, excessively circumscribed or perseverative interests).
4. Hyper- or hypoactivity to sensory input or unusual interest in sensory aspects of the environment (e.g., apparent indifference to pain/temperature, adverse response to specific sounds or textures, excessive smelling or touching of objects, visual fascination with lights or movement)
Specify current severity:
Severity is based on social communication impairments and restricted, repetitive patterns of behavior
C. Symptoms must be present in the early developmental period (but may not become fully manifest until social demands exceed limited capacities or may be masked by learned strategies in later life)

(continued)

Table 27.2 (continued)

Autism spectrum disorder
D. Symptoms cause clinically significant impairment in social, occupational, or other important areas of current functioning
These disturbances are not better explained by intellectual disability (intellectual developmental disorder) or global developmental delay. Intellectual disability and autism spectrum disorder frequently co-occur; to make comorbid diagnoses of autism spectrum disorder and intellectual disability, social communication should be below that expected for general developmental level
Note: Individuals with a well-established DSM-IV diagnosis of autistic disorder, Asperger disorder, or pervasive developmental disorder not otherwise specified should be given the diagnosis of autism spectrum disorder. Individuals who have marked deficits in social communication, but whose symptoms do not otherwise meet criteria for autism spectrum disorder, should be evaluated for social (pragmatic) communication disorder
Specify if:
With or without accompanying intellectual impairment
With or without accompanying language impairment
Associated with a known medical or genetic condition or environmental factor
Associated with another neurodevelopmental, mental, or behavioral disorder
With catatonia

Note: Reprinted with permission from the American Psychiatric Association [1]

Typically ID and ASD are diagnosed during childhood years. ID has been long recognized (albeit by other terms) and generally readily identified where there are developmental delays or more obvious physical, cognitive, communication, and behavioral features. Distinguishing features and subtypes of ID have continued to evolve [7]. Similarly, ASD is increasingly being recognized as important to characterize so as to provide suitable interventions [8]. ASD encompasses a broad array of individual presentations and etiologies. ASD may not be accompanied by developmental delays or ID. Where there are no apparent developmental delays, the ASD syndrome may be recognized later in childhood (e.g., school-age children where social communication differences become more obvious or even in adolescence or adulthood). Some cases of ASD come to light when a family member is diagnosed [9, 10] and there is occasion to look back at family history with phenotypic patterns of communicating, relating, and behaving.

Retrospective verification of ASD can be challenging as the diagnosis rests on knowledgeable informants providing early developmental history as part of interdisciplinary assessment of cognitive, adaptive, and behavioral features over time. Other confounding variables include lingering effects of traumatic events (e.g. posttraumatic stress disorder), confusion with other neurodevelopmental disorders (e.g., attention-deficit/hyperactivity disorder, learning disabilities, social communication disorder), or other childhood-onset psychiatric disorders (e.g., social anxiety disorder, obsessive-compulsive disorder, depressive disorders). These disorders can coexist with ASD or present with features of ASD. Similarly, psychotic-spectrum disorders like schizophrenia may present with similar features or be comorbid with the syndrome of ASD [11]. Even though ASD diagnostic tools are generally developed for children, and adult IDD specialty services are typically sparse, clinicians with expertise in ASD can make the diagnosis if informants can provide valid early histories (medical, developmental, psychological, social).

27.1.2 Aging Issues

Considerations can be both general (to aging) and specific (ID and ASD). Aging is inevitable; it involves decline in various realms of functioning (including neurological) and it is developmental. Indeed, aging itself could be considered a neurodevelopmental condition. With clinical advances (e.g., genetics, medical investigations, treatments) and appreciation for psychosocial support needs, individuals diagnosed with ID and/or ASD now have life expectancies approaching averages for the normative aging population [12, 13]. With advancing age, individuals with IDD can experience the same age-related physical changes and medical and neurocognitive conditions as the general population. Some live with family members who themselves are faced with age-related changes on top of increasing support needs for their dependents [13]. Pressures extend to social services with increasing demands for suitable residential and day supports.

The aging ID population has been found to be more susceptible to major neurocognitive disorders (NCD), commonly referred to as dementia. The emergence of NCD may be masked by an individual's baseline cognitive and speech language deficits. NCD-related comorbidities may be more difficult to detect or differentiate from various baseline conditions (e.g., seizures, incontinence, gait disturbance, respiratory problems, depression), and cardiovascular disease is at least as common in the IDD population as in the general population [13]. Some risk factors vary with the individual's level of independence or types of support they receive (e.g., smoking, substance use, physical activity). Other risk factors depend more on intrinsic factors such as genetics.

Trisomy 21, also known as Down syndrome, has been the most common chromosomal cause of ID with a well-described phenotype. Adults with Down syndrome are at particular risk for earlier onset and more rapid decline in cognitive and adaptive functioning [2, 13–15]. The increased risk of Alzheimer-related NCD with Down syndrome is in part explained by the extra 21st chromosome (trisomy 21) resulting in overexpression of the amyloid precursor protein gene [16]. The prevalence rate of Alzheimer disease in people with

Down syndrome increases significantly with age. Alzheimer-related neuropathological findings (senile plaques and neurofibrillary tangles) are evident by the 30s, although expression varies from no apparent manifestations to Alzheimer disease features appearing in the fourth and fifth decades [15, 16]. The initial presentation typically involves changes in behavior and personality (functions served by the frontal lobes) followed by other global neurocognitive deficits typical of Alzheimer disease [15] (see ▶ Chap. 18, Major or Mild Neurocognitive Disorder due to Alzheimer Disease). Despite the lack of compelling randomized controlled trials of efficacy for cholinesterase inhibitors, it is noted they are often well tolerated and, with the appropriate precautions and specialty consultation (e.g., neurology, geriatrics, psychiatry), could be considered for adults with Down syndrome and Alzheimer disease [17].

Declines in cognitive and/or adaptive function in adults with Down syndrome or ID may be presumptively attributed to NCD or specifically Alzheimer disease when other treatable disorders are contributing to the presentation (e.g., infections, hypothyroidism, B_{12} deficiency, malnutrition, impaired vision or hearing, depressive disorders, medication side effects, sleep apnea) [18]. Circadian sleep-wake rhythm problems can also exacerbate cognitive, emotional, and adaptive functioning in older adults with ID [19]. There may also be syndrome-specific medical conditions that are chronic (e.g., supravalvular aortic stenosis and pulmonary hypertension with Williams syndrome) or episodic (e.g., hypocalcemia with 22q11.2 deletion syndrome). Too often these conditions go unrecognized and untreated [13].

Changes in behavior, personality, and cognition as individuals with IDD age require special attention. In addition to normal aging, people with ID and ASD face further challenges. Those who either cannot express themselves or identify their symptoms due to a lack of insight or poor expressive skills are often misunderstood [20], especially by clinicians and care providers who do not know them. Most studies find that behavioral disorders are more common in the ID population [21]. The trend toward overuse of antipsychotics for behavior disorders in ID and ASD has prompted an urgent emphasis on the need for interdisciplinary interventions as well as research around adverse events and effects of long-term use [21–25].

Although there is growing interest in aging with ID [25], there is scant literature specifically related to individuals with ASD who are aging, and descriptions in the literature are inconsistent. A growing body of evidence suggests that some behavioral problems diminish with age in individuals diagnosed with ASD [26, 27]; however, severity of ID and co-occurring diagnoses influence these changes [28]. Studies on brain structures in individuals diagnosed with ASD [29] and quality of life of aging individuals diagnosed with ASD have been conducted; however, no generalizations can be made [30]. Given the changing diagnostic criteria and significant gaps in knowledge, more research aimed at epidemiology, biological, psychological, and social issues for an aging ASD population will be important for meeting support and service needs [30].

Risk factor awareness and access to suitable healthcare services for the aging population is an important emphasis of the National Task Group on Intellectual Disabilities and Dementia Practices [31]. The National Task Group offers an evidence-based prospectus to guide caregivers who interface with healthcare providers. There is recognition of difficulty accessing timely specialty IDD or geriatric clinics, delaying identification of medical and neuropsychiatric (including neurocognitive) disorders. Consensus and evidence-based primary care practice guidelines for IDD have been developed in Canada [32] and for the United States [33].

27.1.3 Etiology and Comorbidities

ID and ASD include individuals with diverse biological and environmental influences on their development. Etiologies and influences can be grouped under four broad headings: prenatal (e.g., fetal alcohol syndrome, malnutrition, TORCH infections), genetic (e.g., Down syndrome, fragile X syndrome, 22q11.2 deletion syndrome), perinatal (e.g., hypoxia, extreme premature birth), and postnatal (e.g., meningitis/encephalitis, traumatic brain injury). Many of these conditions are well described with the recommended investigation or treatment guidelines [32, 33].

Comorbidities (systemic medical and neuropsychiatric conditions) are much more common among individuals with IDD compared to the general population. It is well known that adults with IDD experience poorer health outcomes (mortality, morbidity, and quality of life) [12, 34]. Reasons for the adverse health outcomes include barriers to satisfactory healthcare (e.g., communication, physical, access, attitudinal) and healthcare providers recognizing they are inadequately trained to care for their specific needs [35]. People with IDD, when they become patients, require high-quality healthcare that meets their unique needs. Where disabilities or behaviors become the sole focus in the medical encounter, inappropriate treatments may result. Of particular note is the high rate of psychotropic medications, particularly antipsychotics, used in adults with ID, often without a supporting neuropsychiatric diagnosis or indication [36]. Dual diagnosis has been used to refer to the combination of intellectual or developmental disability (such as ASD) with other comorbid neuropsychiatric conditions or challenging behavior. Although prevalence of dual diagnosis is hard to determine because of differing definitions of developmental disability and other neuropsychiatric conditions, 40% is considered a reasonable estimate, with the most common type being problematic behaviors [14]. Mental health problems, particularly adjustment disorders, can occur at any time throughout the lifecycle, but are particularly likely to occur at major life transitions such as from adolescence into the adult world or with the various stresses that occur with aging [14]. Mental ill health can be compounded by reduced coping strategies or supportive social networks.

Psychiatric disorders are more challenging to diagnose in those who cannot report symptoms. The National Association for the Dually Diagnosed (NADD) has produced a companion

diagnostic manual for DSM-5 with adapted criteria to facilitate recognition and improve treatment of mental disorders in individuals with IDD. The Diagnostic Manual—Intellectual Disability (DM-ID) aids clinicians in making accurate psychiatric diagnosis with an emphasis on objective and behavioral presentations to mitigate the DSM emphasis on self-report [37, 38]. Accurate psychiatric diagnosis leads to more appropriate treatment and improved quality of life. Psychotropic medications can be helpful for specific psychiatric conditions; however they can also exacerbate problems when used in lieu of an understanding of underlying problems or as a means to suppress behaviors that may be communications of distress [39]. Thus, it is important to recognize behavioral communications of distress, determine underlying reasons, and plan interventions accordingly (e.g., psychotropic medication and/or other therapies). Where psychotropic medications are indicated, the physician must engage the person, their circle of care, and/or substitute decision-maker in the process of informed consent and monitoring of response [40].

27.1.4 Communicate CARE and HELP

The biopsychosocial model provides a framework for thoroughly assessing and intervening in ambiguous presentations of declining health and well-being. A biopsychosocial integrative approach is particularly vital with aging individuals with IDD as new problems may be overshadowed by the disabilities and overlooked by non-specialty clinical services.

Biological ill-health and age-related decline can include multiple realms such as sensory (visual, hearing, gustatory), neurological, metabolic, and musculoskeletal. Psychologically, aging comes with challenges to be faced; however, like the general population, there will be personal differences in temperament, personality, stress triggers, responses and resilience, as well as cognitive capacities. Socially, loss and change are unavoidable, yet personal reactions are variable.

Several tools have been developed to assist clinicians in adapting communication skills and addressing the acute or complex needs of adults with IDD in distress: "Communicate CARE" [41] and "HELP" [39] frameworks have been devised for clinicians seeking to overcome communication barriers and help people with IDD.

Communicate CARE interview guide primes the clinician to communicate an attitude of caring by first allowing sufficient time and providing a comfortable space. Clinicians are to communicate Clearly (on the person's own terms), Attentively (for verbal and nonverbal cues), Responsively (empathically, addressing patient needs), and Engaging the patient first (with others as appropriate) (see Fig. 27.1).

The *HELP* model with mnemonic [39] provides a useful guide for scanning potential reasons for distress or decline: Health (medical and age-related physiological changes), Environment (settings and expectations), Lived experience (difficult circumstances, traumas, abuse, losses), and Psychiatric (neuropsychiatric illness, distress, psychotropic medication side effects) (see Fig. 27.2).

27.2 Case Studies

Case scenarios are provided to illustrate general and IDD-specific issues related to aging for two individuals aging with IDD. Neither case description could be considered truly representative of the heterogeneous ID and ASD populations, but rather are illustrative of the importance of person-centered, biopsychosocial approaches to assess and address the reasons for the changes in baseline presentations (e.g., agitation, decline). Communicate CARE and HELP frameworks are applied.

27.2.1 Case 1: Merle

Case 1 History

Merle (Fig. 27.3) was described by her sisters and support workers as having a "rich personality" and typical features of Down syndrome. As a child through to young adulthood, she was quite healthy and cherished. She liked to help and enjoyed various "chores." Following her parents' death, she resided in an institution for 5 years (age 40–45). On admission to the facility, hypothyroidism was discovered and treated. Institutional records noted "grief at the death of her parents was expressed openly and appropriately." She was treated for depression with the tricyclic antidepressant amitriptyline 100 mg daily. At age 45 she was transitioned into a family home provider's care, a few hours away from her three sisters. Her friendly and feisty personality was a positive addition to the myriad of social activities with which she was involved with her new host family and friends. She had apparently adapted well to the many transitions she had faced.

At age 52, changes in mental status and functioning were noted. She had episodes of disorientation, loss of skills (e.g., dirty dishes put in cupboard versus dishwasher), and dropping out of favorite activities. These episodes lasted several weeks and subsided without intervention. There were no apparent precipitating events or ill health associated with her functional decline. Her only identified recurrent health issue was constipation. Medical investigations (blood count, electrolytes, glucose, liver/renal/thyroid function tests, and urinalysis) were unremarkable.

There continued to be a decline in her overall functioning through her mid-late 50s. This started with flattened affect, diminished social engagement, and less of her sparkling wit. She had difficulties executing familiar chores and manifesting confusion about dates; this was very different from her baseline. She began asking questions repeatedly and misplacing objects while blaming others. She had a harder time completing routine activities such as getting dressed, showering, and making coffee.

Merle enjoyed toast with her morning coffee. Caregivers began finding Merle's toast crusts throughout the home (e.g., in cupboards, her pockets, near the toilet seat). Merle did not want to discuss this. She was becoming more irritable, socially withdrawn, and was expressing negative ideation

Communicate CARE INTERVIEW

Jessica Graham MD, Kerry Boyd MD FRCPC, Amanda Ritsma MD

McMaster University

Communicate **C**learly (verbal and nonverbal) **A**ttentively (listen and observe) **R**esponsively (empathy and assistance) **E**ngaging (person first and others as appropriate)	**WHEN YOU**	**I**nitiate Session and **I**ntroduce Self **N**egotiate an Agenda **T**alk through Concerns **E**xplore Patient's Perspective **R**equest Caregiver's Perspective **V**erify and **V**alidate Concerns **I**nform **E**stablish Plan **W**rap-Up

*Adapted from the Bayer–Fetzer Kalamazoo consensus framework: the HMS Communication Skills Tool

Communicate CARE when you INTERVIEW

Prepare

- Review available information and accommodate physical, cognitive, communication limitations
- Consider sensitivities (sound, lights, smells, commotion, etc) and adjust (preferred appointment times, comfortable and safe environment)
- Utilize checklists, questionnaires, documented collateral information to assist with interaction and streamline the appointment.
- Be aware that expressive language may not be congruent with receptive language or comprehension

Communicate CARE

Clearly (verbal and nonverbal)
Determine the patient's preferred method of communication

Verbal
Choose appropriate language:

- Short words, simple sentences (avoid jargon)
- Concrete language i.e. "show me"; "tell me"; "I'm going to..." (versus abstract language)

Explain clearly

- Speak slowly with frequent pauses (versus speaking louder)
- Repeat and rephrase questions when needed
- Check understanding—"can you tell me how you understand what I just said?"

Non-Verbal

- Use eye contact, facial expressions and body posture to demonstrate care and concern
- Use visual aids i.e. pictures, written words, technology, gestures
- Act or demonstrate procedures

Attentively (listen and observe)

- Allow enough time for answers.
- Be sensitive to verbal communication, vocal cues, changes in body language or signs of distress (avoid excessive note taking)
- Confirm perceptions of body language (may be difficult to read with differences in muscle tone).
- Tell the patient when you have understood, and if you require clarification.

Responsively (empathy and assistance)

Fig. 27.1 Communicate CARE when you *interview* patients with ID (From: Curriculum of Caring for People with Developmental Disabilities ► https://machealth.ca/programs/curriculum_of_caring/m/mediagallery/2196)

- Respond to content and emotion empathically.
- Show warmth and positive regard.
- Where problems are identified, seek solutions and provide agreed upon assistance.

Engaging (the person first and others as appropriate)

- Ask the patient's permission to involve caregiver.
- Use caregivers to better understand the biopsychosocial context.
- Ensure opportunity for the patient to verify and supplement information provided (avoid talking to an adult as thought they are not capable or not present)

When you INTERVIEW

Initiate Session and **I**ntroduce

- Introduce self and role
- Greet patient, establish rapport, put the person at ease.
- Ask simple introductory questions (based on communication profile/preference of the patient).
- Invite patient to introduce caregiver (if present).

Negotiate an Agenda

- Identify/explain the purpose of the encounter
- Elicit patient's full set of concerns
- With permission from the patient, ask caregiver if they have concerns
- Negotiate priorities and establish framework for the encounter

Talk through Concerns

- Gather information (biomedical and background)
- Transition from open to closed questions
- Facilitate and clarify ("tell me more", "help me to understand that")
- Summarize and explain transitions when guiding the interview

Explore Perspectives

- Person's understanding of the problem(s)
- Use nonverbal means to facilitate mutual understanding (visuals/pictures, written words, signs, gestures etc.)
- Ask about feelings, ideas, functions and expectations (FIFE); respond empathetically

Request Caregivers Perspective

- Explore caregivers' understanding of the problem(s)
- Ask about feelings, ideas, functions and expectations (FIFE)
- Complete the biopsychosocial perspective

Verify and **V**alidate Concerns

- Summarize and check understanding
- Provide opportunity for clarification

Inform

- Share your understanding
- Provide the appropriate amount and type of information; pause frequently to avoid overloading information
- Summarize and check understanding

Establish Plan

- Incorporate the patient and caregiver's perspective
- Explain options, risks and benefits
- Assess patient's capacity to understand and make informed decisions; facilitate shared decision-making

Wrap-Up

- Summarize session
- Check for further questions/concerns or missed information and discuss follow-up

Fig. 27.1 (continued)

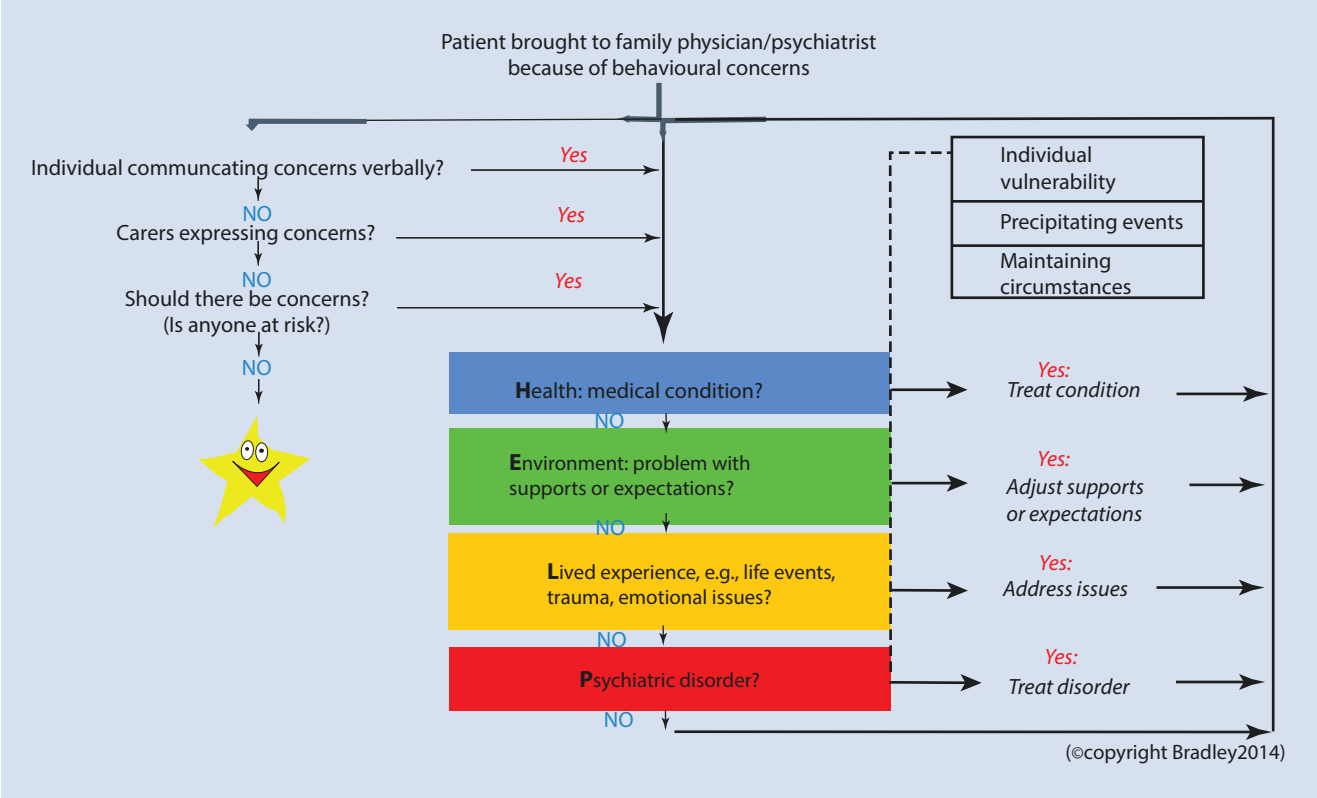


Fig. 27.2 HELP for addressing distress in patients with IDD (From: Bradley and Korossy [39])

(e.g., troubling memories, feeling unloved). There was a progression to agitated ranting that was predominantly incomprehensible, but occasionally related to suspecting someone was taking her things.

After several nights of sleep disruption, yelling at people from her remote past, she was taken to the local emergency department and eventually seen by the psychiatrist on call. She was started on haloperidol (5 mg at bedtime) with apparent relief from the distress of hallucinatory experiences. She remained irritable and appeared to have muscle stiffness. The family physician recognized haloperidol-induced parkinsonism (bradykinesia, cogwheel rigidity, shuffling gait, bilateral pill-rolling hand tremor) and akathisia (restlessness). She was treated with benztropine (2 mg twice daily) for parkinsonian extrapyramidal side effects of haloperidol. This did not help with her restless agitation. She again became uncomfortably constipated. Her family physician reviewed her laboratory studies, finding an increased TSH, and increased her thyroid replacement hormone. Due to her persistent and increasingly complex presentation, she was referred to the specialized geriatric psychiatry outreach team as well as an IDD specialty service.

Teaching Point
Constipation is a significant problem and often secondary to poor diet, inactivity, hypothyroidism, or anticholinergic medications like amitriptyline or benztropine. Bowel impaction is not only a source of discomfort, but a leading cause of morbidity in adults with ID.

Teaching Point
Where there is complexity, consider interdisciplinary involvement. Services specializing in the interdisciplinary assessment and treatment of those with IDD may be accessible. Geriatric teams are increasingly called upon to assess people with IDD at earlier ages than the general population. Though there is scant research about aging with ID specifically, systematic assessment of biopsychosocial variables affecting well-being is foundational and best practice.

Case 1 Questions and Answers

Case 1 Question

? Question 1. What are some treatable conditions that could be contributing to irritability?

? Question 2. How would you assess using HELP?

27

Fig. 27.3 Merle as a toddler

? Question 3. What are Down syndrome phenotypic vulnerabilities that can mimic major NCD and contribute to cognitive and functional decline?

? Question 4. What are non-pharmacological interventions for Merle and her circle of supports?

Case 1 Answers

Case 1 Answer 1 (Question 1—What are some treatable conditions that could be contributing to irritability?)

Teaching Point
Identify and treat comorbidities: delirium, medication adverse effects, sensory impairments, hypothyroidism, malnutrition, B_{12} deficiency, depressive disorder, obstructive sleep apnea, infections, and cancer (e.g., leukemia vulnerability with Down syndrome). Psychosocial stressors can also contribute to a decline or distress (e.g., abuse, neglect, psychosocial losses including death of parents, changes of any sort without adequate preparation or support).

Case 1 Answer 2 (Question 2—How would you communicate CARE and assess using HELP?)

The specialized geriatric psychiatry outreach team members included the nurse and geriatric psychiatrist. The nurse and psychiatrist visited Merle in her home. They let her take the lead and joined her as she sat in her favorite chair. They asked some clear, simple questions. They were attentive to her verbal communication and offered reassurance when there were nonverbal signs of anxiety. They met with two of her sisters and core staff team to review biopsychosocial factors that could be causing her distressed and withdrawn presentation [39]:

Health The Down Syndrome Health Watch guidelines [32] were regularly reviewed at staff meetings with head-to-toe review of systems with her family physician. Physical exam was unremarkable apart from abdominal enlargement attributed to constipation. She did not point to any painful body parts (on herself or a simple picture of a female body). She did not have cataracts or glaucoma, commonly associated with Down syndrome. Her baseline hearing impairment was exacerbated by cerumen impaction. Syringing of the ears was accepted with caregiver reassurance, modeling, and promise of a reward. Hearing aids were not tolerated. Bowel movements were monitored regularly. She had a urinary tract infection that presented as delirium, resolving with antibiotics.

Environment Review of Merle's remote history helped current caregivers to better understand her reactions and behaviors. This assisted in creating environmental and social familiarity. For example, the sisters recalled their mother trimmed crusts from toast or sandwiches shedding light on the mysterious discarding of crusts. Staff observed that when they honored her preferences, she was at ease and there were fewer distressed behaviors. The Alzheimer Society provided education and support for caregivers.

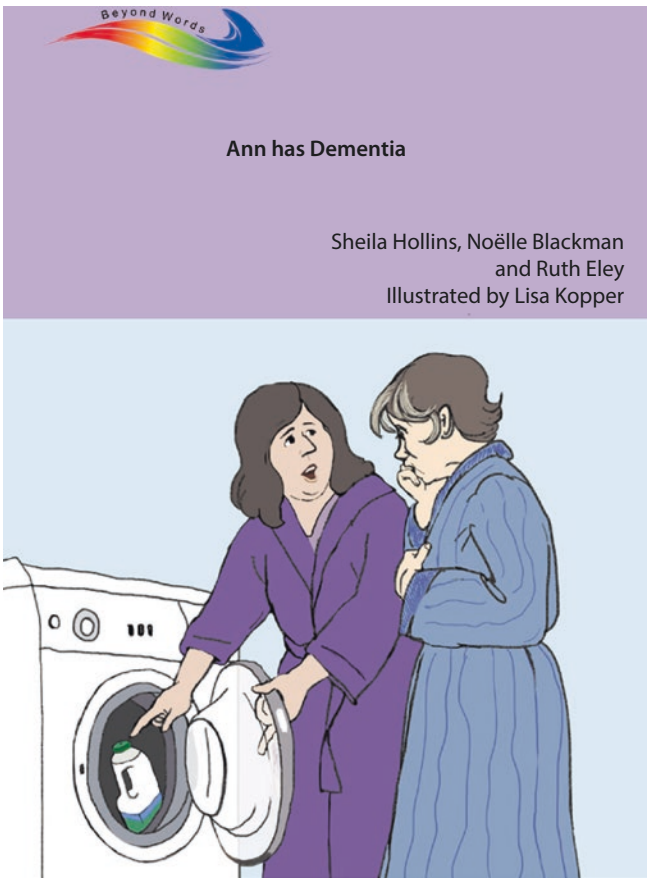
Lived experience Merle was apparently troubled by a new male resident and unfamiliar staff. During her time in the institution, her sisters noted she became increasingly troubled by anyone who would enter her room or space. Abuse had not been suspected in her past; however her current distress and paranoia resulted in a decision to establish a core team of familiar staff and only female coresidents in her part of the home.

Psychiatric A list of current prescribed medication was obtained. It was decided that Merle's haloperidol dose be lowered to 2 mg because of akathisia and parkinsonism. Benztropine and then amitriptyline were slowly and sequentially tapered to the point of discontinuation. Akathisia, sedation, and constipation improved. Due to her personal and

some family history of depression, she was treated with a selective serotonin reuptake inhibitor (SSRI), sertraline 50 mg daily. There were modest benefits to mood, sleep, energy, and overall engagement. Merle had a long history of self-talk; however, during these months this behavior had increased. Although psychosis or delirium was considered, in Merle's case, it was thought that the self-talk was an exaggeration of her baseline habitual patterns, associated with her neurocognitive decline.

Caregivers were aware of the association of Down syndrome and Alzheimer-related NCD. The IDD specialty service psychologist reviewed past reports and the multiple realms of cognitive and adaptive functional decline. Psychometric testing revealed cognitive decline and impaired adaptive functioning well below her baseline suggestive of NCD (moderate stage). Major NCD due to Alzheimer disease was confirmed by the geriatric outreach clinicians. Merle was treated with a cholinesterase inhibitor (donepezil 10 mg daily) with modest improvement in her ability to engage with staff, execute simple daytime routines, and overall contentment. Some of the neuropsychiatric and behavioral challenges also lessened. Side effects to her other psychotropic medications had to be carefully monitored and doses adjusted as her NCD progressed.

Caregivers received training and support from the Alzheimer Society. Her housemate, who also had ID, received support in various forms, but responded best to a picture book called "Ann has Dementia" [42] (see ◘ Fig. 27.4).



◘ **Fig. 27.4** Ann has Dementia

Teaching Point
Visual communication and educational resources for people with IDD are available with samples listed in resource section.

Case 1 Answer 3 (Question 3—What are Down syndrome phenotypic vulnerabilities that can mimic major NCD and contribute to cognitive and functional decline?)

Major NCD can be preceded by personality and behavioral changes followed by more typical neurocognitive dysfunction and rapid progression. The Down Syndrome Health Watch guidelines [31] can assist the physician to assess for and address sensory, medical, or psychiatric problems.

Teaching Point
When there is a significant change in behavior, energy, appetite, mood, and sleep (*BEAMS*) [43], engage in a systematic review of biopsychosocial variables. Consider the *HELP* framework: Health, Environment, Lived experience, Psychiatric (including psychotropic medication side effects) [39].

Case 1 Answer 4 (Question 4—What are non-pharmacological interventions for Merle and her circle of supports?)

Within 2 years from her diagnosis of moderate stage of major NCD due to Alzheimer disease, Merle progressed to later stages. She required a hospital bed, Hoyer lift, and wheelchair for transport and sat most comfortably in a recliner chair. When favorite music was heard (from the musical *My Fair Lady*, "Wouldn't it be Loverly"), she danced, moving her arms and head. Her music therapist brought a smile to her face with familiar songs. She also responded lovingly to voices and touch of familiar staff and her sisters, although she no longer seemed to recognize their faces. Her chaplain continued to provide pastoral care in the comfort of her living area. She was placed on a waiting list for a long-term care facility. It was apparent to her circle of care that Merle was most comfortable in her home. They supported her at home until her passing at age 62 (see ◘ Fig. 27.5).

Case 1 Analysis Literature on aging issues is more extensive with the genetic syndrome of Down syndrome than any other. It is well known that early-onset Alzheimer-related NCD is correlated with trisomy 21. Individuals diagnosed with Down syndrome may present to primary care physician, specialist, emergency department, inpatient units, and long-term care facilities with the earlier onset of aging-related issues. Despite the heightened risk of NCD with Down syndrome, NCD must still be considered a diagnosis of exclusion. Caregivers and medical teams need to consider phenotypic vulnerabilities. Common medical conditions are well described yet may present atypically; review of systems and investigations may identify visual impairment (e.g., cataracts), ear-nose-throat issues including

Fig. 27.5 Merle at home age 60

deafness secondary to cerumen (wax) buildup, obstructive sleep apnea, hypothyroidism, obesity, celiac disease, B_{12} deficiency, leukemia, and musculoskeletal ailments (e.g., arthritis). Depressive disorder is more common with Down syndrome than in the general population [32]. Sensitivity to medications and side effects should also be considered. Delirium can have multiple presentations and herald emerging major NCD.

Ideally, a baseline psychological assessment of cognitive and adaptive functioning would be available. Regular monitoring benefits the patient and care team by providing updates on capabilities, the stage of major NCD, and anticipated progression. This can assist with proactive planning and treatment. An interdisciplinary approach is essential in caring for these patients, and agencies such as the Alzheimer Society can provide valuable consultation and support. Education about major NCD with an emphasis on care for the caregivers is also important. Where long-term care facilities are not accessed, advocacy and referral for in-home supports is important.

27.2.2 Case 2: Leonard

Case 2 History

Leonard (Fig. 27.6) was born in 1941. He was referred for psychiatric consultation in 1997 (age 56) because of new onset of aggressive self-injury (banging his head on floor or walls) and sleep disturbance. The staff team was increasingly concerned about his mental and physical well-being, requesting urgent assessment and medication review. The only documented diagnoses from his days living in an institution were "mental retardation" and "childhood-onset schizophrenia." He was discharged from the institution on high doses of two antipsychotic medications (chlorpromazine 750 mg daily, haloperidol 15 mg daily). As there was no clinical description of psychosis associated with "childhood-onset schizophrenia," a community psychiatrist recommended a gradual reduction of his antipsychotic medications, beginning with chlorpromazine. Within 6 months, caregivers were concerned that the taper was worsening agitation and contributing to the self-injurious behaviors.

Fig. 27.6 Leonard with his mother (1941)

Self-injurious behavior was documented in previous institution reports but was seen infrequently in his group home prior to age 56. After that time, self-injurious behavior in the form of head banging became increasingly frequent and intense. Over the last few months, Leonard had contusions and swelling on his temples and redness of his right cheek. It was clear to the staff that this was a communication of distress, though the reasons were not obvious.

Referral to a service specializing in IDD dual diagnosis was initiated by the staff and family physician, but there was a long wait list. The family physician also made an urgent referral to the specialized geriatric psychiatry outreach team. Referral concerns included the severe self-injury as well as a decline in engagement with even preferred staff. Leonard had been destructive at his last physician's appointment, and subsequently he would not get in a vehicle for any reason.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. What adaptations to the usual clinic-centered model are required?

? Question 2. What additional information would be helpful?

Question 3. What might be contributing to Leonard's changes in behavior, eating, and sleeping patterns? Consider biopsychosocial factors.

Case 2 Answers

Case 2 Answer 1 (Question 1—What adaptations to the usual clinic-centered model are required?)

The geriatric psychiatry outreach nurse and psychiatrist visited Leonard at his group home at a quieter time of day when he generally was less agitated. The residential manager arranged for one of Leonard's preferred, longer-term staff to be present to prepare and reassure him. The manager and support worker assisted the geriatric team to communicate clearly, on Leonard's terms, attend to his nonverbal cues, respond to distress, and engage him with simple interchanges (*Communicate CARE*) [41].

Case 2 Answer 2 (Question 2—What additional information would be helpful?)

Some history was provided by the residential staff. The support worker at the appointment had worked with Leonard since his transition from the institution. The residential team noted over the 10 years following discharge from institutional care that Leonard was generally quiet and did not use words. They recognized nonverbal means of communication including vocalizing and minimal pointing, without eye contact. For the most part, they could interpret facial expressions, body habitus, and general demeanor. He seldom relaxed and was perpetually restless. Leonard seemed to enjoy walks, music, and rocking in his chair on the porch. He retreated to his bedroom when there was commotion, such as when housemates were coming back from their day activities. He previously consumed all meals rapidly, though he would cough frequently. For years his sleep was presumed to be regular, "like clockwork," for about 10 hours. Food refusal and sleep disruption coincided with the onset of self-injury. He was increasingly retreating to his room during the day and napping. The now 9-month history of nighttime wakening with agitation and self-injury (banging of his face/head) was most concerning to the staff team.

Leonard had been in his bedroom, but after about 20 minutes he came into the kitchen, where the staff spoke with the nurse and psychiatrist. Without making eye contact, Leonard took a glass of juice on the counter and returned to his room. He walked quickly despite his crouched posture and wide-based, shuffling gait. He had diminished arm swing and a flat facial expression. There were no obvious dysmorphic features. There was evidence of an indistinct, resolving hematoma on his right temple and upper cheek. Leonard was noted to be tall and thin but with a protuberant abdomen (it was unclear if this was adiposity or related to chronic constipation).

Leonard's favorite staff ushered the visiting clinicians to his bedroom area. Leonard rocked in a lounge chair by his window, with intermittent humming vocalizations. He seemed to understand when asked if the nurse and doctor could see his room and family photos, giving an abrupt nod. He did not respond to interviewer's attempts to engage him. His facial expression remained flat with diminished eye blinking and averted gaze. His bed had no head or footboard because he would hit his head on posts when he would wake in the night. He declined a physical examination. There were no abnormal involuntary movements or tremor. As the geriatric team walked down the driveway, he quickly shuffled out the front door and sat on a favorite porch chair, still rocking.

Teaching Point

When there is agitation or change in behavior, consider HELP [39]. Maintain a high index of suspicion for side effects of psychotropic medications, especially antipsychotics. Extrapyramidal side effects can present with a troubling side effect combination of parkinsonism (e.g., bradykinesia, flat facial expression, diminished blink) and akathisia (restlessness, dysphoria, agitation).

Case 2 Answer 3 (Question 3—What might be contributing to Leonard's changes in behavior, eating, and sleeping patterns? Consider biopsychosocial factors.)

The residential support team subsequently provided additional information about biopsychosocial factors that may have precipitated or be perpetuating his behavior, energy, appetite, mood, and sleep disturbance (*BEAMS*) over the last 9 months. Together, the residential and geriatric outreach teams reviewed *HELP* variables [39]. *HELP* proved to be a helpful framework for review of biopsychosocial drivers of Leonard's agitated behaviors.

Health Further medical assessment included laboratory studies (CBC, B_{12}, electrolytes, calcium, phosphorus, liver/renal/thyroid function, glucose/HbA1c, and lipid profile). No problems were identified. Hearing and visual examinations were not feasible at the time. Leonard had few remaining teeth (most had been extracted in the previous institution). Dental evaluation could only be completed under general anesthetic so was deferred. The speech language therapist was able to look in his mouth, and there were no obvious concerns with his six remaining teeth. The swallowing assessment was completed, indicating dysphagia with risk of aspiration. He tolerated small portions of carefully prepared soft diet and thickened liquids, but continued to lose weight. The geriatric outreach team made the connection of waking in the night agitated and self-injury with gastroesophageal reflux disorder. *H. pylori* infection was identified and treated. Dietary modifications were made for gastroesophageal reflux disorder, and the head of the bed was raised. Some improvements were noted in nighttime wakening, coughing, and pacing. Poor dentition, constipation, and difficulties in urinating were in part attributed to side effects of high doses of chlorpromazine, an antipsychotic with sedating and anticholinergic properties. Restlessness and parkinsonism were appreciated as side effects of the combination of chlorpromazine and haloperidol.

Environmental Environmental sensitivities (loud noises, commotion, "picky eater") were known triggers for Leonard's agitation. The residential team allowed Leonard to choose his preferred settings and interactions.

Lived experience Losses had accumulated (death of his father in middle childhood, move to an institution, reduced family contact, and deinstitutionalization). Leonard could not verbalize or otherwise communicate his institutional experiences; however, staff noted it apparently took him several years to be comfortable with them and coresidents in his current group home. He was agitated by staff changes and peers transitioning out. Leonard's recent losses included the death of a housemate with whom he had a fond relationship. This person was quickly replaced by a louder male.

Psychiatric Mental retardation, childhood-onset schizophrenia, and self-injurious behavior were the documented rationale for his psychotropic medications. He was discharged from institutional care on a combination of chlorpromazine 250 mg three times daily, haloperidol 5 mg three times daily, benztropine 2 mg twice daily, carbamazepine 200 mg three times daily (no reported epilepsy), plus stool softeners and laxatives. Medication tapering may have caused withdrawal symptoms, or he may have been suffering from other sources of distress that he could not report apart from agitated behaviors.

Contact with Leonard's sister was arranged by staff. Leonard's older sister, Judith, was identified as the next of kin with power of attorney, living far away on the west coast of Canada. She was asked to provide any known perinatal, developmental, medical, and family history. Judith was 5 years older than her brother. She shared that he was the youngest of five children. He was born at home but she was unaware of circumstances of his birth, developmental details, or atypical behaviors prior to age five. Leonard was an attractive child with no unusual physical (dysmorphic) features. She did not think there were any health problems. He pretty much kept to himself, made little eye contact, and seemed to enjoy humming and "finger play." Their small-town school was not suitable for his needs. He remained at home. He was quiet but would occasionally yell, rock, and bang his head. Triggers included loud noises and transitions from home, especially in seasons when outerwear was required. He traveled well for the family's annual summer vacations to a waterfront cottage (Fig. 27.7).

After their father's death, he lived in a provincial institution from ages 11 to 51. The family was not notified when he started psychiatric medications. Judith believed it was around puberty and "for behavior." She was alarmed when she visited him in his 30s to find him sedated and unengageable. Their mother died shortly after Leonard was transitioned to the group home nearby. Judith assumed the substitute decision-maker role.

The family history included paternal alcoholism and maternal depression. A brother had posttraumatic stress disorder after returning from war. One of their sisters had a son with obsessive-compulsive disorder and autism. Judith's grandson was recently diagnosed with autistic disorder (a subcategory of pervasive developmental disorder according to DSM IV-TR). Judith now believes Leonard's correct diagnosis is "autism."

Fig. 27.7 Leonard and Judith on vacation

An interdisciplinary team specializing in IDD became involved, building on geriatric psychiatry outreach involvement. The dual diagnosis subspecialist psychiatrist, nurse, and behavior therapist met with Leonard and his residential support team. Judith was able to visit and attend a two-hour meeting in person. The developmental history and behavioral profile confirmed the sister's suspicions that her brother had autistic disorder (DSM IV-TR pervasive developmental disorder-autistic disorder, currently DSM-5 autism spectrum disorder with intellectual disability). Given the family concerns and potential for useful information about Leonard's condition, genetic tests were completed with his laboratory studies. Fragile-X syndrome and chromosome analysis (commonly ordered in the 1990s prior to more advanced genetic screening) came back 3 months later with no detected abnormalities.

Judith and the residential team agreed to continue gradual tapering of antipsychotic and anticholinergic side effect medications since his aggression ("self-injurious behavior") was likely related to his ASD (communication deficits, environmental sensitivities). Psychotropic medication side effects (akathisia, constipation) may have perpetuated his agitation and aggression. Chlorpromazine was tapered (10% per month) followed by discontinuation of benztropine. Anticholinergic side effects of constipation and dry mouth

improved. He became less sedated and more alert. Leonard's predilection for routine was capitalized on by the behavior therapist to reestablish his day/night (circadian) rhythm.

Teaching Point

When initiating a trial of psychotropic medication, follow geriatric medication prescribing guidelines (e.g., start low and go slow), with extra caution for patients who cannot self-report symptoms or side effects. When long-term psychotropic medications are being tapered, obtain historical information, patient assent/informed consent, educate the circle of supports, and reduce gradually (e.g., by 10% every 2–4 weeks), one medication at a time, as tolerated. The aim is lowest effective doses of the right medications for the underlying conditions (e.g., antidepressants for major depression versus antipsychotics to quell unspecified agitation).

An IDD specialized psychological assessment was indicated to obtain an updated and accurate determination of his cognitive profile, communication style, and adaptive skills. He was not willing or able to engage. Major NCD was not strongly suspected based on the history of maintenance of many of his baseline skills. An occupational therapist offered suggestions for accommodating his sensitivities. A speech language pathologist suggested augmentative strategies for communication with others who knew him less well.

Teaching Point

People with ASD can be ritualistic and routine oriented and have heightened sensitivities (e.g., sound, touch, texture, scents, light), communication impairments, and atypical ways of engaging. Some have had adverse reactions or traumatic experiences in institutional, hospital or clinic settings. Communicate CARE can serve as a primer for clinical encounters. Having familiar caregivers to provide not only history but also facilitate successful interactions is important. Where the individual is not capable, a substitute decision-maker will be required [30]. Inclusion of the person and respect for personal choice in assessment and treatment are always the aim.

Leonard's swallowing difficulties, weight loss, agitation, and withdrawal continued, necessitated hospitalization. Leonard's circle of care remained involved. His support workers regularly took shifts to feed him. Leonard was clearly apprehensive and tolerated more proximity from his familiar team while in hospital than when he lived at home. He received extensive workups over the course of his demise. Leonard died 3 weeks later of undetermined causes (Fig. 27.8).

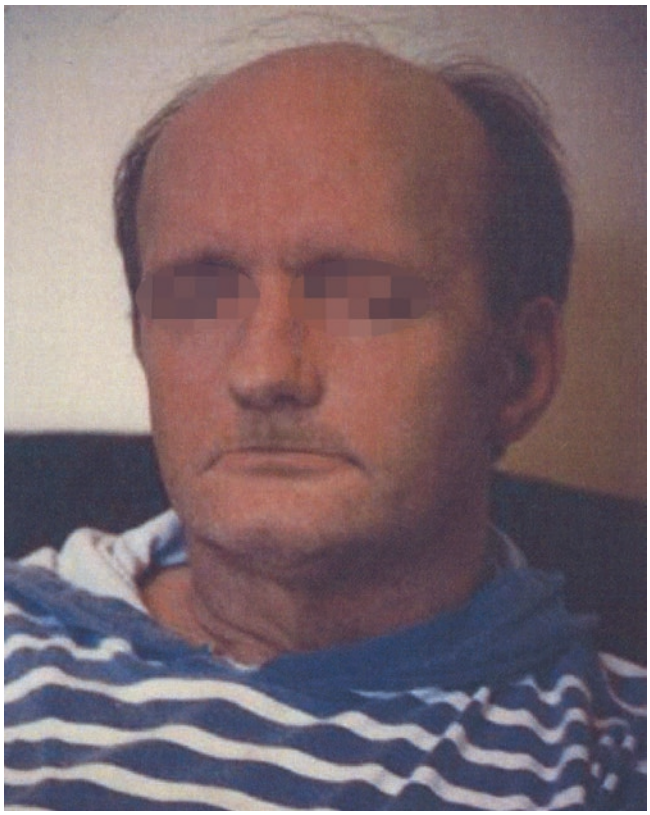


Fig. 27.8 Leonard at age 56

Case 2 Analysis "Autistic disorder" (ASD with ID, according to DSM-5) became the primary neurodevelopmental disorder diagnosis. With interprofessional collaboration, geriatric and IDD specialty disciplines were able to assist in clarifying underlying reasons for distress and initiate treatment planning. Autism was misunderstood as a psychotic rather than neurodevelopmental disorder when the early diagnostic term childhood-onset schizophrenia followed him into adulthood [11, 44]. As a result, Leonard was inappropriately maintained on excessive amounts of antipsychotic medications.

Leonard was nonverbal and communicated discomfort with behavior rather than words. It is important to circle back to potential biopsychosocial precipitating and perpetuating factors, especially with individuals diagnosed with IDD and communication impairments. By following the HELP framework, acute and intermittent mental and physical issues are more likely to be identified and managed. In Leonard's case, institutional health information was unknown; however, as he aged, discomfort related to gastroesophageal reflux disorder and constipation were identified as potential precipitating and perpetuating factors. Age-related issues could not be fully assessed (e.g. vision, hearing, arthritis). Psychotropic medication-related issues contributed to poor health, dentition, sleep, and emotional state. Gradual reductions in antipsychotics were associated with some improvements; however, there were likely some withdrawal symptoms or other unidentified medical issues. Leonard's experiences in the institution remained a mystery; however, he transitioned into a welcoming, ASD-friendly environment with care providers who were attuned to his needs. The residential team continued as strong advocates for the other men and women with ASD and ID who followed Leonard.

Leonard represents the many non- or barely verbal "spokespeople" for the necessity of bridging communication gaps to understand biopsychosocial variables affecting well-being. Even those who cannot use words speak loudly through their behavior. Health professionals of all disciplines will encounter people with IDD and different ways of communicating their needs. Those with ASD (with or without comorbid ID) represent a very diverse group of individuals with varying underlying etiologies, cognitive profiles, communication styles, comorbidities, atypical presentations, environmental sensitivities, and aging issues (both what is "common to man" and specific to their condition). It behooves us to be listeners to more than words, collaborative in our attempts to understand the multiplicity of contributors to suffering, and compassionate in our efforts to better their lives. As we do this, we too become the beneficiaries.

In summary, medical professionals including nurses, primary care physicians, physician specialists (e.g., geriatricians, neurologists, psychiatrists), and interdisciplinary teams (e.g., geriatric outreach or developmental disability specialist services) may be involved to varying degrees through the senior years of people with IDD. Psychiatric and other medical assessments are possible with an adaptable and flexible approach [45]. Collaborative, person-centered care, with involvement of those who know and care for the individual, is fundamental. A holistic, biopsychosocial approach helps each member of the circle of care to contribute to multimodal person-centered and developmentally attuned intervention.

27.3 Key Points: Aging with Intellectual and Developmental Disabilities

- The population of people with IDD is heterogeneous; however, some general points can be made. Medical and other neuropsychiatric and psychosocial problems are more common in IDD. IDD patients can have the same problems as aging individuals from the general population, plus particular problems associated with IDD (e.g., genetic phenotype, congenital anomalies). Dual diagnosis (IDD with other mental health or behavior problem) is common (estimated at 30–40%). Antipsychotics prescribed for behaviors in the absence of psychotic illness can mask underlying reasons for behavior and exacerbate problems with side effects.
- Barriers to person-centered healthcare include limited access, impairments in verbal communication, and complexity of their needs. Communicate CARE provides some best practice guidance for improving the clinical encounter (adapting communication with responsiveness to needs).
- HELP provides a framework for systematically evaluating variables that can contribute to "distressed" patient presentations (changes in BEAMS: Behavior, Energy, Appetite/eating, Mood/affect, Sleep). Health, environmental, lived adverse experiences, and psychiatric factors, once identified, can lead to more effective multimodal management.
- Primary care physicians, physician specialists, and interdisciplinary services (e.g., geriatric outreach, IDD specialty teams) may be involved at various times across the lifespan of people with IDD. Key clinical concepts include collaborative, person-centered care, with involvement of circles of support and advocacy for the special needs of aging adults with IDD.
- Resources and some emerging research are available to guide the clinician in caring for individuals who are aging with IDD. Primary care practice guidelines, health watch checklists for ASD and genetic syndrome information are available via Internet. Patient and caregiver resources and associations are also readily accessible. Some current examples are provided.

27.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Since intellectual disabilities (ID) and autism spectrum disorder (ASD) have an onset of symptoms in childhood (developmental period) and are lifelong neurodevelopmental disorders, can they (should they) be diagnosed retrospectively in adulthood?

A. ID and ASD can only be diagnosed prior to 18 years of age.
B. They may be diagnosed in adulthood; however, history must indicate presence in developmental years, and applicable diagnostic criteria must be met, including consideration to other reasons for the presentation (exclusion criteria).
C. ID and ASD can be diagnosed in adulthood with appropriate psychometric testing (cognitive, adaptive tools) alone.
D. Only IDD specialty services can provide assessment and care for patients with ID and ASD.

Answer: B

People with milder ID and ASD may not have been properly diagnosed in earlier eras when diagnostic criteria were not specified or the features were not readily apparent. The diagnosis of both disorders rests on history indicating that diagnostic criteria were met within the developmental period (generally accepted as prior to 18 years of age).

MCQ 2. Which of the following will most significantly confound a geriatric team and/or psychiatrist's ability to identify other DSM-5 psychiatric disorders (comorbidities) with a senior who has autism spectrum disorder?

A. Diminished eye contact and repetitive speech with social anxiety in unfamiliar settings
B. Sensitivities to sound, bright lights, and scents
C. A history of "aggression" resulting in polypharmacy, including sedating antipsychotics
D. Absence of past medical or psychiatric records

Answer: C

Aggression may occur within the spectrum of agitation. Antipsychotic medications have been used to "treat aggression," sometimes without identifying the underlying reasons for the agitation. Low-potency antipsychotics such as chlorpromazine can be sedating, with additional side effects including constipation. Higher-potency antipsychotics, such as haloperidol, or others in higher doses, or with sensitive individuals, can cause parkinsonism or akathisia. These medication side effects can mimic or mask underlying neuropsychiatric comorbidities.

MCQ 3. When a geriatric patient with IDD presents with new onset of distressed behaviors and cannot verbally describe symptoms, which of the following must be considered?

A. Unrecognized health issues may be contributing to the change in behavior.
B. This person may be able to report on the sources of distress by alternate means and or with the right supports.
C. Adverse experiences (past and present) in the physical or social environment may be discerned by paying attention to the topography and history of the behavior.
D. Psychiatric disorders are more common in IDD, and carefully administered and monitored treatments can be effective for specific conditions.
E. All of the above are true.

Answer: E

HELP is a useful framework for considering biopsychosocial variables that could be influencing behavior. In addition, a careful history with behavior as the presenting problem from knowledgeable informants is helpful in guiding further assessment and specific treatments.

27.5 Additional Resources

- Books Beyond Words
- ► http://www.booksbeyondwords.co.uk/bookshop/paperbacks/ann-has-dementia
- Curriculum of Caring for People with Developmental Disabilities
- ► CommunicateCARE.machealth.ca
- Diagnostic Manual—Intellectual Disability (DM-ID-2): A Textbook of Diagnosis of Mental Disorders in Persons with intellectual Disability—edited by Robert J. Fletcher, Jarrett Barnhill, & Sally-Ann Cooper, 2016
- National Down Syndrome Society (NDSS). Aging and Down Syndrome: A Health and Well-Being Guide
- ► http://www.ndss.org/PageFiles/2594/Aging%20and%20Down%20Syndrome%20A%20Health%20and%20Well-Being%20Guidebook.pdf
- National Task Group on Intellectual Disability and Dementia Practices
- ► https://aadmd.org/NTG
- ► http://aadmd.org/ntg/products as an attachment with reference to Barbara's email invitation
- Surrey Place Centre: Health Watch Tables ► http://www.surreyplace.on.ca/documents/Primary%20Care/HWT_ASD.pdf
- ► http://www.surreyplace.on.ca/documents/Primary%20Care/Down%20Syndrome.pdf
- Tools for the Primary Care of Adults with Developmental Disabilities: Developmental Disabilities Primary Care Initiative, Sullivan, W & Developmental Disabilities Primary Care Initiative Co-editors (2011).
- ► http://www.surreyplace.on.ca/resources-publications/primary-care/
- Vanderbilt Kennedy Center: Health Care for Adults with Intellectual and Developmental Disabilities: *Toolkit for Primary Care Providers*
- ► http://vkc.mc.vanderbilt.edu/etoolkit/
- ► http://vkc.mc.vanderbilt.edu/etoolkit/physical-health/health-watch-tables-2/down-syndrome/
- World Health Organization; ► http://www.who.int/en/

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Psychiatric Emergencies in Older Adults

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28.1 Background

28.1.1 Introduction

As a result of our aging population, there has been a corresponding consistent increase in the number of geriatric patients visiting emergency departments across North America [1]. According to Canadian data, older patients have significantly higher rates of emergency department use compared with their younger counterparts: 44,043 per 100,000/year population aged 65 years and older versus 29,485 per 100,000/year population aged 20–64 years [2]. Once in the emergency department, seniors are also more likely than younger adults to be admitted as inpatients. From the same report, in 2009–2010, about 25% of seniors were admitted to inpatient care via the emergency department, compared with only 8% of non-seniors [2].

Clinicians who see older patients do so in different settings, such as medical wards, intensive care units, coronary care units, and long-term care units. When they see ill patients, they frequently encounter symptoms that cannot be readily categorized dichotomously as "psychiatric" or "physical" [3]. Older patients with psychiatric disorders commonly present with physical symptoms, and older patients who are physically ill have accompanying psychiatric symptoms. Furthermore, medications prescribed to treat other (systemic) medical illnesses may cause psychiatric symptoms, and psychotropic medications may have side effects that mimic other systemic medical or neurologic disorders. Thus, when older patients with behavioral disturbances are identified, regardless of the setting, clinicians should attempt to rule out other contributing and comorbid systemic medical disorders including infections; electrolyte imbalances; cardiovascular, neurologic, and endocrine disorders; and medications as causes for the disturbances, which may present as confusion, including delirium, depression, major neurocognitive disorder (formerly dementia), substance intoxication/withdrawal, and psychosis. Table 28.1 provides a classification of psychiatric emergencies.

This chapter reviews the most common psychiatric emergencies that occur in older adults organized into acute onset confusion, suicide, aggression, abuse, and medication-induced adverse events.

Table 28.1 Classification of psychiatric emergencies

Emergency	Specifiers
Presentation	Confusion Suicidality Aggression Abuse Cardiovascular/neurological instability
Site of presentation	Emergency department Intensive care unit Psychiatric unit Medical/surgical ward Long-term care facility Retirement home Outpatient clinic Home
Etiology	Delirium Major neurocognitive disorder (dementia) Depressive disorder Bipolar disorder Psychotic disorder Substance-induced or substance withdrawal disorders including severe side effects to medications Neuropsychiatric disorder (e.g., traumatic or anoxic brain injury, developmental delay) Neurologic disorder Another systemic medical condition
Type of intervention	Psychosocial intervention Pharmacologic intervention Medical/surgical intervention Behavioral intervention

28.1.2 Confusion

Diagnosis

The most common cause of acute confusional state in patients over the age of 65 is delirium [4]. Delirium is an acute onset confusional state characterized by a loss of function, fluctuating consciousness, and disturbances in attention and disorganization. The acute onset and loss of function are the most important features distinguishing delirium from other causes of confusion. The presentation can be extremely variable from person to person but typically is associated with other cognitive deficits, changes in arousal, and perceptual disturbances including hallucinations, delusions, and an altered sleep-wake cycle. Disturbances in affect can be seen with depression, irritability, and anxiety/fear. (See ▶ Chap. 17 for further details.)

Delirium is not a disease per se but rather a clinical diagnosis based upon a collection of symptoms. The following diagnostic criteria are summarized from the *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition* (DSM-5) [5]:

1. Disturbance in attention and awareness.
2. Change in cognition that is not better accounted for by a preexisting, established, or evolving major neurocognitive disorder.
3. The disturbance develops over a short period of time and tends to fluctuate during the course of the day.
4. There is clinical evidence that the disturbance is caused by a direct physiologic consequence of a systemic medical condition, substance intoxication/withdrawal, and/or medication use.

The DSM-5 provides several possible specifiers including substance intoxication delirium, substance withdrawal delirium, and medication-induced delirium. There are also specifiers regarding length of illness, acute versus persistent, and a specifier for activity level: hyperactive, hypoactive, or mixed [5].

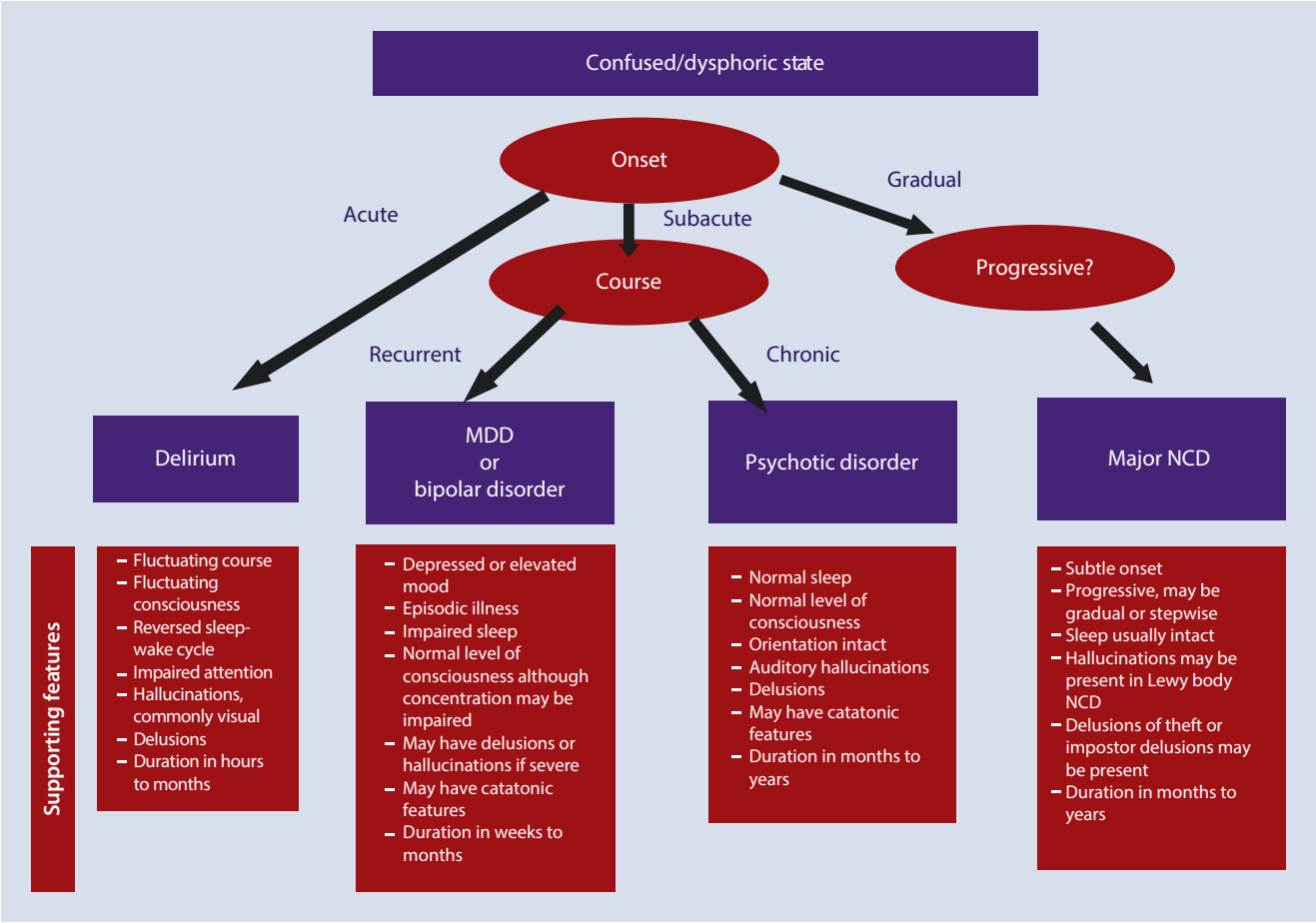
Medication (e.g., anticholinergics), infection (e.g., urinary tract or pulmonary), and cardiovascular events (e.g., pulmonary distress or heart failure) are the leading causes of delirium in older patients [4].

There are many psychiatric illnesses that present as an acute/dysregulated confusional state. The onset, sleep pattern, fluctuations in level of consciousness, disturbance in attention or orientation, the presence of hallucinations or delusions, and duration can all provide clues to the cause of a confused dysphoric state as ◘ Fig. 28.1 illustrates [1].

Major neurocognitive disorder can usually be differentiated from delirium by history. Screening tools like the Confusion Assessment Method Instrument, the Geriatric Depression Scale, the Mini Mental State Examination, the Montreal Cognitive Assessment, and the Clock Drawing Test can all be helpful in establishing the diagnosis [6] (see ◘ Fig. 28.2). Major neurocognitive disorder due to Alzheimer disease, the most common cause of major neurocognitive disorders in Western societies, typically has a gradually progressive, deteriorating course, measured in months to years. Sleep is not usually impaired in major neurocognitive disorder unless in severe stages; by contrast, reversed sleep-wake cycle is frequently seen in cases of delirium. The Alzheimer's Disease 8 (AD8) is a brief informant interview to detect major neurocognitive disorder which is sensitive in detecting early cognitive changes associated with many common neurocognitive disorders [7].

Teaching Point

There are several neuropsychiatric illnesses that present as an acute confusional state. The most common cause of acute confusional state in patients aged 65 or older is delirium, and its differential diagnosis is crucial. For example, major neurocognitive disorder with Lewy bodies may have some sleep-related problems including rapid eye movement (REM) sleep behavior disorder which are part of the minor criteria for the diagnosis [8] (see ► Chap. 20.) Patients who suffer from psychotic disorders are typically not disoriented. In the case of psychotic disorders, there is usually a history of a similar disturbance, distinct stereotypical auditory hallucinations, and less prominent cognitive dysfunction.



◘ **Fig. 28.1** Exploring the cause of a confused/dysphoric state. *MDD* major depressive disorder, *NCD* neurocognitive disorder

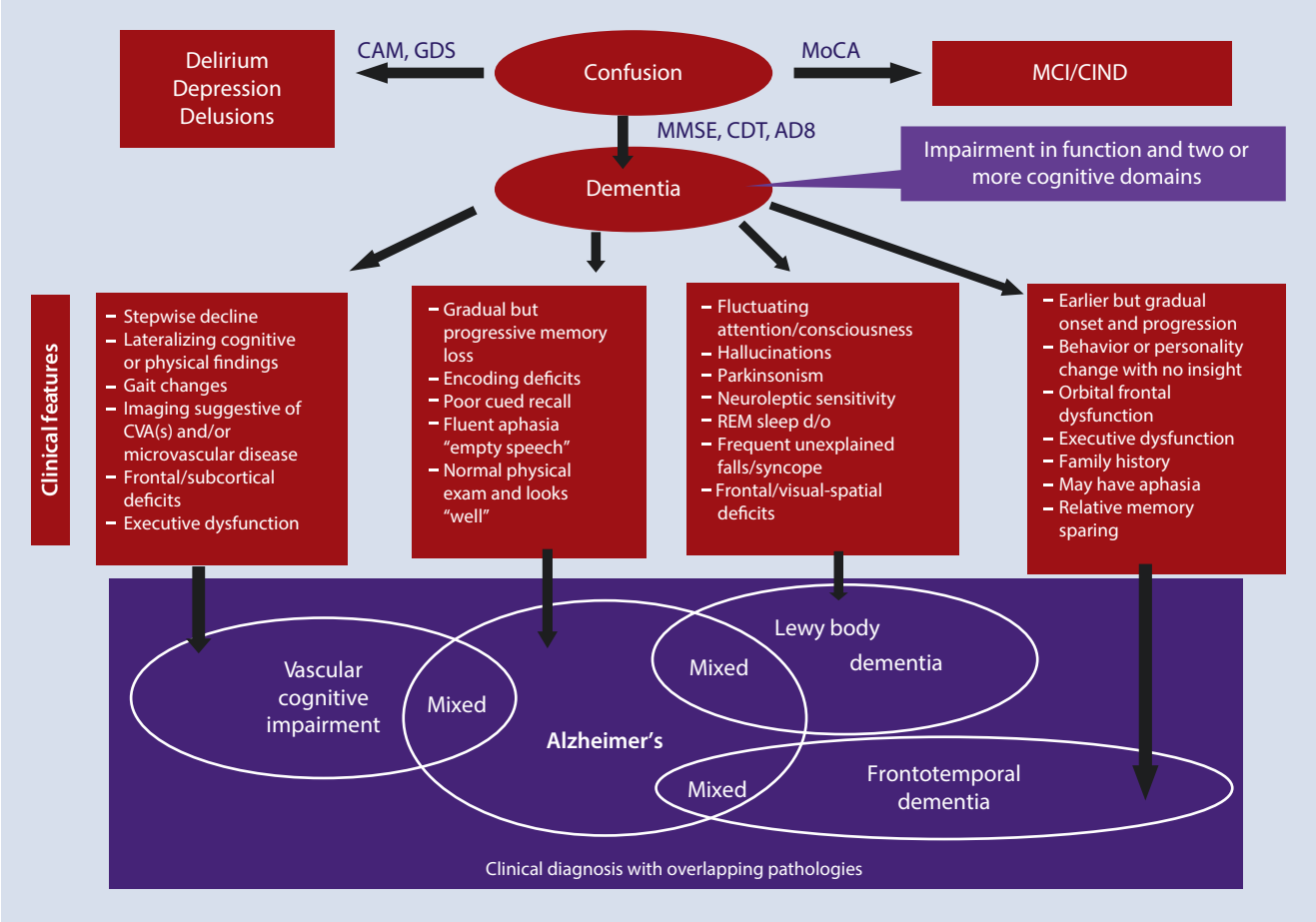


Fig. 28.2 Clinical diagnosis and screening tools. Depression and delirium screens include the GDS and CAM. The MoCA can be helpful in identifying mild cognitive impairment and early major neurocognitive disorder. The MMSE and CDT are universally used screening tools for cognitive impairment. The AD8 informant interview can be helpful in identifying Alzheimer disease. *CAM* Confusion Assessment Method, *GDS* Geriatric Depression Rating Scale, *MoCA* Montreal Cognitive Assessment, *MCI/CIND* mild cognitive impairment/cognitive impairment not dementia, *MMSE* Mini Mental State Exam, *CDT* clock drawing test, *AD8* Alzheimer's disease 8, *P/E* physical exam, *REM* rapid eye movement, *d/o* disorder, *CVA* cerebrovascular accident

Why Is Delirium an Emergency?

Delirium is associated with a 1-year mortality of 35–40% and should be considered a life-threatening emergency [4]. In a prospective study of older patients admitted to an internal medicine service, delirium was shown to be a powerful independent predictor of mortality [9]. It is the most common complication of hospitalization among geriatric patients. Delirium is associated with a number of adverse consequences including increased morbidity, prolonged hospitalization, and increased risk for institutionalization, in addition to diminished physical and cognitive rehabilitation at 6 and 12 months [4]. In intensive care settings, it is associated with an increased length of intensive care stay and total hospital days and an increased time spent on mechanical ventilation [4]. Delirium affects approximately 30%–50% of hospitalized older patients, although may be missed up to 70% of the time [4, 10]. A prospective study of older patients presenting to an emergency room found a delirium prevalence of 10%; however, it was only diagnosed by emergency physicians 35% of the time [11].

Teaching Point

Delirium is the most common complication among hospitalized geriatric patients and is an independent predictor of mortality. It is associated with prolonged hospitalization, increased risk for institutionalization, and decreased physical and cognitive rehabilitation at 6 and 12 months [4].

Management

Approximately 30–40% of cases of delirium are preventable. It has been suggested that several non-pharmacologic interventions may help prevent delirium [12]. There is evidence that the multicomponent targeting of modifiable risk factors, including sleep deprivation, immobility, hearing and/or visual impairment, and dehydration, prevents delirium in hospitalized older adults [13]. The Hospital Elder Life Program (HELP) for prevention of delirium has been studied in many different settings across North America, and the

Table 28.2 Non-pharmacologic strategies in the management of delirium

Intervention	Examples of strategies/comments
Family involvement	Allow family members to visit frequently and often
Remove lines if possible	This includes IV and Foley catheters
Reorient	Clocks and calendars in the room
Correct day-night reversal	Leave lights on during the day
Nutrition	Ensure adequate oral intake
Decrease environmental stimuli	Try to reduce noise, evaluate need for noisy monitors and alarm bells
Mobility	Mobilize out of bed early if possible
Review medication list	Reduce or stop medications associated with delirium risk unless clinically indicated
Correct sensory impairment	Glasses and hearing aids should be brought in and be available at the bedside

findings have been replicated in other countries including Australia and the Netherlands [14–16].

Teaching Point
Finding the cause(s) and trying to reverse the cause(s), if possible, are the first goals of treatment for delirium.

Prompt reversal is predicated on the prompt identification of the cause(s) of delirium. The standard work-up usually includes a complete blood count, electrolytes (sodium, chloride, potassium) and extended electrolytes (calcium, phosphate, magnesium), urea, creatinine, glucose, liver-associated enzymes, ammonia, thyroid-stimulating hormone, B_{12}, folate, urinalysis and urine culture, electrocardiogram (ECG), and chest x-ray. Computed tomography (unenhanced) of the head is also frequently done, particularly when there is a history of falls, anticoagulation, incontinence, decreased level of consciousness, or focal neurological findings.

In addition to trying to reverse the cause(s), the main components of delirium management include supportive therapy and pharmacologic treatment [4]. Supportive therapy includes trying to facilitate an environment that is stable, quiet, and well-lit during the day. Additionally, facilitating a normalized sleep-wake cycle and allowing family members to be present are interventions that are now recognized to be extremely helpful. Reorientation techniques or memory cues (e.g., calendars, clocks, family photos) may also be helpful. Finally, maintaining adequate fluid intake and minimizing the use of Foley catheters and restraints are important. Table 28.2 lists non-pharmacologic strategies of delirium. (See ▶ Chap. 17 for further details regarding non-pharmacologic interventions.)

Pharmacologic management includes the removal of medications that may be contributing to confusion if possible. While delirium is a multifactorial process, it is estimated that medications alone may account for 12–39% of all cases of delirium [17]. Observational studies show that the most common drugs associated with delirium are sedative hypnotics (e.g., benzodiazepines), analgesics (e.g., opioids), and medications with an anticholinergic effect. Other medications in toxic doses can also cause delirium. Medications may indirectly contribute to delirium by causing syndromes such as serotonin syndrome, neuroleptic malignant syndrome, or syndrome of inappropriate antidiuretic hormone (SIADH) secretion [17]. Table 28.3 lists common medications associated with delirium.

Teaching Point
It is important to keep in mind that the effect of medications that cause cognitive impairment may be additive, particularly in the case of anticholinergic medications [18, 19]. Depending on the type of medication and the clinical indication, these medications may need to be discontinued.

Alcohol intoxication and withdrawal can be medical emergencies as well, independent of the presence of delirium. In the case of intoxication, the associated risk of falls and an impairment in driving ability are potential emergencies. With moderate to severe intoxication, an inability to protect the airway and aspiration are main concerns. In the case of alcohol withdrawal, seizures and delirium tremens are the primary safety concerns. In patients where alcohol withdrawal is suspected, thiamine administration can be beneficial.

As a recent Cochrane review suggests, cholinesterase inhibitors and melatonin have not proven to be effective treatments for delirium [20]. Depending on the behaviors that accompany the delirium, medications may be required to promote the safety and well-being of patients and staff members. Low-dose antipsychotics are the most commonly used medications for this indication. Haloperidol has historically been the most commonly used antipsychotic for use in delirium. Doses of haloperidol used in the management of delirium in older patients are generally much lower than those used for antipsychotic purposes in psychotic disorders or in acute agitation in younger patients. Typically, haloperidol doses of 1–5 mg per day are used in divided doses. Side effects of haloperidol include QTc prolongation and extrapyramidal symptoms (e.g., parkinsonian symptoms, akathisia). When used intravenously, there is greater risk for QTc prolongation but less risk for extrapyramidal symptoms. Other medications used include atypical (second and third generation) antipsychotics such as risperidone, quetiapine, olanzapine, and aripiprazole. Atypical antipsychotics have similar efficacy to haloperidol in the management of delirium. Some of these medications have greater propensity for metabolic

Table 28.3 Common medications associated with delirium

Type	Subtype	Comment
Psychotropic medications	Tricyclic antidepressants	Dose-dependent effect, through anticholinergic effects
	Antipsychotics	Particularly typical (first generation), through anticholinergic effects
	Lithium	Dose dependent, often associated with ataxia, tremor, slurred speech
	Sedative hypnotics (e.g., benzodiazepines such as diazepam and lorazepam, barbiturates)	Dose-dependent effect
	Anticonvulsants (e.g., valproic acid, carbamazepine)	Cognitive slowing effect of all anticonvulsants Hepatotoxicity Hyperammonemia (valproic acid)
	Antiparkinsonian agents (e.g., benztropine)	Through anticholinergic effects
Analgesics	Opioids	Especially high dose Opioid crisis (fentanyl)
	NSAIDS	Potential for drug-drug interactions, decreased renal function
Antihistamines	Diphenhydramine	Dose-dependent effect
Gastrointestinal agents	Antispasmodics	Through anticholinergic effect
	H_2 blockers	
Antinauseants	Scopolamine	Through anticholinergic effect
	Dimenhydrinate	
Antibiotics	Fluoroquinolones	Variable
Cardiac medications	Antiarrhythmics	
	Digitalis	Dose-dependent effect
	Antihypertensives (e.g., beta-adrenergic blockers)	
Miscellaneous	Skeletal muscle relaxants	
Over-the-counter	Cold, allergy, and insomnia remedies (e.g., dextromethorphan, dimenhydrinate)	Through serotonin toxicity or anticholinergic effect
	Alcohol	Both intoxication and withdrawal. Rarely delirium can be caused by an associated thiamine deficiency

side effects than first-generation agents, orthostatic hypotension, and sedation, and they can all increase the QTc as well.

Teaching Point
All antipsychotics are also associated with increased risk of death in older adults, and informed consent should be obtained and documented prior to the use of these medications [20, 21].

Benzodiazepines often are used for withdrawal states, seizures, and catatonia but otherwise can make delirium worse and should usually be avoided or minimized otherwise. Ultimately the reason why delirium is an emergency is that the prompt identification and management of the causes, in addition to addressing risk factors in a supportive fashion which promotes safety, can reduce delirium impact, severity, and duration and result in better outcomes for older patients [4, 10].

28.1.3 Suicidality

Assessment

Older adults have high rates of suicide worldwide, including in Canada and the USA [22]. In the USA, persons over the age of 65 make up approximately 12% of the population but account for 25% of completed suicides [3]. For older adults, the suicide prevalence is four times higher than in the general adult population. Older white males, ages 80–84 years, in particular, are the highest-risk group for suicide in the USA [23].

That group's suicide rate of 73 per 100,000/year is six times the rate of the adult population [24]. Many older adults may end their lives by refusing food and/or needed medications or stopping renal dialysis; however, these deaths are typically not officially deemed as suicides [25]. Suicide in older persons may be underreported by 40% or more. Suicides may be hidden among undetermined deaths, as coroners might be less likely to consider the death of an older adult as suicide [26].

While major depressive disorder is the most common diagnosis associated with late-life suicide, schizophrenia, adjustment disorder, and alcohol abuse are also identified disorders of victims. Psychological autopsy studies suggest that psychiatric disorders are present in 85% to 90% of older adults who die by suicide. These studies suggest that depressive and bipolar disorders are diagnosed in 80%, substance use disorders in 60%, and schizophrenia in 10% of completed suicides in older adults [3, 27]. Alcohol abuse is less common in late-life suicide than depressive disorder, and alcohol abusers comprise a significantly smaller proportion of suicide victims in older when compared to younger age groups [27].

Most of our understanding of late-life suicide is based on epidemiologic data, which provide information only about general demographic risk factors or psychological autopsy studies that do not collect information directly from the suicide victims. Because of low prevalence, it is difficult to conduct prospective studies of late-life suicide; consequently, such studies are rare. A large prospective study of over 14,000 community-dwelling older persons who were followed for 10 years found that depressive symptoms, perceived health status, sleep quality, and absence of a relative and/or friend to confide in predicted late-life suicide. In their study, suicide victims did *not* have greater alcohol use and did *not* report more physical illness or physical impairment as would be expected given the usual association between substance abuse/physical illness and suicide [28].

Teaching Point

An important feature of suicide in older adults is the higher lethality associated with suicidal means.

Attempted suicide is far less frequent in later life than in younger age groups (the ratio of suicide attempts to completed suicide is 4:1 in seniors versus 20:1 in the general population). Older white males often commit suicide by violent methods such as guns, hanging, jumping, and carbon monoxide poisoning [29]. The reasons for increased lethality in older adults may be multifactorial and include the use of more violent means, decreased physical resilience, and social isolation [27].

There are several warning signs for suicide risk that should prompt further questions. These include:

- Withdrawal from activities and a loss of interest.
- Decline in self-care and grooming.
- Loss of health management compliance (e.g., going off diets, prescriptions).
- Experiencing or expecting a significant personal loss (e.g., spouse).
- Feeling hopeless and/or worthless.
- Putting affairs in order, giving things away, or making changes in wills.
- Stock-piling medication or exploring other lethal means.
- Preoccupation with death and finality; e.g., comments like "this is the last time that you'll see me" or "I won't be needing anymore appointments" should raise concern and further questions.
- The most significant indicator of suicide risk is an expression of suicidal intent.

From the American Association of Suicidology (AAS) website (► www.suicidology.org) comes an acronym identifying warning signs:

"IS PATH WARM?"

I - Ideation
S - Substance use
P - Purposelessness
A - Anxiety/agitation
T - Trapped
H - Hopelessness/helplessness
W - Withdrawal
A - Anger
R - Recklessness
M - Mood changes

The presence of depressive symptoms should prompt physicians to introduce questions about death wishes, thoughts of suicide, intent to harm self, and access to lethal means. All potentially suicidal older patients should be asked about mood, sleep habits, appetite, interests, and feelings of hopelessness. Questions concerning suicidal thoughts, plans, and intentions related to an interpersonal crisis should also be elicited, from all sources, including a clinical interview and collateral information [30].

Assessment tools that are quick and easy to administer are helpful in both primary care settings and in the emergency department. Three brief measures that can be used are the Depressive Symptom Index Suicidality Subscale (DSI-SS), Suicidal Behaviors Questionnaire-Revised (SBQ-R), and Suicidal Ideation Attributes Scale (SIDAS). The Scale for Suicide Ideation and the Chronological Assessment of Suicide Events scale can also be used to improve detection of suicidality. Three other measures recommended by the Canadian Coalition for Seniors Mental Health include the Harmful Behaviors Scale, the Reasons for Living Scale Older-Adult version, and the Geriatric Suicide Ideation Scale. The Geriatric Suicide Ideation Scale (GSIS) is a new measure of suicide risk and resiliency developed with Canadian seniors [31].

The SAD PERSONS scale (SPS), although frequently and widely used as a risk assessment tool for both younger and older patients, has not been shown to successfully predict suicide; however, none of the other scales that are in use have been proven to be clearly effective in this regard. They do provide a framework for a reasoned assessment based on known risk factors [32].

28

Table 28.4 Geriatric Depression Scale-Suicide Ideation Screening Items[a] [33]

GDS item no.	Question
3	Do you feel that your life is empty?
7	Do you feel happy most of the time?
11	Do you think it is wonderful to be alive?
12	Do you feel pretty worthless the way you are now?
14	Do you feel that your situation is hopeless?

[a]Scoring for the Geriatric Depression Scale (GDS) items involves assigning a response of "yes" or "no" to each item. These items were drawn from the GDS

As the Geriatric Depression Scale (GDS) is often used as a clinical screen for depression, there is a scale derived from elements of the GDS. This scale is called the Geriatric Depression Scale-Suicidal Ideation (GDS-SI) which offers screening for late-life suicide ideation with a brief, validated suicide assessment scale [33]. The five items of this empirically derived subscale assess perceived hopelessness, worthlessness, emptiness, absence of happiness, and lack of perception that it is "wonderful to be alive," all of which are variables theoretically and empirically associated with suicide ideation (see Table 28.4).

Both the 15-item GDS and 5-item GDS-SI appear to differentiate older primary care patients who expressed suicidal ideation from those who do not. This suggests that this screen may effectively identify individuals for whom a more in-depth suicide risk assessment would be warranted. The GDS-SI demonstrated sensitivity and specificity equivalent to that of the 15-item GDS in terms of identifying people at risk for suicide [33].

Diagnostic assessment should be structured in a way that includes a detailed review of the spectrum of psychiatric illnesses including psychosocial factors in addition to the review of other systemic medical and neurological problems, concurrently used medications and drugs, screen for substance use disorders, and a standardized evaluation of cognition [34]. It is important to note that in older adults the report of being depressed or even the appearance of depression may not be as evident as in younger patients [30, 35, 36]. However, mental status examinations on older suicidal patients may demonstrate despondency, hopelessness, and, sometimes, agitation. The presence of psychosis and anxiety or loss of rational thinking capacity should heighten the safety concerns for older patients and suggests a greater need for close supervision.

Management and Disposition

The key to proper decision-making with managing suicidal geriatric patients is obtaining adequate history and collateral history. Balancing static and dynamic risk factors is the key. Static risk factors (e.g., age, sex, history of depressive disorder and/or suicide attempts) have to be considered in the context of dynamic risk factors (e.g., current mental status: depressed, psychotic, anxious, and/or disorganized; intoxication; access to lethal means; presence of a supportive environment: family and friends who they can confide in and be with), which reflect the current state of clinical suicide assessment (see Fig. 28.3).

Older patients assessed as likely to commit suicide should be hospitalized on a secure psychiatric unit. Suicidal older patients should be observed closely or constantly depending on the state of clinical acuity during the first 24 hours of admission. Suicide is not a specific disorder but a painful process typically mediated by a number of complex vulnerabilities—only some of which are modifiable (see static risk factors in Fig. 28.3).

Prevention

Identifying and targeting high-risk older adults with clinical and social interventions is more effective in preventing suicide than interventions directed at older adults with active suicidal ideation and intent [27]. Keeping in mind that the biggest risk factor for suicide is depressive disorder, the best way to prevent suicide would be the improved recognition and effective treatment of depressive disorders. An approach that includes best practices for assessing and managing major depressive disorder in older patients is recommended as is more fully described in ▶ Chaps. 6, 7, and 10.

Antidepressants are considered safe and effective in targeting depressive symptoms; clinical recommendations favor selective serotonin reuptake inhibitors (SSRIs). As first line, SSRIs are generally well tolerated and have fewer sedative and anticholinergic adverse effects as well as a reduced risk of lethal overdose compared with tricyclic antidepressants. Of note, older adults are more likely to experience hyponatremia/SIADH with SSRI use compared to younger adults.

Several medications are thought to confer protection from suicide including lithium and clozapine; however, the evidence is limited [37]. There is a novel repurposing and some emerging evidence for the use of ketamine for acute suicidal ideation; however, this remains at an investigational stage [38]. Various forms of psychotherapy including cognitive and supportive psychotherapy, with family involvement, may provide significant benefits in suicidal older patients. Psychotherapeutic interventions that enhance adherence to treatment, provide education, increase self-esteem, strengthen social supports, increase a sense of meaning, and diminish hopelessness are clinically recommended [25]. Interestingly, the Prevention of Suicide in Primary Care Elderly Collaborative Trial (PROSPECT) found that combined antidepressant (citalopram) and psychotherapeutic (interpersonal psychotherapy) treatment helped resolve depressive disorders and reduce suicide ideation among older primary care patients in a collaborative care context [39].

Electroconvulsive therapy (ECT) can be lifesaving, particularly for patients who are not eating or drinking,

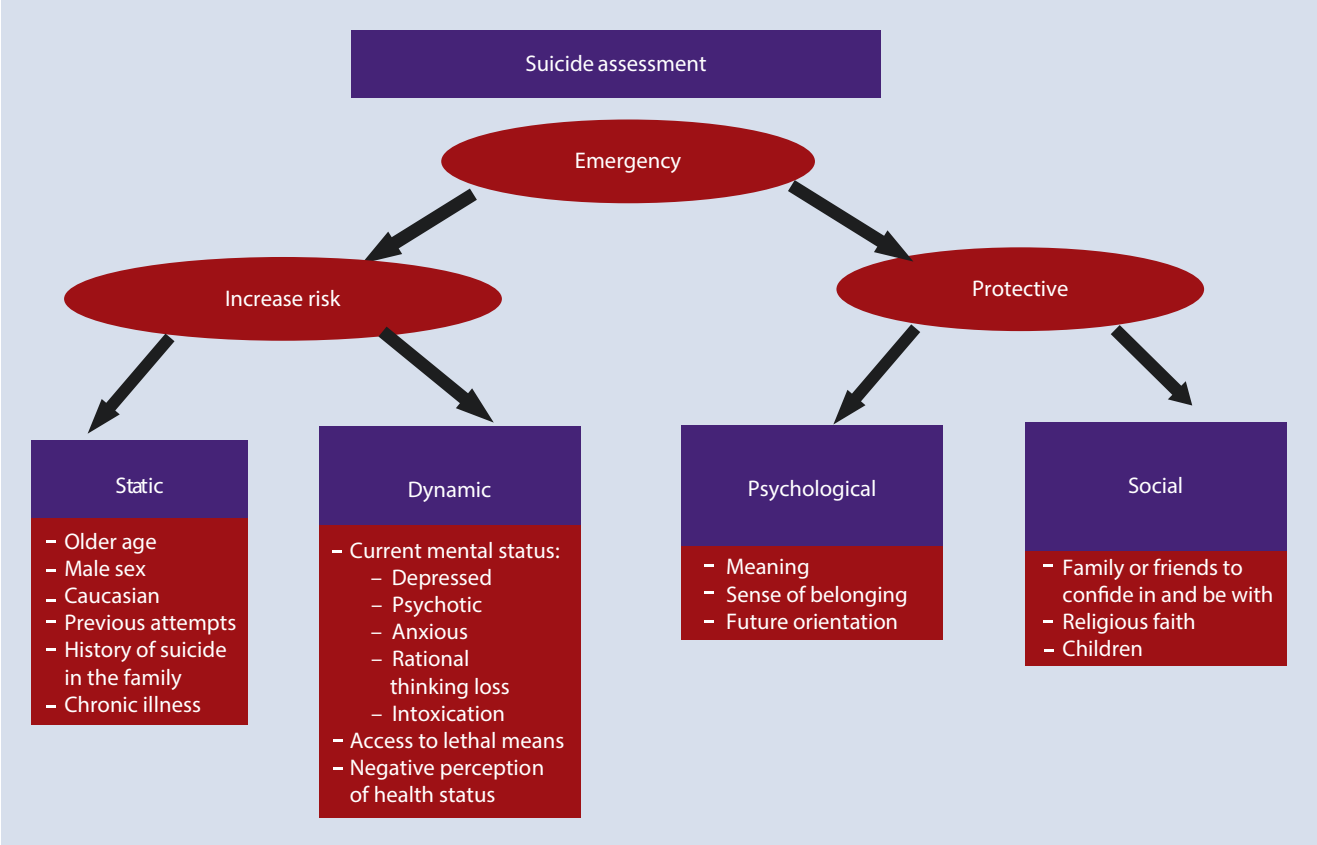


Fig. 28.3 Suicide assessment: the balancing of static and dynamic risk factors against protective factors

psychotic, and refusing medications and where other treatments have failed. A large number of studies support the effectiveness of ECT for treatment of late-life depression, but adverse effects (e.g., cardiac complications, cognitive decline, and/or delirium) limit its use in some older patients.

Depression in Older Adults with Suicidality

Late-life depression is a common and potentially life-threatening illness. It is often undiagnosed and undertreated. One of the challenges of diagnosis is the attribution of the symptoms of depression or other psychological conditions to aging or to systemic medical conditions. Depression presents differently in late life than in earlier years [40]. Often, late-life depression is not accompanied by dysphoria or sadness which characterizes depression in younger individuals. Family members can often see that "something is wrong" without knowing "what it is." Although clinicians know to look for changes in appetite, sleep patterns, and loss of interest in previously enjoyed activities, as these are often important symptoms of depression in later life, many adults have a difficulty calling this illness "depressive disorder" without manifest dysphoria [40].

The DSM-5 provides the diagnostic criteria for major depressive disorder. Older adults are more likely to endorse feelings of worthlessness and guilt; they are more likely to suffer sleep disturbances and to complain about concentration, memory, and attention problems [29, 41, 42]. In addition, older adults frequently present with vague somatic complaints or have physical problems that mask or mimic depression [40]. Standard screening tools, such as the self-rated GDS, can be helpful in identifying depression in older persons [29].

Older adults with depressive disorder or other psychiatric conditions receive treatment at surprisingly and concerningly low rates [43]. A study which examined 348 participants aged 55 years and older who met criteria for prevalent DSM-IV mood and anxiety disorders from the National Comorbidity Survey Replication (NCS-R) found that approximately 70% of older adults with prevalent depressive and anxiety disorders did not use clinical services [44]. Furthermore, only one in ten patients with severe symptoms of psychiatric illness sought treatment [44].

Late-life depression is heterogeneous; some patients have early-onset depressive disorder with recurrent episodes in older age, and in some, de novo depressive episodes develop late in life. Patients with late-onset depressive disorder tend to have a less frequent family history of depressive or bipolar disorders, a higher incidence of systemic medical and neurological comorbidities (particularly vascular disease), and a higher prevalence of cognitive impairment. In turn, depression can exacerbate cognitive and physical limitations that lead to social isolation. Social disruption further exacerbates both depressive disorder and cognitive dysfunction and contributes to late-life suicide risk.

Teaching Point
Highlighting the life and death nature of treating depressive disorder in older adults is the finding that two thirds or more of older patients who die by suicide are seen by primary care physicians within a month of their deaths and up to one half within 1 week [30, 45].

28.1.4 Aggression

Epidemiology and Diagnosis

Homicidality and physical assault in older adults have not been well studied. There are only a few case reports, case series, and investigational studies examining homicidal behaviors in patients over the age of 65. Some of these include a review of murders/suicides in older patients [3]. Older patients who are aggressive and/or agitated usually suffer from a systemic medical or psychiatric illness. The most common causes for aggression and agitation in older adults are delirium, major neurocognitive disorder, and psychotic disorder. In the field of long-term care, studies have uncovered high rates of interpersonal violence and aggression toward older adults; in particular, abuse of older residents by other residents in long-term care facilities is now recognized as a problem that is more common than physical abuse by staff members [46]. Increasingly, as a result of coroner's cases, the reality of aggression from patients suffering from major neurocognitive disorder to other patients and caregivers has become a public and workplace safety concern especially for healthcare providers in hospitals and long-term care setting. The police are now frequently called to respond to nursing homes as a result of this heightened awareness.

Major Neurocognitive Disorder

The neuropsychiatric symptoms (NPS) of a major neurocognitive disorder are among the most complex, stressful, and costly aspects of care, and they lead to a myriad of poor patient health outcomes, other healthcare problems, and income loss for family caregivers. These symptoms are the prominent safety concern associated with this illness and are a frequent cause of visits to the emergency room and urgent consults to psychiatrists [47]. The NPS include agitation, depression, apathy, repetitive questioning, psychosis, aggression, sleep problems, wandering, and a variety of inappropriate behaviors. These symptoms are also known as behavioral and psychological symptoms of dementia (BPSD).

Agitation (a broad category that includes excessive psychomotor activity such as pacing, following, restlessness, dressing, and undressing) and emotional distress are common and persistent and may vary through the progression of the disease. While the prevalence of aggression and agitation may be as high as 50% in the course of the illness, one or more of these NPS will affect nearly all people with major neurocognitive disorder over the course of their illness. (See ▶ Chap. 22.)

The causes include neurobiologically related disease factors, unmet needs, caregiver factors, environmental triggers, and interactions among individual, caregiver, and environmental factors. The complexity of these symptoms and their causes imply there is no single solution that will work in all patients. Individually tailored care plans for patients and the caregivers are very much needed. Non-pharmacologic approaches should be used first line, although these have their own risks as well. Aside from issues related to aggression toward caregivers and family and workplace safety, the main challenge with these approaches is their availability and the staff to support these interventions. Non-pharmacologic approaches with the strongest evidence base involve family/caregiver interventions and are best when they involve face to face time with caregivers.

Regarding pharmacologic treatments, antipsychotics, including risperidone, aripiprazole, and, to a lesser extent, olanzapine, have the strongest evidence base, with a modest effect size (0.13–0.16), although the risk to benefit ratio is a concern. Any such benefits must be balanced against the risk of severe adverse events, including mortality which appears to be a relative risk increase of approximately 2% in short-term studies [47]. When the behavioral symptoms are causing severe safety concerns, the calculus is clearer. In that instance, antipsychotics are the medication class of choice. Katz's meta-analysis of the risperidone trials demonstrated clearer efficacy and separation from placebo when the symptoms are more frequent or severe [48]. Antidepressants, in particular citalopram, have demonstrated efficacy on agitation although higher doses were needed and, surprisingly, a negative effect on cognition was seen. Further studies are needed given the concern of QTc prolongation and an effective dose of 30 mg/day which was needed in the CitAD trial [49].

28.1.5 Abuse of Older Adults Including Neglect

Although first described in medical literature in the 1970s, elder abuse is now being recognized as a virtual epidemic [46]. It constitutes an emergency given both the extent and frequency of the problem but also because of the nature of what is now coming to light. Nearly one in ten older adults experiences some form of abuse or neglect every year, and the incidence is increasing [46]. There are several definitions for describing elder abuse all of which highlight the urgent nature of the problem. The essential elements include an intentional or neglectful act by the caregiver or trusted person, which may result in harm or threaten the well-being of older adults. This abuse may take various forms, such as physical abuse, psychological abuse, sexual abuse, financial abuse, and caregiver neglect. ◘ Figure 28.4 describes the supportive features of various types of elder abuse [46].

There are both individual and perpetrator factors, as well as relationship and environmental factors that contribute to the increased risk of elder abuse. In a systematic review of 49

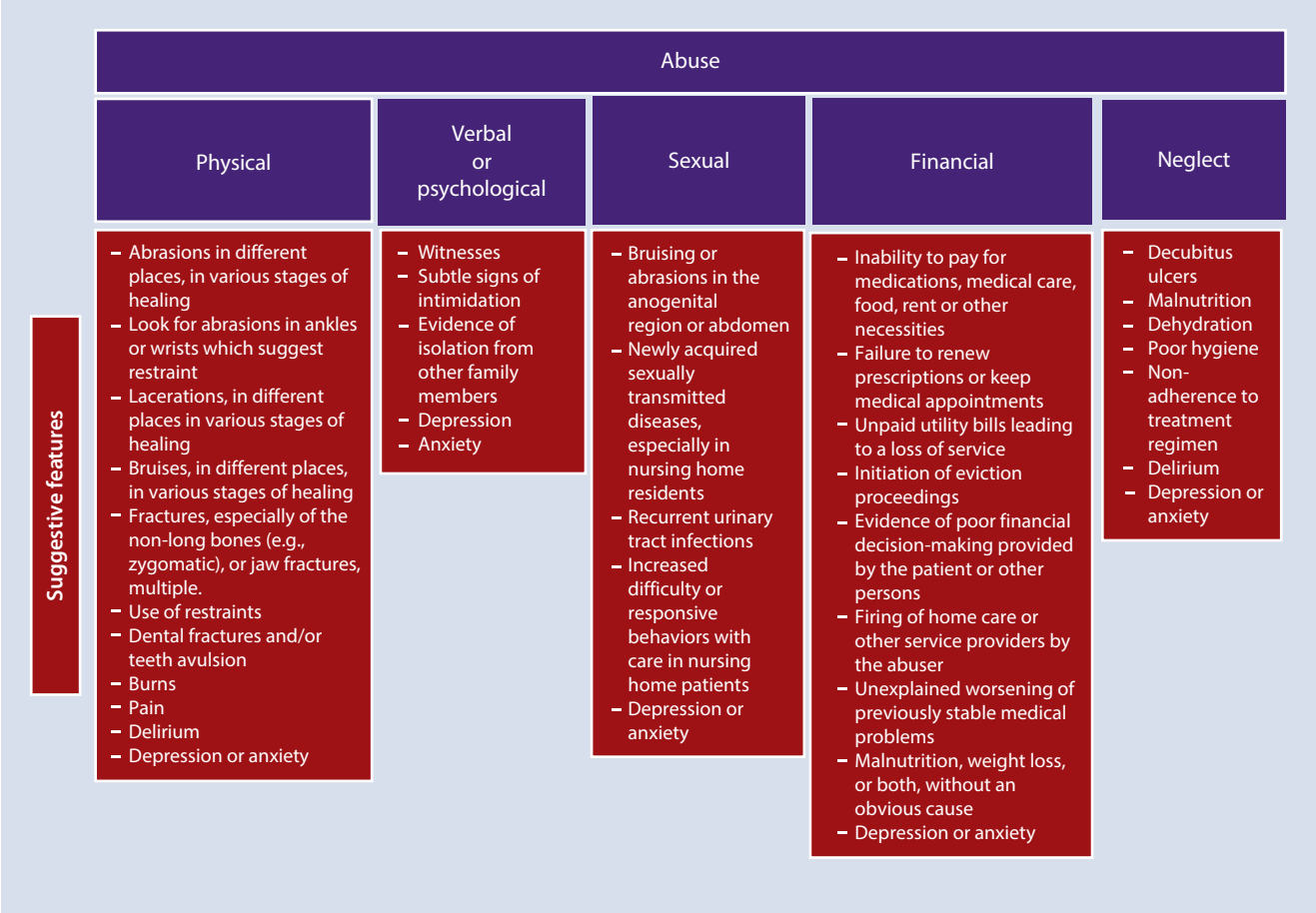


Fig. 28.4 Supportive features of different types of abuse of older persons (Features suggested from reference [46])

studies, individual risk factors include cognitive impairment, behavioral problems, psychiatric illness, functional dependency, poor physical health, frailty, low income, and trauma or past abuse. Factors related to the perpetrator include caregiver burnout or stress and psychiatric illness. Poor social supports and familial discord and conflict are other factors that contribute to an increased risk of abuse [1, 50]. The pattern of injuries may point toward elder abuse as the underlying etiologic factor. Fractures of the jaw or zygoma suggest that the patient had sustained head or facial trauma, as opposed to fractures of the long bones which may occur in the context of falls [46]. A study of older adults presenting to the emergency department demonstrated that penetrating injuries were often seen in victims of severe traumatic abuse [46]. The most common types were open wounds (56%), internal injuries (24%), and fractures (22%). They were more likely to suffer injuries to the head and trunk. Another study assessing the use of emergency department by victims of elder abuse found that 15.4% of the visits had physical injuries as their presenting complaint [51].

Suspicion of elder abuse may be made in older adults who present with multiple injuries, with wounds, abrasions, and cuts in various stages of healing, evidence of multiple fractures of different ages (as may be shown on imaging investigations), poor general hygiene including nail and oral hygiene, malnutrition, dehydration, and nonadherence to medical care. Evidence of dental fractures, teeth avulsions, burns, and decubitus ulcers also may suggest abuse and neglect. Signs of financial abuse include the inability to pay for the necessities of life, malnutrition, and evidence of poor financial decision-making that may favor the abusers. A listing of the types of abuse with clarifiers is given in Fig. 28.4.

Uncovering abuse or other mistreatment of older adults may be challenging for several reasons. Older adults often suffer from isolation and loneliness. This dependency may lead older adults to misinform the healthcare providers on account of a fear of being chastised, abandoned by the caregiver, or being placed in a nursing home. It is prudent to consider interviewing older adults in the absence of the caregiver if abuse is suspected. Consideration to notifying the proper authorities and the systems in place for patient advocacy is the compassionate and caring thing to do. Involving a social worker is often a good idea in these difficult circumstances as supports may exist in the communities in which these older adults live.

The use of multidisciplinary teams in the context of the abuse of older adults has emerged as one of the intervention strategies to address the complex and multidimensional needs and problems of victims of elder abuse. Such teams are

an important resource for physicians. These new developments suggest an expanded role for physicians in assessing and treating victims of elder abuse and in referring them for further care [46].

Teaching Point

Management of elder abuse should be dictated by the immediate safety concerns for the patient. A desire to protect the victim may conflict with the desire to maintain patient autonomy and privacy. However, safety issues should generally supersede personal rights in potentially dangerous situations. Depending on the legal jurisdiction, a treatment plan usually includes reporting suspected abuse and neglect to appropriate government agencies. Also, hospitalization to ensure safety may also be indicated.

28.1.6 Adverse Medication Side Effects

Life-threatening emergencies in older patients may be the result of substances of abuse or medications, including prescription and over-the-counter medications. Alcohol is the substance of choice for many older adults, especially older males. Life-threatening emergencies caused by medications can be organized by drug class (see ◘ Table 28.5) and adverse effect (◘ Table 28.6) [52–57].

Antipsychotics and tricyclic antidepressants, like chlorpromazine and amitriptyline, which because of their antagonism of various classes of receptors (e.g., anti-alpha-adrenergic, anticholinergic, antihistaminergic) cause a myriad of side effects, can be life threatening. For example, these medications are known to cause orthostatic hypotension which can be particularly serious if it leads to falls and syncope. Among the atypical antipsychotics, the risk of orthostatic hypotension is highest with clozapine and quetiapine, and among the typical antipsychotics, the risk is highest with low-potency agents (e.g., thioridazine, chlorpromazine) [58]. These medications also have anticholinergic side effects that can lead to delirium and urinary retention.

QT Prolongation

Tricyclic antidepressants have long been known to cause cardiac conduction abnormalities including QRS and QTc prolongation [58]. QTc prolongation can occur with all antipsychotics, but an increased risk is seen with phenothiazines, haloperidol (especially if intravenously given or increased dose), quetiapine, amisulpride, and ziprasidone. Antidepressants such as mirtazapine, citalopram (dose > 40 mg/day or > 20 mg/day in older adults), escitalopram (dose > 20 mg/day), tricyclic antidepressants, atomoxetine, and lithium can cause QTc prolongation. QTc prolongation is a marker of arrhythmic risk. Torsades de pointes (TdP), a specific arrhythmia, may lead to syncope, dizziness or ventricular fibrillation, and sudden death. The incidence of TdP ranges from 2% to 12% depending on the medication, dose, and other risk factors [52, 59]. ◘ Table 28.7 lists some psychiatric medications with risk of TdP [52, 59, 60].

Antipsychotics

Antipsychotic drugs may be associated with adverse effects, which are predictable including akathisia, dystonias, parkinsonism, and tardive dyskinesia [61]. Although these are not usually life threatening, they may be distressing and constitute an emergency because of the distress. Dystonias, including axial dystonias, can be painful and require urgent intervention to prevent falls. Oculogyric crisis, for example, requires urgent intervention for relief in the form of anticholinergics (e.g., benztropine) or antihistamines (e.g., diphenhydramine). Rarely, the use of antipsychotics may result in life-threatening complications, such as neuroleptic malignant syndrome (NMS), which may present with hyperthermia, autonomic instability, muscular rigidity, cardiac arrhythmias, and renal failure [61]. It is often difficult to differentiate NMS from serotonin syndrome, which is caused by toxicity caused by SSRIs. ◘ Table 28.8 differentiates NMS from serotonin syndrome [55]. For further details on these syndromes, please refer to ▶ Chap. 5.

There are side effects specific to certain medications (see ◘ Table 28.6). Clozapine is rarely associated with agranulocytosis at a rate of less than 0.5% with regular monitoring. Even more rarely, phenothiazines, mirtazapine, and carbamazepine are also associated with agranulocytosis. Heart muscle disease presents most commonly in older adults as chronic heart failure, but myocarditis and cardiomyopathy, although relatively rare, are devastating complications of psychotropic drug therapy that have been particularly linked to clozapine treatment. The incidence is very rare at 0.015–1.2% [56]. There is an associated 23% mortality rate; 85% of cases occur within the first 2 months of starting clozapine [57] with a median onset of 2–3 weeks. In such cases, clozapine should be stopped immediately.

Antidepressants

Selective serotonin reuptake inhibitors (SSRIs) are relatively safe medications compared to tricyclic antidepressants (TCAs) with a wider therapeutic window and less toxicity with overdose. SSRIs are associated with side effects but they are not usually life threatening. The exception to that rule is serotonin syndrome which may occur when different medications increase the amount of serotonin that the nervous system is exposed to. SSRIs are associated with an increased risk of gastrointestinal (GI) bleeds, particularly in those over age 85 and those with a history of GI bleeds and/or platelet deficiency/dysfunction. A recent Cochrane

Table 28.5 Emergency side effects of commonly prescribed medications, by drug class

Class	Specifier	Comments
Antipsychotics	Low potency	Hypotension, cardiac conduction delays, urinary retention, anticholinergic symptoms, exacerbation of close-angle glaucoma, NMS
	High potency	Dystonia, parkinsonism, NMS
	Atypical	Hypotension, agranulocytosis with clozapine, NMS, SIADH
Antidepressants	Tertiary amine tricyclics	Hypotension, cardiac conduction delays, urinary retention, anticholinergic symptoms, exacerbation of close-angle glaucoma, SIADH, serotonin syndrome
	Secondary amine tricyclics	Less severe side effects than the tertiary amine tricyclics, SIADH, serotonin syndrome
	Monoamine oxidase inhibitors	Hypertensive crisis, serotonin syndrome when combined with other serotonergic medications
	SSRIs	Hyponatremia (SIADH), rarely orthostatic hypotension, prolonged QTc with citalopram/escitalopram, increased risk of GI bleeds, serotonin syndrome
	SNRIs	Hyponatremia (SIADH), hypertension, serotonin syndrome, hepatotoxicity
	SARIs	Hyponatremia (SIADH), priapism, hypotension, serotonin syndrome
	NaSSA	Hyponatremia (SIADH), agranulocytosis with mirtazapine, serotonin syndrome
Anxiolytics	Long half-life benzodiazepines	Falls, ataxia, delirium, confusion/cognitive impairment, sedation, impaired driving ability
	Short half-life benzodiazepines	Falls, less severe ataxia, confusion/cognitive impairment, sedation, impaired driving ability
	Buspirone	Restlessness, drowsiness, dizziness, blurred vision
Mood stabilizers	Lithium	Sinoatrial node dysfunction, lithium toxicity: ataxia, renal failure, delirium, coma, hyperparathyroidism, hypothyroidism
	Anticonvulsants	Fulminant hepatic failure, thrombocytopenia (valproic acid), agranulocytosis (carbamazepine), Stevens-Johnson syndrome (lamotrigine and carbamazepine), hyperammonemia (valproic acid), pancreatitis (valproic acid), SIADH (carbamazepine/oxcarbazepine)
Cognitive enhancers	Acetylcholinesterase inhibitors	Sinoatrial node dysfunction, arrhythmia, bradycardia
Opioids	Fentanyl	Respiratory depression; especially high dose Opioid crisis (fentanyl)

Note: NaSSA noradrenergic and specific serotonergic antidepressant, *NMS* neuroleptic malignant syndrome, *SARI* serotonin antagonist and reuptake inhibitor, *SIADH* syndrome of inappropriate antidiuretic hormone, *SNRI* serotonin norepinephrine reuptake inhibitors, *SSRI* selective serotonin reuptake inhibitors

review of 15 case-control studies (including 393,268 participants) and four cohort studies demonstrated that there was an increased risk of upper GI bleeding with SSRI medications in the case-control studies (OR 1.66, 95% CI 1.44–1.92) and cohort studies (OR 1.68, 95% CI 1.13–2.50). The number needed to harm for upper GI bleeding with SSRI treatment in a low-risk population was 3177, and in a high-risk population, it was 881. The risk of upper GI bleeding was further increased with the use of both SSRI and nonsteroidal anti-inflammatory drugs (OR 4.25, 95% CI 2.82–6.42) [62].

Hyponatremia due to SIADH is also a rare but foreseeable side effect of antidepressants, including SSRIs. A retrospective, population-based, matched-cohort study suggested that

Table 28.6 Emergency side effects of commonly prescribed medications, by adverse effect [52–57]

Adverse effect	Presenting symptoms	Medications	Incidence/risk of death	Comments
QT prolongation	QTc > 450 milliseconds on ECG, arrhythmia, bradycardia, shortness of breath, syncope	Antipsychotics (phenothiazines, haloperidol, quetiapine, amisulpride, ziprasidone) Antidepressants (mirtazapine, citalopram, escitalopram, TCAs) Atomoxetine Lithium	The incidence or prevalence of drug-induced prolonged QTc in the general population has not been determined QTc prolongation can lead to torsades de pointes (TdP); the incidence is 2–12% depending on the drug, dose, and other risk factors	Many medications have been associated with QTc prolongation Risk factors include bradycardia, congenital long QT, hypokalemia, hypomagnesemia, advanced age, female, hypothyroidism Effects of different drugs can be additive Drug interactions can also increase risk of QTc prolongation
Myocarditis	Fatigue, shortness of breath, chest pain, tachycardia, palpitations, fever, leukocytosis ECG abnormalities (note: patient presentation can be nonspecific and highly variable)	Clozapine	Incidence reported with clozapine 0.015–1.2%; 23% mortality rate	Stop clozapine immediately; 85% of cases occur within the first 2 months of starting clozapine with a median onset of 2–3 weeks
Agranulocytosis	ANC < 0.5×10^9 cell/L. Signs and symptoms of infection	Clozapine, phenothiazines, mirtazapine, carbamazepine	Less than 1%	Risk is well managed by clozapine monitoring systems currently in place (requirement for weekly blood monitoring in first 6 months followed by biweekly blood monitoring months 6–12 and monthly blood monitoring after month 12)
Serotonin syndrome	Delirium, agitation, myoclonus, hyperthermia, diaphoresis, tremor, hypertension, convulsions; may progress to rhabdomyolysis, coma, and death	Serotonergic agents when used in combination (SSRIs, SNRIs, TCAs, MAOIs, buspirone, St. John's wort, mirtazapine, metoclopramide, ondansetron, opioids, triptans, tramadol, meperidine, dextromethorphan) Overdose on serotonergic medication(s) (Lithium can potentiate risk for serotonin syndrome)	14–16% of patients that overdose on SSRIs	Stop medication and initiate supportive care in a hospitalized setting (BP control, myoclonus) Usually occurs within 24 hours of medication initiation Consider cyproheptadine, atypical antipsychotics for treatment of severe cases
Hypertensive crisis	Severe headache (usually the first symptom), nausea/vomiting, sweating, neck stiffness, visual disturbances, tachycardia, chest pain	MAOIs (most commonly as a result of an interaction with tyramine containing foods)	Incidence is dependent on consumption of tyramine containing foods	Known as the "cheese reaction". Withhold medication and provide medical attention immediately
Neuroleptic malignant syndrome (NMS)	Hyperthermia, muscle rigidity (unresponsive to anticholinergics), tremor, delirium, autonomic instability, elevated CK and elevated WBC, coma, and death	Antipsychotics (risk is highest with high-potency first-generation agents and lowest with second-generation agents, proportional to degree of dopamine blockade) (Lithium can potentiate risk for NMS)	0.01–0.2% incidence 10% fatality rate	Often requires ICU support When suspected, antipsychotics should be stopped immediately. Nearly all cases develop within the first few days to weeks of starting antipsychotic or with dose increase Consider dantrolene, bromocriptine, ECT for severe/refractory cases

Table 28.6 (continued)

Adverse effect	Presenting symptoms	Medications	Incidence/risk of death	Comments
Acute dystonia	Severe muscle spasm in any part of the body (eyes, tongue, neck, torso, arms, legs)	Antipsychotics Increased risk with high-potency antipsychotics (e.g., haloperidol)	10% incidence but incidence is lower in older adults	Can be very painful and frightening for patients. May cause problems swallowing or speaking. More common in young males and in antipsychotic-naïve patients. Can occur within hours of starting antipsychotic
Syndrome of inappropriate antidiuretic hormone (SIADH) secretion	Hyponatremia (in mild-moderate cases can present with delirium, nausea, headache, and lethargy. In severe cases can develop seizures and coma; serum osmolality low, urine osmolality high	Antidepressants (SSRIs, TCAs, SNRIs, MAOIs), atypical antipsychotics, anticonvulsants	Incidence of SSRI-induced SIADH is 0.5–32%	Usually develops in the first few weeks of treatment. More common in hospitalized older patients
Steven-Johnson syndrome (SJS)	Severe mucocutaneous reaction—extensive necrosis and detachment of the epidermis, fever, flu-like illness	Lamotrigine, phenobarbital, carbamazepine, phenytoin	< 1% incidence, 10% mortality rate	Generally seen in the first 8 weeks of medication treatment
Priapism	Painful penile erection that lasts > 4 hours	Risperidone, olanzapine, clozapine, chlorpromazine, quetiapine, sertraline, citalopram, escitalopram, fluoxetine, trifluoperazine, trazodone, lithium, methylphenidate, atomoxetine	< 1% incidence, antipsychotics have been implicated in 20% of drug-induced cases	Considered a urological emergency. Associated with alpha-1 blockade. Onset is idiosyncratic with no clear relationship to dose or duration of treatment
Anticholinergic toxicity	Delirium, visual hallucinations, urinary retention, dry mouth, blurred vision, tachycardia, no sweating	Chlorpromazine, clozapine, loxapine, methotrimeprazine, perphenazine, olanzapine, quetiapine, trifluoperazine, carbamazepine, oxcarbazepine, TCAs, paroxetine, amantadine, benztropine, lithium	Unknown	In severe cases may need ICU support. Over 600 medications are known to have anticholinergic activity
Alcohol withdrawal	First 24–48-hour coarse tremor, agitation, diaphoresis, confusion, headache, diarrhea, vomiting Within 2 days—seizures ("rum fits"), hallucinosis Within 5 days—delirium tremens (DTs) Hours to days—Wernicke encephalopathy	Alcohol		Assess severity and need for medical care, thiamine for prevention of Wernicke encephalopathy, regular doses of benzodiazepines for short-term management of symptoms and to reduce risk of seizures
Benzodiazepine withdrawal	Rebound insomnia, nervousness, GI distress, muscle tension, delirium, psychosis, seizures	Benzodiazepines. Short-acting agents are generally associated with more problems on withdrawal than longer-acting agents		Withdrawal symptoms can occur after 4–6 weeks of continuous use

Table 28.7 Risk of torsades de points (TdP) with psychiatric medications[a] [52, 59, 60]

Medications with a known risk of TdP	Medications with a possible risk of TdP	Medications with a conditional risk of TdP (conditional risks = bradycardia, low serum K or Mg, excessive dose, impaired elimination or use of concomitant QT/TdP drug)
Chlorpromazine	Asenapine[a]	Amisulpride[a]
Citalopram[a]	Atomoxetine[a]	Amitriptyline
Donepezil[a]	Clomipramine	Aripiprazole
Escitalopram[a]	Clozapine[a]	Chloral hydrate
Haloperidol[a]	Desipramine[a]	Doxepin
Thioridazine[a]	Flupentixol[a]	Fluoxetine[a]
	Iloperidone[a]	Fluvoxamine[a]
	Imipramine	Galantamine[a]
	Lithium	Olanzapine
	Mirtazapine[a]	Paroxetine
	Nortriptyline	Quetiapine[a]
	Paliperidone[a]	Sertraline[a]
	Perphenazine[a]	Trazodone
	Risperidone[a]	Ziprasidone[a]
	Trimipramine	
	Venlafaxine[a]	

[a]The medications in this table all have the potential for QT prolongation and TdP, but those with a "[a]" are for those categorically established side effects in the product monographs

Table 28.8 Distinguishing serotonin syndrome from neuroleptic malignant syndrome (NMS) [55]

Feature	Serotonin syndrome	NMS
Onset	Abrupt	Gradual
Course	Rapidly resolving	Prolonged
Other clinical findings	Myoclonus, tremor, sweating	Diffuse rigidity, bradykinesia
Reflexes	Increased/clonus	Decreased
Pupils and extraocular movements	Mydriasis and nystagmus	Normal
Laboratory studies		Elevated CK (> 1000 IU/L), LAEs, WBC, low serum iron

Note: CK creatine kinase, *LAEs* liver associated enzymes, *WBC* white blood cell count

the use of a second-generation antidepressant in routine care by older adults is associated with an approximate fivefold increase in 30-day risk for hospitalization with hyponatremia compared to nonuse. However, the absolute increase in 30-day incidence is low [63].

The interruption, dose reduction, or discontinuation of antidepressant drugs, including SSRIs or serotonin norepinephrine reuptake inhibitors (SNRIs), may lead to antidepressant discontinuation syndrome. The symptoms of this condition include flu-like symptoms and disturbances in sleep, senses, movement, mood, and thinking.

Mood Stabilizers

Lithium is commonly used in patients with bipolar disorder and, in major depressive disorder, as an augmenting agent. It has a narrow therapeutic window, and older patients are at a greater risk for developing lithium toxicity, particularly if their oral intake or renal function is compromised. Caution is recommended when lithium is taken with other medications, such as nonsteroidal anti-inflammatory drugs, hydrochlorothiazide, furosemide, and lisinopril, as these may precipitate lithium toxicity. Lithium toxicity is evident by a coarse tremor, nausea, vomiting, ataxia, confusion, myoclonus, convulsions, delirium, hypothyroidism, hyperparathyroidism, cardiac conduction system abnormalities, and renal failure. Salt restriction and dehydration may worsen lithium toxicity; hence, adequate replenishment of fluids and electrolytes is important at home and for patients that present to the emergency department. In severe cases, lithium can be removed from the body by emergency hemodialysis.

Anticonvulsants may precipitate acute hepatic failure as well as blood dyscrasias. Benzodiazepines are frequently prescribed for older patients for anxiety and insomnia as the perception is they are safer than other medications. However, benzodiazepines may result in fatigue, somnolence, gait disturbances, slowed processing, memory difficulties that lead to increased confusion, impaired performance driving, and an increased fall risk. When patients experience physiologic dependence, hallucinations, confusion leading to a type of major neurocognitive disorder, aggression, and respiratory depression may occur. In cases of toxicity caused by benzodiazepines, flumazenil can be effectively used for reversal of symptoms.

Polypharmacy

Older adults, owing to multiple comorbid conditions, are the patient population most at risk for polypharmacy, with nearly 100,000 patients being admitted annually through the emergency department for adverse drug events [1]. On average, older patients, who present to the emergency department, receive 4.2 medications per day, with 91% receiving at least one and 13% receiving eight or more drugs [64]. In keeping with this, 11% of emergency department visits in patients older than 65 years are caused by adverse drug reactions

compared with only 4% in the general population [1]. There are several likely reasons, not the least of which is polypharmacy and a combination of increased sensitivity, decreased reserve, and decreased clearance.

Teaching Point
A consult from a geriatrician or geriatric or psychosomatic medicine psychiatrist often leads to the cessation of unnecessary medications which, in a frail state, may be causing more harm than good.

28.2 Case Studies

The following case-based studies are meant to illustrate some of the emergencies that present with older adults.

28.2.1 Case 1

Case 1 History

Mr. Y. is a 72-year-old community dwelling married man with an established diagnosis of major neurocognitive disorder who was brought to the emergency department for an urgent evaluation by his wife, as earlier that day, he pushed her against the wall as she was trying to prevent him from leaving the house. There was a similar incident a few weeks ago when Mr. Y. was frustrated that his wife was offering him coloring papers and pushed her resulting in her breaking two ribs. He was placed on a crisis waitlist for several long-term care facilities, but no beds were available at that time, and those that reviewed his case rejected placement at their facility due to these behaviors. Mrs. Y. describes a long course of cognitive impairment that began about 6 years ago when he was becoming suspicious of neighbors and telephone and cable TV workers on his street. A year after this, he was diagnosed with major neurocognitive disorder (dementia) by a geriatrician and his driver's license was revoked. This led to a period of increased agitation in Mr. Y., and he would attempt to elope at nighttime leading his wife to call 911. Mr. Y. was enrolled in an adult day program which he enjoyed, but he could not continue due to increasing irritability and outbursts toward peers in the program. In the past year, he has been argumentative with his wife which can lead to physical violence such that Mrs. Y. finds that she has to be "extremely careful at all times" to avoid any of his triggers.

Case 1 Questions and Answers

Case 1 Questions

Question 1. What other information about this patient do you need to make an accurate diagnosis?

Question 2. How would you approach the safety assessment in a patient with a major neurocognitive disorder?

Question 3. What measures can be taken to manage this patient's agitation due to major neurocognitive disorder in the emergency room setting?

Question 4. How would you manage this patient after the initial evaluation?

Case 1 Answers

Case 1 Answer 1 (Question 1—What other information about this patient do you need to make an accurate diagnosis?)

Obtaining a comprehensive history to delineate that progression of cognitive impairment as well as to identify the antecedents for the behaviors would be important. While the patient presents with a long-standing history of cognitive impairment, indication of a likely diagnosis of major neurocognitive disorder, new onset, or increase in aggression can be due to other reasons. A sudden onset may indicate a medical etiology with comorbid delirium, whereas a more subacute onset may indicate changes in the environment, patient ability, or functional decline, as well as caregiver exhaustion or burnout. For example, a patient with a history of wandering which has extended into nighttime hours can quickly lead to caregiver burnout due to lack of sleep for both and prompt an urgent evaluation.

Presentation to the emergency room implies that the behavior is distressing to the family or the patient or is not tolerable in the setting for long-term care. Some families or caregivers may describe the presenting complaint as "agitation" or "aggression"; however, it is critical to get a clear description of behavior. Completing a scale such as the Cohen Mansfield Agitation Inventory can help define the problematic behaviors and offer a sense of how often these behaviors are occurring. The clinician can also ask the caregiver to describe the events before, during, and after the concerning behavior. These would help identify if there is a specific pattern, trigger, or time of day. For example, a patient who is always irritable around 11:00 AM, an hour before lunch, but is calm after lunch might indicate hunger as an unmet need. As many patients with moderate to severe major neurocognitive disorder are unable to meet their basic needs, especially in institutional settings, pain, hunger, thirst, constipation, full bladder, and/or fatigue can all lead to agitation. In the case example, many of the behaviors were preceded by either perceived failure and frustration on the patient's part or difficult communication between the patient and caregiver.

A thorough physical exam and laboratory tests to rule out delirium and other medical conditions will have to be completed. This is further covered in ▶ Chaps. 17 and 22.

While it might not be possible to make a definitive diagnosis of the type of neurocognitive disorder in the emergency room, it would be important to gather enough history to rule out a major neurocognitive disorder due to Lewy body disease and due to Parkinson disease as these patients can be very sensitive to medications commonly used in the treatment of agitation in an emergent setting such as an antipsychotic. A thorough review of medications taken at home and

recent changes in medications or doses will be important in ruling out both deliriums due to certain medications as well as side effects. For example, if a patient has recently started an antipsychotic and develops increased restlessness and agitation, this may reflect akathisia due to the antipsychotic rather than increased agitation due to the neurocognitive disorder.

Case 1 Answer 2 (Question 2—How would you approach the safety assessment in a patient with a major neurocognitive disorder?)

The following are various aspects of safety that have to be considered and assessed in patients with neurocognitive disorder as they are some of the most vulnerable members of our community:

A2.1. Risk to the patient from the environment at home, e.g., as burns from hot stoves or ovens, ingestions of inappropriate substances, mishandling electrical tools, or equipment. Mr. Y.'s wife had to install a lock on their microwave oven because she walked into the house to a burning smell and found that the patient had microwaved food with silverware.

A2.2. Risk due to wandering from home can be a common reason for emergency evaluation especially in winter months. Enrolling patients in local registries for vulnerable individuals and having arm bands or bracelets with important contact or medical information are useful in helping other identify older adults who are unable to fund their way back home. Installing special locks at home can also be helpful.

A2.3. Risk to self due to poor self-care and resistance to care including refusal to take medications.

A2.4. Risk to others at home including caregivers as well as minors such a grandchildren living at home. In this patient's case, this was the primary reason for evaluation. The frequency and severity of the incidents as well as the capability of the caregiver to manage these behaviors have to be taken into consideration before discharging a patient from the emergency room.

A2.5. Risk to the patient due to neglect or abuse. Loved ones who are caring for patients with major neurocognitive disorder with severe neuropsychiatric symptoms are often under tremendous stress. Unfortunately, this can result in inadequate supervision leading to accidents, neglect, and, at times, physical abuse. Many of these patients are also at high risk of being financially exploited by others, and healthcare providers have to be vigilant for signs of this.

Case 1 Answer 3 (Question 3—What measures can be taken to manage this patient's agitation due to major neurocognitive disorder in the emergency room setting?)

A visit to the emergency room can be a confusing and frightening experience for someone with cognitive impairment who has poor insight into their deficits and are unable to quickly process the various cues and sounds being presented to them in rapid succession. Recognition of the unique needs of these patients at triage can help decrease agitation triggered in the emergency room. Providing a quiet space and allowing a familiar caregiver to stay with the patient can be helpful. Similarly, it may be important to attempt to unmet needs such as hunger, thirst, pain, or a soiled personal care product before the patient might allow an interview or physical exam.

If environmental approaches alone fail, then the patient may need a medication to provide sedation to complete a thorough exam and to enable laboratory tests. For example, patients who are no longer continent will need temporary sedation prior to attempting an in and out catheterization to obtain a urine sample. While antipsychotics are often used in the treatment of agitation in the emergency room, it is important to remember that an older patient without a preexisting history of psychotic disorder may not tolerate the same dose of antipsychotic as a younger patient who has been on antipsychotic treatment for years. Thus, tailoring the dose to the patient is important. In patients with an established diagnosis of Parkinson disease or neurocognitive disorder with Lewy bodies, a benzodiazepine may be considered for agitation in lieu of an antipsychotic.

Case 1 Answer 4 (Question 4—How would you manage this patient after the initial evaluation?)

Management of this patient would involve the following steps:

A4.1. Establish immediate safety of the patient and staff by attending to unmet needs, modifying the environment, and providing medications for managing his aggression.

A4.2. Rule out acute medical conditions leading to agitation, including pain, and treat if any underlying conditions are discovered.

A4.3. Weigh the risks and benefits of admitting a patient compared to discharging patient to the environment they came from. In this case, there have been several incidents of bodily harm to the caregiver which are increasing in intensity. Even if there are no obvious medical concerns, this patient will have to be admitted to the hospital until a safety plan has been established for the caregiver or a different environment such as long-term care setting is made available to this patient.

Case 1 Analysis Mr. Y. was admitted to the inpatient geriatric psychiatry unit. He was started on an SSRI escitalopram 10 mg daily, and it was observed that there was a decrease in some of his irritability and reactivity. However, he continued to have episodes of attempting to strike others especially late in the afternoon. He would often say that someone was trying to kill him and that they were trying to find him on the unit. He was started on a low dose of risperidone 0.25 mg bid, which decreased the paranoia. He was engaged in several individualized programs on the unit which were helpful in distracting him and giving him a sense of purpose during the day. He was eventually discharged to a long-term care facility as his behav-

ior was considered unsafe to be discharged home with his wife. This case illustrates the importance of a thorough evaluation, including risk of violence toward others and management implementation in cases of older adults with neuropsychiatric symptoms of neurocognitive disorder who present in the fast lane of the emergency department setting.

28.2.2 Case 2

Case 2 History

Mr. X. is a 72-year-old man, previously diagnosed with depressive disorder, who is brought to the emergency room by his wife after he cut his hands with a hacksaw sustaining damage to various structures and needing surgical intervention. His wife describes that she was going back to work after an extended leave to care for her husband after a recent hospital admission and that this was his first day home by himself. Her son came to check on Mr. X. and found him on the floor bleeding profusely and called the ambulance.

Mr. X. retired from his job as an electrician about 8 years ago. Over the past 5 years, his wife describes an increasing indifference to events. For example, when their basement was flooded due to a water leak, Mr. X. opened the door to the basement, saw the water, and closed the door saying nothing. This was uncharacteristic of him in the context of his job and training. Mrs. X. tells you that the first symptom noted was "not caring about things," which could be interpreted as apathy. Mrs. X. notes that the reason he retired early was that he could not keep up with the requirements of his job. There has been an obvious functional decline. While he is independent for all his activities of daily living, other than cooking, he is dependent on most instrumental activities of daily living. His most recent MoCA score was 16 out of 30. There are several comorbid medical conditions of concern including hypertension, type 2 diabetes mellitus, and obstructive sleep apnea.

He was assessed for depressed mood by a psychiatrist and started on escitalopram 10 mg daily 1 year ago. There was mild improvement, but after a few months, he attempted suicide through an overdose. He was admitted to the inpatient psychiatric ward. During that admission, he used shoe laces to tie a ligature around his neck and to the bedroom furniture in an attempt to end his life. His mood improved over the following few weeks, and he was discharged home with supports including a mental health nurse visiting once a week. His wife had stayed with him at home during the past month as he was distressed when she left him even for short periods of time. He was often tearful even when she was at home and felt that things would never get better. The current episode of self-harm happened on the day she went back to work.

Case 2 Questions and Answers

Case 2 Questions

Question 1. What other information about this patient do you need to make an accurate diagnosis?

Question 2. How would you perform a risk assessment for this patient?

Question 3. What would your management for self-harm be for this patient?

Case 2 Answers

Case 2 Answer 1 (Question 1—What other information about this patient do you need to make an accurate diagnosis?)

The following are important steps in making an accurate diagnosis for this patient: gathering a detailed history from the patient's spouse, other family members, as well as community providers involved in the care of this patient is essential. The two main illnesses to consider are a major depressive disorder and depression in the context of a neurocognitive disorder. Apathy in patients with neurocognitive disorder can present like depressive disorder. Apathy is characterized by reduced experience of negative as well as positive emotions, occurring in the context of marked executive dysfunction on cognitive testing and frontal release signs, such as grasp reflex or utilization behavior, lack of concern about symptoms, and displaying an emotional "emptiness." (For further details, see Fig. 19.4 in ▶ Chap. 19.) While apathy is in general a lack of emotion, this patient displays several depressive symptoms such as tearfulness, hopelessness, and anxious distress when he is by himself. He has also had two potentially lethal suicide attempts. Therefore, even if this patient had an underlying neurocognitive disorder, he would still meet diagnostic criteria for a major depressive disorder.

Case 2 Answer 2 (Question 2—How would you perform a risk assessment for this patient?)

A comprehensive risk assessment would be of utmost importance in the management of a patient presenting with self-harm to the emergency department. The risk factors can be divided into static or dynamic, otherwise known as nonmodifiable and modifiable. Mr. X. is an older man with three past suicide attempts. They were potentially lethal and if not found in time, he could have died on two occasions. He has a major neurocognitive disorder as well as a depressive disorder, both of which can contribute to an increased risk of suicidality. While his depressive disorder might contribute to suicidal thoughts, his neurocognitive disorder contributes to poor problem-solving ability and his making impulsive decisions. Mr. X. also has some protective factors which include a supportive spouse, treatment of depressive disorder (although partial response), and the absence of substance abuse (see Fig. 28.3). The presence of many static risk factors increases the risk of future self-harm substantially compared to the general population. It would be important to document this risk and have a discussion with the family and the primary medical team about this risk as well as to monitor any changes in modifiable or dynamic factors such as mood state, anxiety, access to means of self-harm, presence of active intent or plan, as well as environmental supports.

Case 2 Answer 3 (Question 3—What would your management for self-harm be for this patient?)

The management of this patient in the emergency department setting is focused on maintaining immediate safety. Given the proximity of event, the near lethality, as well as a depressed mood state with poor problem-solving abilities due to underlying neurocognitive disorder, this patient is at a high risk of attempting self-harm again without significant changes in his mood as well as environmental supports. The safest option would be to admit this patient to an inpatient setting for further observation and treatment of depressive symptoms as well as make changes to environmental support.

Case 2 Analysis Mr. X.'s mood improved over the next few weeks with augmentation of his primary antidepressant with mirtazapine 15 mg at bedtime. His wife could not take any more time off work. The team collaborated with the community agency to enroll patient in a day program for patients with neurocognitive disorder on the days that his wife worked so as to decrease the time that he spent by himself at home. He continued to have close follow-up with his community psychiatrist upon discharge.

28.3 Key Points: Psychiatric Emergencies in Older Adults

- Prevention is clearly better than treatment or even cure. However many of the emergencies highlighted in this chapter are multifactorial and complex both in terms of etiology and treatment.
- The clinician, faced with these emergencies in older patients, has three essential responsibilities:
  1. Maintain the physical safety of everyone involved.
  2. Identify the acute safety concerns (is it confusion, suicidality, aggression, abuse, severe medication side effects?).
  3. Provide care to patients for life-threatening emergencies including appropriate assessment and triage to the appropriate treatment setting.
- As some psychiatric emergencies in older adults may occur at home, in nursing homes, in emergency departments, in intensive care units, or in medical, surgical, or psychiatric wards of hospitals, the importance of the appropriate treatment setting cannot be underestimated.
- As it is often difficult in many cases to separate psychiatric from systemic medical or psychosocial factors in an emergency, an approach that is open, flexible, and multidisciplinary and recognizes the urgency of the situation and need for collaboration is clearly the best practice.
- If the older adult is not an inpatient, consideration of hospitalization for psychiatric emergencies clearly makes sense. Many jurisdictions base involuntary commitment on dangerousness or the inability to care for one's basic needs. Observation for a period of time may help determine this. For example, if a patient who is being assessed for suicidal or violent behavior in the community continues to behave in an erratic manner without an explanation, this supports the decision that hospital admission is necessary.

28.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following is characteristic of delirium?

A. Disturbance in mobility
B. Visual hallucinations
C. Vital sign abnormalities
D. Acute onset
E. Behavioral disturbance

Answer: D

Acute onset (statement D) is the hallmark and one of the distinguishing features of delirium. All of the other answers can be seen but are not specific to delirium.

MCQ 2. Which of the following is recommended as an intervention for management of delirium?

A. Haloperidol, low dose, preventatively.
B. Encourage family members to stay with patients.
C. Bed alarms and restraints.
D. Leave lights on at night.
E. Insertion of Foley catheters to measure urinary output.

Answer: B

Studies have examined the role of pharmacologic strategies in delirium prophylaxis. Prophylactic treatment with low-dose haloperidol in postoperative patients demonstrated no efficacy in reducing the incidence of delirium, but it reduced the severity and duration of delirium and length of hospital stay and was well tolerated [65]. However, there is no clear evidence that antipsychotics or other medications prevent delirium [66]. Therefore, statement A is incorrect. There is strong evidence supporting multicomponent interventions to prevent delirium in hospitalized patients [66]. Non-pharmacologic approaches are the most successful to preventing delirium by addressing risk factors that may trigger an episode. Hospital environments present a special challenge due to frequent room changes, invasive procedures such as catchers, use of restraints, loud noises, poor lighting, and lack of natural light, which can trigger or worsen delirium. Helping prevent medical problems or other complications, promoting a good sleep, and helping the patient remain calm and well oriented by allowing a family member to stay with the patient can be helpful strategies to prevent or reduce severity of delirium. Therefore, statement B is correct, while C, D, and E are incorrect.

MCQ 3. A 75-year-old man with major neurocognitive disorder is brought to the emergency room with significant agitation. He is convinced that you and your team are part of a conspiracy to kill him, and he is trying to defend himself by swinging his walking stick at the staff. The last ECG on file shows that his QTc interval was 489 milliseconds. Which of the following antipsychotics will you use in the management of his agitation?

A. Haloperidol
B. Risperidone
C. Chlorpromazine
D. Quetiapine
E. Olanzapine

Answer: E

This patient presents with QTc prolongation (QTc in prolonged if > 450 milliseconds in men and > 470 milliseconds in women), which is associated with increased risk of TdP. The typical antipsychotic haloperidol has historically been the most commonly used antipsychotic for use in delirium. Side effects of haloperidol include QTc prolongation, and when used intravenously, there is greater risk for QTc prolongation. Atypical antipsychotics have similar efficacy to haloperidol in the management of delirium, and they can all increase the QTc as well. As Table 28.7 shows, olanzapine may have a conditional risk for QTc prolongation if other patient risk factors are met, while other medication options clearly have a known or possible risk for QTc prolongation. Therefore, statement E is most appropriate in this case.

MCQ 4. A 68-year-old man with a history of bipolar disorder has been managed on lithium carbonate for more than 20 years. He presents with tremors, nausea, and falls, and his lithium level is 2.1 mEq/L (mmol/L). He was recently seen for a regular checkup by his primary care physician, and some medication changes were made. Which of the following is *unlikely* to have caused this increase in lithium level?

A. Naproxen
B. Hydrochlorthiazide
C. Ibuprofen
D. Rosuvastatin
E. Furosemide

Answer: D

This clinical presentation in the context of increased serum lithium level is indicative of lithium toxicity in this patient. Caution is recommended when lithium is taken with other medications, such as, in this case, nonsteroidal anti-inflammatory drugs (naproxen and ibuprofen) and diuretics (hydrochlorothiazide and furosemide), as these may precipitate lithium toxicity. Statins (rosuvastatin) are not known to significantly interact with lithium; therefore, the correct answer is D.

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Geriatric Forensic Psychiatry: Risk Assessment and Management

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29.1 Background

29.1.1 What Is Forensic Psychiatry?

The American Academy of Psychiatry and the Law defines forensic psychiatry as a "subspecialty of psychiatry in which scientific and clinical expertise is applied in legal contexts involving civil, criminal correctional, regulatory or legislative matters, and in specialized clinical consultations in areas such as risk assessment or employment" [1]. Forensic psychiatrists are called upon to provide opinions and testimony regarding issues of criminal responsibility and competency to stand trial, with the older as well as with younger offenders. They also practice in correctional environments, where they provide psychiatric assessment and treatment to offenders. Forensic psychiatrists may be called upon to assess a variety of other capacities including consent to treatment, testamentary capacity, and financial capacity. Furthermore, they may be consulted in cases of elder maltreatment or neglect. Since these latter issues will be examined elsewhere in this volume, they will not be dealt with in the present chapter. This chapter will focus on the issue of psychiatrically ill geriatric patients, their risk of violence, and their interactions with the criminal legal system. Table 29.1 lists the roles of the forensic psychiatrist.

Aging, Psychiatric Illness, and Violence

Aging may be associated with losses in many spheres. Physical health and function may deteriorate; there may be a loss of social position or financial security; support networks may dissipate. These stresses may predispose older persons to a variety of psychiatric illnesses. A conservative estimate of the prevalence of psychiatric illness in persons aged 65 and over is 25%. According to the National Institutes of Mental Health Epidemiological Catchment Study, the most common psychiatric disorders in old age include depressive disorders, major or mild neurocognitive disorders (NCD), phobic disorders, and alcohol use disorders [2]. The presence of many of these may also predispose individuals to behaviors which may bring them into contact with the legal system.

The potential for violence has been examined in many psychiatric disorders. For example, Fazel et al. [3] concluded "people with schizophrenia and related disorders are at an increased risk of adverse outcomes, including conviction of a violent offense, suicide, and premature mortality." Data leading to such statements must be scrutinized though, as it can fuel stigmatizing public perceptions of psychiatric illness [4]. For instance, what does being convicted of a violent offense mean? And was the act perpetrated as a response to being victimized? Monahan et al. [4] examined the frequency of and characteristics associated with three forms of violence among persons with psychiatric illness. The group involved in at least one form of violence was much less likely than the group that was uninvolved with violence to be diagnosed as having schizophrenia or bipolar disorder. A systematic review of studies examining the relationship between paranoia and aggression by Darrell-Berry et al. [5] revealed a somewhat mixed result, but the authors concluded that, "when study quality was taken into account, more methodologically rigorous studies tended to show a positive association between factors." However, it is important to note that violent victimization of patients with psychiatric illness occurs more frequently than violent offending by the patient. Additionally, the groups studied that were involved in violence were much more likely than patients who were uninvolved in violence to be diagnosed as having a substance use disorder [4].

Teaching Point
Violent victimization of patients with mental illness occurs more frequently than violent offending by the patient.

Of particular importance in an aging population is the association of major NCD (formerly dementia) with violence. A recent review by Cipriani et al. [6] highlighted this relationship and outlined a number of risk factors to consider, including the presence of comorbid depressive or bipolar disorder, psychotic symptoms, alcohol use, and frontal lobe dysfunction. Therefore, there exists no causal relationship between a specific psychiatric disorder and violence. There are various contextual and individual elements that must be taken into account before drawing conclusions or making correlations.

The Geriatric Offender

Criminal behavior is generally uncommon in old age and the offenses tend to be minor, such as shoplifting and driving offenses [7]. Nnatu et al. [8] have argued that many crimes perpetrated by seniors go unreported. Reasons for this may include the limited seriousness of the offenses or to the concomitant presence of psychiatric illness leading to less criminal justice system involvement. Serious crime in this population is rare in comparison to younger groups. Attrition is a potential explanation for that difference; people with severe psychiatric illnesses or personality disorders might have died younger from comorbidities, suicide, or accident. Seriously violent offenses are, however, sometimes perpetrated by older adults and may lead to incarceration or forensic psychiatric hospitalization.

Table 29.1 Roles of the forensic psychiatrist

Types of forensic assessments	Capacity to stand trial Criminal responsibility Assessment and treatment of psychiatric disorders in correctional settings Consent to treatment Testamentary capacity Financial capacity Elder abuse/neglect Risk assessment

The relatively high prevalence of psychiatric morbidity in forensic evaluees has been known for decades. In 1991, Rosner et al. [9] suggested that the criminal justice system should begin planning for the geriatric offender population. He warned that "special medical and psychiatric treatment facilities will be needed to cope with the range of physical illnesses this geriatric population will present and to cope with the psychiatric conditions that are likely to be more prevalent in the geriatric offender population than in the general American geriatric population." Fazel and Grann [10] examined a large cohort of individuals referred by the courts for psychiatric assessment and reported that older offenders were less likely to be diagnosed with schizophrenia and personality disorder but that affective psychosis (also known as major depressive and bipolar disorder with psychotic features) and major NCDs (dementia) were more common in this group. They also found that, as a group, older offenders were more likely to be convicted of homicides and sexual crimes although their relative contribution to these crimes remained low. Curtice et al. [11], in a retrospective survey of forensic psychiatric referrals in Bristol, United Kingdom, reported that 56% were referred for sex offenses and 25% for violent offenses, including 9% for murder or manslaughter. They found that 44% had a diagnosable psychiatric disorder. The most common diagnosis was major NCDs, found in 17% of the cases.

Many studies have attempted to characterize the prevalence of psychiatric illness in prison populations. Cloyes and Burns [12] noted that "elderly prisoners, many of whom have poor physical and mental health, present a complex array of medical, psychological and logistical needs that complicate the provision of psychiatric care for this group." They went on to highlight the high rates of chronic systemic medical illness, anxiety disorders, depressive disorders, and chronic stress which are prevalent in this group. Fazel et al. [13] reported that, in a sample of over 2000 inmates, 1 in 3 had a treatable psychiatric disorder, including 5% with psychotic disorder, and over a third had a diagnosis of personality disorder. In a recent review based on a Canadian population, Iftene [14] reported the following rates of psychiatric disorder in older inmates: depressive disorder 24.4%, anxiety disorder 17.3%, bipolar disorder 3.6%, schizophrenia 3%, and major NCD (dementia) 4.6% (see Table 29.2). These studies consistently illustrate the need for correctional authorities to remain sensitive to the health needs of older inmates and to provide optimal ongoing physical and psychiatric care to this complex group.

Table 29.2 Prevalence of psychiatric diagnoses in older inmates [14]

Diagnosis	Prevalence rate (%)
Depressive disorders	24.4
Anxiety disorders	17.3
Major neurocognitive disorders	4.6
Bipolar disorders	3.6
Schizophrenia	3

Teaching Point
Older offenders as a group have high rates of physical and psychiatric morbidity. Many of the disorders with which they present can predispose to violent behavior.

29.1.2 Evaluating the Geriatric Offender

Geriatric Evaluees

As with younger age groups, older individuals with a wide variety of psychiatric illnesses may become embroiled in the legal system. Some patients present with disorders which may have had a lifelong course (e.g., schizophrenia), some patients' illnesses may present at any time of life (e.g., bipolar disorder, delusional disorder), and other patients present with illnesses (e.g., major NCD, delirium) which are more likely to have onset in old age. The latter problems, some of which may be reversible, require the clinician to be vigilant for the potential presence of systemic medical illnesses which may account for the behavior in question, including violence. The principles of evaluation overall, however, are the same as those for any thorough psychiatric assessment. These include a thorough history and mental status examination as well as consultations, neuroimaging, and laboratory investigations as indicated by the symptomatic presentation.

The Psychiatric Interview

In addition to the typical challenges of forensic psychiatric assessment (e.g., suboptimal interviewing environments, often limited background information and corroboration, the potential for malingering), certain specific characteristics of geriatric offenders may pose obstacles. Sprehe [15] has described a number of these characteristics, including guardedness and difficulty forming rapport, aberrations in self-psychology, sensory limitations, and cognitive slowing. He suggests that spending effort to put the individual at ease and to build rapport, compensating for any sensory impairments, and slowing the pace of the interview are important strategies to enhance the success of the interview. Another challenge regarding the forensic interview, one of an ethical nature, is the dual role issue. Forensic assessments are usually done at the request of a third party. It is therefore imperative that the person being evaluated should be made aware of this and the consequent limitations on confidentiality. See Table 29.3 for examples of such challenges and corresponding strategies.

Teaching Point
The standard interview and mental status examination must be modified to take into consideration the specific challenges posed by the older forensic evaluee.

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Table 29.3 Challenges of the geriatric forensic assessment

Barriers	Strategies
General	
Suboptimal interviewing environment	Safety for the clinician (panic button), find a quiet space
Limited background information and corroboration	Play detective (observe if visitors or relatives calling to talk to patient); access collateral info
Circumstances (patient not evaluated at his/her own request)	Explain your role, the steps of the process, what to expect
Patient related	
Potential for malingering	Screening
Guardedness	Build rapport
Aberrations in self psychology (personality disorder)	Develop an understanding of the defense mechanisms; foster alliance
Sensory limitations	Compensation (e.g., written materials)
Memory impairment	Collateral information
Cognitive slowing	Slow the pace of the interview
Clinician related	
Dual role	Inform the patient about the consequent limitations on confidentiality

Once the barriers to conduct a full assessment have been removed, it is important to explore the social history. In the study done by Monahan et al. [4], both groups of patients involved in at least one form of violence and those involved in all three forms of violence were more likely to report having been physically abused as a child than the patients who were not involved in violence. Moreover, the patients involved in violence were more likely to report that their fathers had been arrested two or more times during their childhood. (See ACE study in ► Chap. 14.)

Psychological Assessments and Rating Scales

Psychological assessments including formal psychometrics can strengthen the validity of a comprehensive forensic evaluation. These may include personality assessment, intellectual and neuropsychological assessment, as well as specific tests to assist with the determination of malingering. Where available, psychological consultation can be an invaluable aid to formulation and diagnosis.

Competence (Fitness) to Stand Trial

One of the most common reasons for forensic psychiatry referral is the assessment of competence to stand trial. An accepted principle in English common law has been that an individual who is not competent by virtue of a mental illness should not be permitted to proceed with a trial. This remains the case throughout North America although there is some degree of variation in the standards in different jurisdictions. In the United States, most jurisdictions adhere to a tripartite definition of competence. The defendant must have an understanding of the charges against him, must understand the nature and purpose of the court's proceedings, and must be able to cooperate with an attorney in his own defense [16]. In Canada, the criteria guiding the assessment of fitness to stand trial are defined in the Criminal Code as the following: "The accused is unable on account of mental disorder to conduct a defense at any stage of the proceedings before a verdict is rendered or to instruct counsel to do so, and, in particular, unable on account of mental disorder to (a) understand the nature or object of the proceedings, (b) understand the possible consequences of the proceedings, or (c) communicate with counsel." Table 29.4 summarizes the criteria for competency to stand trial. The specific legal interpretation of these criteria has been clarified over time by the courts, and a review of these for the many relevant jurisdictions is beyond the scope of this chapter.

Table 29.4 Parameters that define competency to stand trial

The defendant must	A. Understand the charges against him B. Understand the nature and purpose of the court proceedings C. Understand the possible consequences of the proceedings D. Be able to collaborate with an attorney for his own defense

Nevertheless, the general principles related to the assessment of trial competency can be examined. The primary matter which the evaluator must establish is the presence of a mental disorder of sufficient severity to impair the accused's ability to meet the legal criteria. The nature and degree of impairment should be characterized as accurately as possible. In addition, the assessment must review the specific criteria relevant to the jurisdiction in question. Generally, an inquiry will be made into the offender's understanding of the charges, their knowledge of the court's officers and procedures, and the potential consequences of a trial. The level of complexity which the offender is required to understand will vary, with some jurisdictions requiring a "rational" or "analytic" component to their understanding while others, such as that of Canada, requiring a demonstration of basic or "limited" cognitive capacity [17]. Although most forensic psychiatrists perform such evaluations based on their training and professional experience, structured interviews exist which provide specific guided interview questions which may be mapped onto to relevant statutes of a particular jurisdiction. An example of such a tool is the FIT-R created by Roesch et al. [18].

Criminal Responsibility

Forensic psychiatrists are often called upon to render an opinion and provide testimony regarding an accused person's criminal responsibility. The insanity defense, as it is sometimes known, is based on a longstanding principle in

law that there are individuals who, because they suffered with psychiatric illness at the time of their offense, should not be held morally or legally responsible for their act. Such individuals are found not criminally responsible (NCR) or not guilty by reason of insanity (NGRI) depending on the jurisdiction. It has been, and continues to be, a very controversial area with many feeling that criminals with psychiatric disorders should not be allowed to "get away" with their crimes. Much of this is due to a great deal of misunderstanding about the criteria for and consequences of such outcomes. Adding to the confusion is that, as in the case of trial competence, there are wide jurisdictional variations in the legal criteria for these defenses.

Historically, the main consideration was the individual's ability to have an understanding of an act and its wrongfulness. This concept has a lengthy and complex history dating back centuries in English law. Much current legislation can be related to the M'Naghten rule of 1843 which stated that "to establish a defense on the ground of insanity, it must be clearly proved that, at the time of the act, the party accused was laboring under such a defect of reason, from disease of the mind, as to not know the nature and quality of the act he was doing; or if he did know it, that he did not know he was doing what was wrong."

Since that time much effort has gone into the interpretation and reinterpretation of this legislation but, in many jurisdictions, such as Canada, the actual legislation has changed very little. In the United States, many jurisdictions have chosen to keep this test, while others have elected to add additional components, such as the "irresistible impulse test" wherein the individual is unable to exert control over their actions due to a mental illness or the "product test" in which it must be proven that the act was a product of a mental disorder [16]. Since the criteria for exemption from criminal responsibility vary with jurisdiction, it is necessary for the evaluator to be familiar with the relevant statutes in their jurisdiction.

Despite the wide variations in legislation, the components of a criminal responsibility assessment are generally applicable. These include the establishment of the presence or absence of a mental disorder at the time of the offense in question; if present, the characterization of its features; and clear explication of the relationship between the symptoms of the illness and the legal test involved. The determination of criminal responsibility requires a retrospective reconstruction of the mental state of the accused at the time of the offense. This will involve the gathering of information from all available sources both current and historical, with particular attention to any descriptions or recordings of the accused contemporaneous with the act. It should be emphasized that, whatever the opinion of the expert witness, it is ultimately up to the court to decide regarding criminal responsibility.

Teaching Point
The forensic psychiatrist is also called "expert witness."

29.1.3 Risk Assessment

Love and hate, kindness, and violence are woven into the fabric of society and our lives. Impulses are present from an early age and self-regulatory skills must be taught and developed throughout life to express intense affects appropriately. As we age, those elements continue, alter, and, on occasion, amplify. Physicians, especially psychiatrists, are called upon to manage aggression in its various forms in any of our patients, but also in the geriatric psychiatry context. For a multitude of reasons, it is not uncommon for psychiatrists to be asked to deal with patients who have either displayed aggression or have the potential of displaying aggression.

The ability to conduct risk assessments is part of the skill set of psychiatrists and other mental health clinicians. At one point in time, those skills and expectations fell to a discrete group of clinicians, but rather now are a component of psychiatric clinical practice. There are some fundamental issues that are important in considering risk assessment. Firstly, the idea of risk and the principles behind risk assessment are not purely directed to assessing violence [19]. This section concerns itself with the assessment of the risk of violence. "Risk assessment" in fact is a broad term. It is usually more helpful to consider the very elements involved in risk processes within psychiatry (See ◘ Fig. 29.1).

Risk Assessment

The first component is the risk assessment. Risk assessment is the process whereby one gathers pertinent information to allow one to predict and manage risk. It is the gathering of information relevant to the likelihood of a particular act occurring at some point in the future, in this case risk of violence. Suicide risk is another frequent theme to assess. Embedded in that are the aspects of the behavior being examined. In other words, not only would one want to gather information about risk, but one needs to be clear about the particular type of behavior of concern. For instance, assessing the risk of homicide is much more complicated and more likely to be associated with false negatives than the likelihood when predicting risk of a lower base rate aggressive incident, such as common assault.

Risk Prediction

The next aspect is the risk prediction. This is the assignment of the likelihood of a particular act occurring at some point in the future. In other words, having conducted the risk assessment, and having obtained the relevant information, one would then use a process to predict the likelihood of that particular act occurring at some point in the future. Clinicians are mostly concerned with the here and now and are less concerned with what might happen in 7 or 10 years. In fact, frontline clinical staff sometimes might get frustrated by a risk prediction tool that talks about 1 year violence rates, as it is rather their concern about what might happen today, tomorrow, on the weekend, for the person in front of them that is the predominant issue.

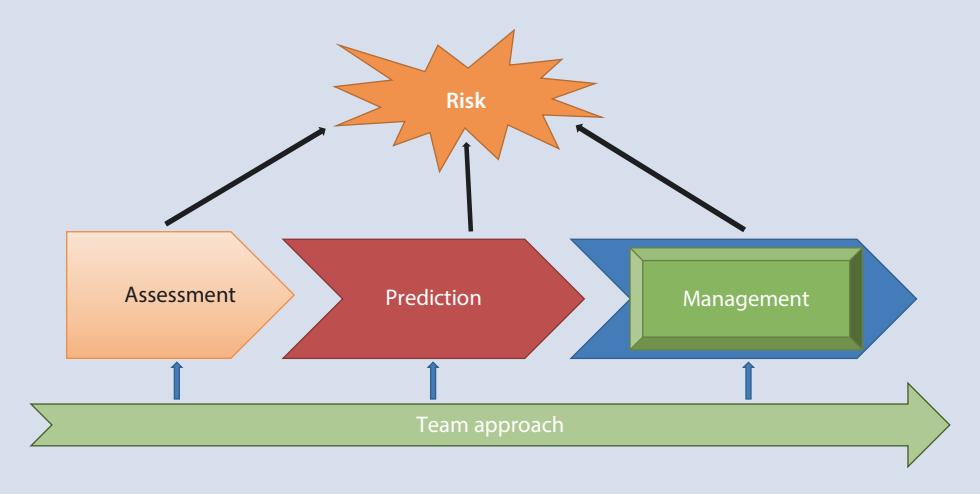

Fig. 29.1 The three steps and four components of risk assessment

Risk Management

The next aspect, and the aspect that is the most important for mental health professionals, is the risk management. That is, having assessed risk, and having predicted risk, one then puts in place mechanisms or processes to mitigate, reduce, or even extinguish the likelihood of the identified aggressive behavior as occurring. Of course, all of these components need to have occurred to be able to effectively mitigate risk. In other words, mental health professionals need to be able to *assess*, to *predict*, and to *manage* risk [20].

There are a number of factors that are critical to consider when one assesses risk. Numerous studies have identified key risk factors pertinent to the likelihood of violence occurring at some point in the future. These have been variously described, but include historical factors such as major psychiatric disorders (including major NCDs), personality disorders (specifically antisocial and borderline), substance use disorder, comorbid systemic medical problems as well as employment instability, housing instability, and financial difficulties. See Table 29.5 for a summary of these risk factors.

Risk factors can be both static and dynamic. For some time now, researchers have not only identified static risk factors as being significant in predicting long-term recidivism, but they look at remote static (historical) factors as well (e.g., age at onset of violence, prior criminal history). The use of static factors only was a large component in the second generation of risk assessment (actuarial risk assessment), which will be detailed later in ▶ section History of Risk Assessment. Dynamic risk factors are potentially changeable factors, including negative peer associates and substance use. Static risk factors are factors that are associated with violence, but are not amenable to any intervention. Dynamic risk factors (factors that can impact risk as they change) supported by evidence include mood symptoms, psychotic symptoms, impulse control, influence of peers, support, substance use or misuse, medication adherence, stress management, and anger management [21]. These factors all need to be considered, and the evidence is sufficiently strong for the link to violence that they are embedded in the variety of risk assessment tools available to assess, predict, and manage risk.

Table 29.5 Risk factors to be screened for when assessing for potential violence

Risk factors	Major psychiatric disorders (including neurocognitive disorders) Personality disorders (especially antisocial and borderline) Substance use disorders Comorbid systemic medical conditions Medication side effects Employment precariousness Housing instability Financial difficulties Lack of social support

Emerging evidence reveals the importance of temporal relationship between victimization and subsequent violent behavior. For instance, it was found that violent victimization in the past 6 months significantly predicted violent behavior in the subsequent 2 years in a sample of 167 patients [22]. Therefore, this finding is of particular relevance among older, frailer patient populations, whose various vulnerabilities put them at risk of being further victimized.

History of Risk Assessment

Risk assessment has been a part of life over the millennia. These issues have been and continue to be of concern to armies, to politicians, to businesses, and to any sort of policing force, and also in the news media. Several decades ago, psychiatrists relied on clinical judgment in assessing and predicting risk. Research suggested that clinicians' ability to assess risk was poor, that they overestimated risk, and their risk estimates were not much different from uninformed assessors or "guessers" of risk. That time period was the first generation of risk assessment. This was followed by the development of a number of actuarial tools, developed primarily by psychologists. These tools did not require clinical input,

and in fact many psychologists who favored the actuarial tools eschewed clinical input, suggesting that clinical input would in fact weaken the ability to predict risk. These tools, such as the Violence Risk Appraisal Guide (VRAG), gave a likelihood of any particular act (e.g., serious physical or sexual violence), occurring at the 7 or 10-year mark [23]. Wisely this was followed by the third generation, that of Structured Professional Clinical Judgment (SPJ), or also called Structured Clinical Judgment. These are processes whereby the assessor is guided to consider evidence-based risk factors, but also allowing for the input of clinical judgment. We believe that this has evolved into the fourth generation of risk assessment, that of team involvement. In other words, when assessing, predicting, and managing risk, the theory here is that a structured professional judgment tool is much more powerful when done in a team or group setting. There is a great deal of evidence to suggest that teams tend to be much more accurate in risk assessment than individuals, notwithstanding strong individual skill sets.

Further use of big data sets to assess and predict risk, as well as some of the more recently developed tools such as the Hamilton Anatomy of Risk Management [24] in its electronic form (eHARM), has given some hope to psychiatry for the greater use of data analytics in its assessment, prediction, and management of risk [24, 25].

One of the curiosities of clinical work, especially on inpatient psychiatry units or in residential environments, is that the very behaviors that are the early and granular manifestations of aggression and risk (i.e., all levels of aggressive incidents) are poorly and unevenly measured. Fortunately, there have been a number of tools that have been made available to quantify the gravity and frequency of aggressive incidents. These include the Modified Overt Aggression Scale and the Aggressive Incidents Scale [26]. When it comes to aggressive incidents, it is critical that all such acts are recorded and managed. Thus, identifying, managing, and then measuring the impact of intervention will be more focused and based on actual behavior. The often used quotation "you cannot manage what you cannot measure" applies aptly here.

The ability to assess, predict, and manage risk requires a good understanding of the evidence that supports which risk factors are the most important [27]. It is also important to be able to conduct a detailed interview and obtain collateral information, especially important to the geriatric population where self-report may not be as reliable. Then, if using a structured professional judgment process, taking into account the history, past history of violence (considered at one point probably the most powerful predictor of future violence), considering risk factors and behaviors, hopefully in a team-based setting and aided by analytical tools, a clinician would be able to much more accurately manage the risk of the person in front of them.

Geriatric populations have a higher proportion of individuals with cognitive impairment. Cognitive impairment, whether it is a function of major NCD or delirium, is associated with increased risk of violence. Comorbid systemic medical problems, side effects of medications, and lack of social support are specific risk factors for violence in the geriatric population. Obtaining collateral information is important with individuals who are either nonverbal or unable to give a good sense of their own histories.

Once the relevant risk factors are identified, one should make attempts to reduce the impact of the risk factors. For example, improving pain control, medication streamlining and minimization, and creating a supportive environment less likely to create confusion would all be important risk mitigation strategies. Additionally, the use of certain medications (e.g., mood stabilizers, SSRI antidepressants, antipsychotics) has been reported to have helpful effects on reducing violence. Certain major NCDs (especially those affecting frontal lobe function) may lead to disinhibition and thus the potential for sexual assault. These situations are quite specific and need both sensitivity and skill in management.

Intervention strategies should not only be directed to patients but also families and caregivers. Many individuals have lived upstanding and prosocial lives, but in the latter part of their lives may act out violently or sexually as a function of a variety of causes, some identified above. The nature of the precipitating illness may reduce the likelihood that the individual is to be held criminally responsible for their actions. However, routing these patients into the criminal justice system by charging them, or into the forensic system by finding them unfit to stand trial/incompetent to stand trial or not criminally responsible/not guilty by reason of insanity, may not prove to ultimately be an ideal or fair outcome. In fact, such a stance increases the risk of re-traumatization or re-victimization. A trauma-informed approach that is attentive, unbiased, yet mindful of potential triggers of violent behavior is standard of care at all levels of intervention and involves all the workforce susceptible of coming into contact with them, from law enforcement to medical professionals (See ► Chap. 26).

Psychiatry continues to struggle to fully understand what drives human behavior. Much of what we see clinically are proxies for what is happening within the brain. In terms of risk assessment, often what we deal with are symptoms and, in the case of managing aggression, violent behavior. There are a number of studies that have examined the various risk factors that can contribute to violence. However, despite numerous clinical risk guides constructed and utilized for helping the assessor formulate risk in persons that they are evaluating remain aids to the clinician, rather than definitive descriptors [27]. The assessment of risk of violence requires understanding of the various factors that can contribute to violence [20]. Although the field continues to evolve in terms of the evidence for risk factors, some of the key risk factors already have robust evidence for them. As an example, one of the most widely used risk assessment guides, the Historical Clinical Risk Management-20 (HCR-20), highlights 20 of the main factors contributing to risk of violence [28]. These factors in the HCR-20 are key factors to be examined as we evaluate and assess risk. What structured professional or clinical judgment guides do is, as Chris Webster indicated, function more as an "aide-mémoire" for assessing risk. One of the many traps associated with utilizing numerical scores

from risk tools is that they do not necessarily describe the risk posed by the specific individual "scored," but rather describe *groups* of individuals like the individual scored. Scores and checklists provide some guidance, but they are not in and of themselves definitive descriptors of future risk.

It is axiomatic that when clinicians assess risk, it is critical that they gather all the information pertinent to the patient, including past history, collateral history, as well as conducting a detailed mental status examination. Without a thorough understanding of the person in front of you, it is difficult, if not impossible, to be able to conduct a solid risk assessment, and to predict and manage risk. Developing a relationship with your patient while assessing the patient's capability to develop relationships can be especially important. This can go a long way in risk reduction in situations where individuals might be alienated or disconnected from their surroundings.

One of the unique benefits in assessing individuals in later life is that, with detailed history taking, one has much more information to assist the clinician to be able to understand the various triggers and early warning signs for violence that may have occurred over this person's life. There is likely a gold mine of significant information about risk, historical risk factors, stressors, and patterns of behavior. Thus, in managing and predicting risk in the geriatric population, it makes a lot of sense to put weight on looking to the past, not so much of an indication of past violence predicting future violence (which is always important), but also looking for some of the precursors or early warning signs for violence. History is always important, but in geriatric populations it may be a treasure trove.

Ultimately, as one begins to think more about risk, it is important to recognize that risk assessment, prediction, and management are not just skills that can be acquired through training. Managing risk also involves a change in approach for physicians who may have been trained to accept the patient's reality as reality, and for clinicians whose approach is not to question the patient's perspective or their history. That approach may be problematic when risk is paramount. The world has changed for mental health-care providers, and it is expected that psychiatrists, and especially psychiatrists managing geriatric populations, have risk assessment as a skill. That skill is acquired by being aware of the literature, conducting appropriate assessments, and then taking an approach to the patient that not only addresses their overt psychiatric needs but also contains a risk framework. Risk factors in the geriatric population can be complex, change rapidly, or evolve, which subsequently can affect prediction of risk. Occasionally, with change and careful ongoing assessment of such changes comes potential risk reduction or effective risk management.

In summary, the relationship between psychiatric illness and violence is a complex interplay of biological, psychological, and social (biographical) factors. Certain conditions such as NCDs, substance use disorder, and certain personality disorders might be associated with more violent behavior. But it is important to assess the history of victimization as it is an important predictor of future violence. Endorsing common misconceptions to the effect that people with psychiatric illness are more violent than the general population is not only creating an unfounded paranoia but is damaging for the patients who might be deprived from essential services. Trauma-informed care can address the issue victimization and ultimately break the cycle of violence.

29.2 Case Studies

The following case examples are meant to illustrate clinical situations that are encountered in geriatric forensic settings.

29.2.1 Case 1

Case 1 History

Mr. G. has been referred to you for a risk assessment. He is an 82-year-old retired teacher who has been married to the same partner for 54 years. He has suffered with high blood pressure and arthritis for many years and had his left hip replaced 15 years ago. He takes antihypertensive medication and occasionally uses over-the-counter analgesics. Mr. G. has been a "drinker" for most of his life and reports that he has a "few beers" every day. Approximately 6 years ago, he began to have short-term memory problems which gradually worsened over time, and he was eventually diagnosed with major NCD due to Alzheimer disease. According to his family, about 2 years ago, Mr. G.'s personality began to change. He became sullen, demanding, and short tempered with his wife. Although his uncharacteristic behavior was challenging, she felt she could manage his "moods." In recent months, Mr. G. began having more frequent outbursts, and, during these, his wife reports that he began accusing her of having affairs behind his back. Two weeks ago, after Sunday dinner, and without apparent provocation, Mr. G. began hurling insults at his wife. In a fit of rage, he assaulted his wife with his closed fists, causing severe bruising. She escaped to the bedroom and called emergency services. Mr. G. was subsequently arrested and charged with assault. You have been asked by the court to make recommendations. On mental status exam, the patient is calm and alert. He says he wants to speak to his attorney. He does not remember his attorney's name. "I must call him now, I don't want to be locked up and raped!" When you ask him if he has a psychiatric illness, he mumbles something that sounds like "How would I know?!"

Case 1 Questions and Answers

Case 1 Questions

- Question 1. What are the risk factors (both static and dynamic) for violent behavior in Mr. G.'s case?
- Question 2. What goes for and against fitness to stand trial?
- Question 3. What would be your treatment recommendations?

Case 1 Answers

Case 1 Answer 1 (Question 1—What are the risk factors (both static and dynamic) for violent behavior for this man?)

In this case, there is a gradual but clear pattern of psychiatric deterioration and increasing risk of aggression. This is worsened by the presence of alcohol use. It is not uncommon for family members to adapt to and minimize escalating aggression. The presence of psychotic symptoms is a particularly concerning feature. Male sex, the diagnosis of major NCD due to Alzheimer disease and recent history of assaultive behaviors are the static, non-modifiable, risk factors. His alcohol use, physical pain, psychotic symptoms, and psychosocial support are dynamic factors, that is to say, they can be addressed to reduce the risk of violence. Within the static factor of the diagnosis of major NCD (which, to this date, is incurable and has a poor prognosis), there is also a dynamic component of the major NCD (the disease process potentially can be slowed down by interventions). Other dynamic factors to explore would be the presence of mood symptoms, premorbid coping style (e.g., anger or frustration management), and medication adherence. Insight or lack of (which seems to be currently the case for Mr. G.) can be either static (based on personality structure) or dynamic (lack of insight can be reversible in delirium or even psychotic illness).

Case 1 Answer 2 (Question 2—What goes for and against fitness to stand trial in Mr. G.'s case?)

For: (a) the understanding of the charges and possible consequences (he is aware he can be "locked up"), and (b) the presumed ability to collaborate with counsel (as evidenced by his request to contact him).

Against: (a) agitation (due to possible trauma reactivation, paranoid fear of being raped, major NCD, or delirium), (b) unpredictable alterations in behavior and mental status (such as in delirium), (c) intoxication (from alcohol), and (d) cognitive impairment that would be severe enough to interfere with the understanding of the court proceedings, charges, and possible consequences.

Paranoia does not constitute a criterion in and of itself, unless it prevents collaboration with counsel, for instance. Therefore, the impairment is more important than the symptom per se, which should always be put into context.

Case 1 Answer 3 (Question 3—What would be your treatment recommendations?)

Ruling out a medical cause (such as major NCD, intracranial mass, delirium) should be the first step. A careful history of symptoms (psychiatric and physical, such as pain) and a review of medications are crucial. Addressing the precipitant of the delirium is necessary. Once the underlying cause of a delirium has been addressed or a psychiatric cause for the behavior has been established, the behavioral symptoms should be addressed to reduce the risk of violence. Low-dose antipsychotics can be used but with caution, and the benefits must outweigh the risks of cerebrovascular accidents in older population. The patient should be referred to a general practitioner or internist for any other medical condition. Since there was a diagnosis of a major NCD, the appropriate disposition will involve placement in a supervised facility which can treat the patient's symptoms while at the same time maintaining a level of observation and environmental control commensurate with his clinical condition.

Case 1 Analysis After your examination, you learned that Mr. G. became increasingly agitated. You found that the results of his urinalysis came back. He was diagnosed with a urinary tract infection. A delirium was a likely consequence of and was superimposed on his major NCD due to Alzheimer disease, altering his mentation further. Because of his unpredictable and acute presentation, he was not competent to stand trial. The medical team addressed the medical issues (he received antibiotherapy). His competency was restored and he went to court. The forensic psychiatrist had concluded that he presented with new-onset paranoia (from major NCD) and that a delusional disorder, jealous type was not substantiated after getting collateral info from his family. The judge followed the expert's recommendations, and Mr. G. was found not criminally responsible for his recent assaultive behavior.

29.2.2 Case 2

Case 2 History

Mr. T. is a 68-year-old, single male with a history of schizophrenia since the age of 21. He has had a lifelong history of poor adherence to treatment with psychiatric medications resulting in multiple hospitalizations and a lengthy criminal record involving largely minor property offenses, although he had been charged with assault on two occasions. He had used alcohol and a variety of substances for decades and had rarely been abstinent for any length of time. He had not had any contact with his family since his early 30s. Mr. T. never worked and relied on social assistance for intermittent financial support. Five years ago Mr. T. stabbed a stranger on a street corner in an acute state of psychotic decompensation. He was found not criminally responsible and hospitalized in a secure forensic facility. Mr. T. is currently an outpatient in your institution's forensic psychiatry clinic. After 5 years of hospitalization with progressively lower levels of security and increasingly liberal passes, Mr. T. was discharged to the community at his last annual board of review procedure. You are now responsible for his treatment and rehabilitation.

Case 2 Questions and Answers

Case 2 Questions

- Question 1. How will you manage his risk of harm to the public?
- Question 2. What did it entail for this person to not be held criminally responsible for his previous assaultive behavior?
- Question 3. How do you approach the issue of confidentiality with this particular situation?

Case 2 Answers

Case 2 Answer 1 (Question 1—How will you manage his risk of harm to the public?)

The management of this patient will not be appreciably different than that of a younger individual with these risk factors. The key to managing any potential violence will be monitoring of treatment adherence and abstinence from substance (including alcohol) use. This will be facilitated by therapeutic engagement in rehabilitation activities and other forms of social support. The maintenance of psychiatric stability will be the cornerstone of ongoing risk management.

Case 2 Answer 2 (Question 2—What did it entail for this person to not be held criminally responsible for his previous assaultive behavior?)

The psychiatrist might have included in the report for the court that at the time of committing the crime, the patient had a mental illness with symptoms serious enough that they affected his contact with reality and his judgment, making him unable to tell right from wrong. More specifically, there could have been compelling evidence (for instance, recordings) that at the time of committing the violent act, he had a psychotic decompensation (with paranoid thinking), and he acted based on his delusional beliefs. Therefore, he was found noncriminally responsible because of his psychotic symptoms from a severe mental illness interfering with his judgment and ability to understand the nature of his act.

Case 2 (Continued)

During a follow-up visit, Mr. T. presents with an ethylic smell. When you inquire about substance use, he denies but you confront him gently after the urine toxicological screen came back positive, and he becomes guarded. He reluctantly admits that he drinks on occasion but does not want you to tell anyone. "I don't want to end up in jail again."

Case 2 Answer 3 (Question 3—With this new element, how do you approach the issue of confidentiality?)

Since he was discharged from the board of review (the psychiatric treatment equivalent of "sentence"), he is considered free and not bound to the justice system at this time. Unless there were specific recent charges associated with his alcohol use (e.g., disruptive behavior, or fights that would have led to the request of a new forensic evaluation by a judge), you must keep this information confidential. But your role, as his treating psychiatrist in the community, is to provide explicit psychoeducation about the potential consequences of a relapse and monitor closely any exacerbation of psychotic illness. Risk management is an ongoing process. To minimize recidivism of violent acts, developing a strong therapeutic alliance might help the patient acknowledge there is an addiction problem, and this could lead him to seek help (rehabilitation).

Case 2 Analysis Mr. T. felt reassured and started to trust you more. Two months later, he asked for your opinion as to whether or not he should relocate to go live with his younger sister who has a ranch and thought farm life could do him good. His affect brightened up as he spoke of a newly found purpose to his life. Also, he said his sister would help him make sure he was taking his medications. "She'll keep me out of trouble." You organized a phone conference with his sister to coordinate this new transition and heard that Mr. T.'s sister had already made an appointment at a mental health clinic for Mr. T. to establish care there. He agreed to have all his medical records forwarded to his new physician, including his legal history. "I was not quite myself back then." You convey to him that it is a good idea because it will help the new team work with him on consolidating his recovery, and you emphasize that you will send detailed notes about his recent visits and how well he had been doing recently. He also was proud to tell you that he was 55-day sober.

29.3 Key Points: Geriatric Forensic Psychiatry: Risk Assessment and Management

- One of the most common reasons for forensic psychiatry referral is the assessment of competence to stand trial.
- A conservative estimate of the prevalence of psychiatric illness in persons aged 65 and over is 25%. Some untreated psychiatric illnesses or systemic medical illnesses such as delirium may increase the risk of violent behavior.
- Of particular importance in an aging population is the association of major NCDs with violence.
- The relationship between paranoia and aggression revealed a somewhat mixed result. On the other hand, a statistically significant relationship between victimization and violent behavior by patients with severe psychiatric illness has been clearly established in cross-sectional studies and in one recent prospective longitudinal study.
- Violent victimization of patients with psychiatric illness occurs more frequently than violent offending by the patient.
- Criminal behavior is generally uncommon in old age and the offenses tend to be minor, such as shoplifting and driving offenses.
- When assessing, predicting, and managing risk, a structured professional judgment tool is much more powerful when done in team.

29.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. The assessment of violence may be based on:

A. Clinical judgment
B. Actuarial methods
C. Structured Professional Clinical Judgment
D. All of the above

Answer: D

Table 29.6 Screening tools and scales in forensic psychiatry

Tools	Characteristics
VRAG (Violence Risk Appraisal Guide)	Gives a likelihood of any particular act occurring at 7 or 10 years
SPJ (Structured Professional Clinical Judgment)	Considers evidence-based risk factors and clinical judgment
eHARM (Hamilton Anatomy of Risk Management)	Extensive data set
Modified Overt Aggression Scale	Quantifies the gravity and frequency of aggressive incidents
Aggressive Incidents Scale	Quantifies the gravity and frequency of aggressive incidents
HCR-20 (Historical Clinical Risk Management-20)	Highlights 20 of the main factors contributing to risk of violence
MacArthur Violence Risk Assessment	Measure of violence towards others

Clinical judgment is integrative and takes into account a complex variety of factors. It is a pragmatic process also enriched by the expertise level of the clinician; therefore, it is an essential step in risk assessment. Actuarial methods increase the validity of the assessment by using data from big samples. Screening tools or scales like the Structured Professional Clinical Judgment (which considers evidence-based risk factors and clinical judgment) are also valuable (Table 29.6). Therefore, A, B, and C are true and then the accurate, inclusive answer is D.

MCQ 2. In a geriatric population, which of the following is least likely to be associated with an increased risk of violence?

A. Paranoid psychosis
B. Alcohol use
C. Anxiety disorder
D. Frontal lobe impairment

Answer: C

Severe psychiatric illness, especially when there is a history of victimization and other factors such as homelessness, can be associated with an increased risk of violence. Alcohol or mind-altering drugs can affect judgment, cause disinhibition, and exacerbate or trigger psychotic symptoms, which could lead to violent acts. Major NCDs (like frontal lobe impairment) are also a risk factor for violence in older patients. So A, B, and D are true. Anxiety disorders in general are not typically associated with higher risk of violence especially if there are no associated conditions like substance use or personality disorder. On the contrary, because of hypervigilance and avoidance, these patients tend to internalize rather than externalize their emotional experiences. Therefore, statement C is the correct answer.

MCQ 3. Which personality disorders have the highest correlation with violence?

A. Paranoid and schizotypal
B. Borderline and avoidant
C. Sadistic and passive aggressive
D. Antisocial and borderline

Answer: D

Numerous studies have identified key risk factors pertinent to the likelihood of violence occurring at some point in the future. These have been variously described, but include historical factors such as major psychiatric disorders (including major NCDs), personality disorders, (specifically antisocial and borderline type; therefore, statement D is true), substance use disorder, comorbid systemic medical problems, as well as employment instability, housing instability, and financial difficulties (See Table 29.5). Schizotypal personality disorder is more associated with social isolation and withdrawal and less acting outs, just like avoidant and passive aggressive, who tend to internalize feelings of aggression. Therefore, statements A, B, and C are not particularly associated with violence.

MCQ 4. Which one of the following is *not* a role for the forensic psychiatrist?

A. Assessment of competence to stand trial
B. Decision about criminal responsibility
C. Diagnosis and treatment of psychiatric disorders
D. Risk prediction in team

Answer: B

The assessment of fitness to stand trial and risk management (preferably in team, for more optimal assessment, see Background section and Fig. 29.1) are frequent tasks for the forensic psychiatrist (thus, statements A and D are true). Diagnosis is implicit to the process of risk assessment, and treatment of psychiatric disorders to restore competency to stand trial or reduce risk is also another role; therefore, statement C is true. A psychiatrist can give a professional opinion about whether or not a patient was criminally responsible at the time of committing the act, but the ultimate decision comes from a judge, therefore statement B is false and is the correct answer.

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Marginalized Geriatric Patients

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30.1 Background

30.1.1 Anti-oppressive Practice

Anti-oppressive practice is an approach to the assessment and treatment of patients that considers issues such as privilege, oppression, identity, context, and power relations as important elements. An anti-oppressive approach involves a commitment to social justice, including the integration of practices designed to minimize power imbalances and promote equity and empowerment for patients. Fundamental to this approach is an understanding that practitioners bring their own personal and social history and lived experience to clinical practice, and, therefore, their interactions with patients are undoubtedly shaped by these aspects of self. In order to mitigate the potential barriers between patients and healthcare practitioners, as the more powerful parties in the process, healthcare practitioners have a responsibility to engage in critical reflexivity. This means that the practitioner must understand their own social location and how this affects their relationship to their practice and their behaviors and approaches to patient care [1]. Anti-oppressive practitioners develop a deep understanding of who they are as an individual, who they are as a professional, and their role in the specific intervention they are undertaking in the moment [2].

For geriatric patients, receiving care that reflects an anti-oppressive approach allows for consideration of the specific vulnerabilities this population faces when they access services and supports. Assessment from an anti-oppressive approach, when used to support the care of geriatric patients, enhances the capacity of mental health practitioners to understand the predisposing, precipitating, and perpetuating (as well as the potentially protective) factors in a patient's presentation.

Good quality psychiatric assessment and treatment requires a holistic consideration of the patient's biological, emotional, social, and spiritual needs while also taking into account the social and institutional contexts surrounding the patient. Through assessment, the healthcare practitioner has the opportunity to consider how the patient shares their own identity and how this is understood given the practitioners' values, beliefs, and professional context. When the healthcare practitioner makes these phenomena conscious and explicit, the patient remains at the center of the assessment because the meaning made by the practitioner becomes more transparent and, therefore, more negotiable.

Social location should be considered as part of the assessment categories. Social location challenges a unitary understanding of identity, but rather frames identity as a complex convergence of many aspects of self and socially constructed identity categories. Each of us has identities that are complex and multiple, identities that we as individuals may accept and others that we may reject [3]. We possess identities that are fluid rather than fixed and identities that are context bound rather than always present [4]. Therefore, when an older marginalized patient rejects a particular label or identity placed upon them, this rejection may not be a matter of pathology or psychological resistance, but rather a desire for a more careful understanding of how they see themselves.

Traditional assessment categories like biological, psychological, and social characteristics are enhanced through the use of anti-oppressive practice assessment techniques. In an anti-oppressive practice assessment, understandings of privilege, oppression, identity, context, and power are considered [1]. While anti-oppressive practice is in its early phases of development in the field of medicine, other healthcare professions such as nursing, social work, and psychology have embraced anti-oppressive practice since the mid-1990s [5, 6]. The scholarship of anti-oppressive practice within these other disciplines acknowledges the interdisciplinary nature of psychiatric care, while context-informed understandings and a holistic framing of patient needs are also considered, thereby expanding assessment beyond the traditional medical model approach [7]. Anti-oppressive practice is a model of patient-centered care that takes into account both the individual and institutional aspects of care. According to Larson [8], anti-oppressive practice is defined as a commitment to social justice that includes:

- A clear theoretical and value base that promotes power sharing and egalitarianism
- An understanding of one's own social location and how it informs practice behaviors and relationships
- Specific practice behaviors and relationships that minimize power imbalances and promote equity and empowerment for patients

Healthcare professionals experience professional social status and social and economic privilege. With these benefits comes the responsibility to recognize the power we gain as a result and also to educate ourselves about life experiences different from our own. We can learn a great deal from patients who experience marginalization when we listen to their stories about the challenges they face in navigating the systems in which we work. Practitioners can assist patients by demystifying these systems and by sharing information about how to navigate through medical bureaucracy. Furthermore, anti-oppressive practice involves advocacy for individual patients that involves challenging oppression in the institutions and contexts in which we experience privilege and have greater power [9].

When traditionally marginalized populations access psychiatric services, they may experience barriers to access and possibly even exclusion. Patients from various minority groups (e.g., patients with disabilities, patients who identify as LGBTQ, patients who are immigrants or refugees, patients who come from low socioeconomic backgrounds, or patients who are racialized) all face forms of oppression that are sometimes hidden and, therefore, difficult to identify [8] especially when these oppressions are coupled with ageism and the realities of aging. Table 30.1 illustrates examples of some dimensions of diversity/identity and potential associated types of oppression [1]. Using an anti-oppressive practice approach offers potential resources to challenge these realities by promoting activities and skills to challenge the status quo. Table 30.2 provides a summary of common examples

Table 30.1 Dimensions of diversity/identity and types of oppression

Dimensions of diversity	Examples of types of oppression
Age	Ageism, elder/child abuse/neglect
Gender/gender identity/ gender expression	Sexism, patriarchy, misogyny, chauvinism, transphobia, cisnormativity
Family or marital status	Sexism, patriarchy, misogyny, chauvinism, heteronormativity
Country of origin/creed/ ethnicity	Xenophobia, racism, Eurocentrism, Westernism, othering, cultural imperialism, ethnocentrism
Immigration/citizen status	Xenophobia, racism, colonialism, cultural imperialism
Socioeconomic background/class	Classism, elitism
Race/color	Racism, racialism, supremacism, colorism, othering
Sexual orientation	Homophobia, lesbophobia, biphobia, heteronormativity
Ability (physical and developmental)	Ableism, ablecentrism, disability oppression
Religion	Xenophobia, Islamophobia, anti-Semitism, Christocentrism
Mental health status	Mental health stigma, sanism, mentalism, pathologization
Place of residence	Regionality, regional stereotypes, "rural" vs. "urban"
Physical size/weight	Sizeism, weightism, thinnism, fat phobia

Note: Identities can form a system of interlocking oppressions (From Veltman and La Rose [1]; reproduced with permission of Springer Nature)

Table 30.2 Examples of elements of anti-oppressive practice

Goals and objectives	Management tips
Patient-centered goals and activities	Focus on patients' strengths and uniqueness, not on pathology Avoid judgments in the form of diagnostic categories and labels Listen to and take seriously what patients say about their own mental distress and experience—e.g., treating them as "experts in their own experience" Assure patients that they have the right to ask questions and to feel as they choose to feel Empower patients by involving them and their families in all decision making about their care and inviting them to participate in agency activities at all levels, including staff meetings and their own case conferences Sharing information with patients and their families and providing them with access to clinical records
Clinician-focused goals and objectives	Reflect on personal values, beliefs, and attitudes and how these may affect patients' assessments and treatment Reflect on the meaning of professional identity and its capacity to create distance between colleagues and patients Reduce the us-and-them distinctions between patients and professionals Not pretending competence and knowledge when they are not present; acknowledging what you do not know
Institutional goals and objectives	Reflect on the meaning of the institution to patients using the services Consider the effect of the physical environment on the experiences of patients, families, and staff members Provide public access to information about policies and procedures including complaint procedures Encourage transparency in the operation of the institution Establish egalitarian relationships with the communities served by the institution

References: [1, 5, 6, 10, 11] (From: Veltman and La Rose [1]; reproduced with permission of Springer Nature

of anti-oppressive practice elements in healthcare settings and may be helpful in answering some of the questions from the case studies presented later in this chapter [1, 5, 6, 10, 11].

Using an anti-oppressive practice approach does not necessarily mean investing more time or energy in an intervention, but it does require a differential approach to each intervention. Anti-oppressive practice centers relationship as a fundamental aspect of what makes for good practice. While relationship building may require a little more energy in the beginning of an intervention, by improving relationships with patients and their caregivers, practitioners can enhance the quality of the information obtained during assessment [10, 12, 13]. Listening and asking inductive questions based on what the patient is telling you can help practitioners avoid standardized questions that may lead patients and practitioners down the wrong path. Patient-centered care suggests that the narratives that patients share during assessments reveal patient needs, goals, and values.

Psychiatric assessments generally focus on "what's wrong" and the level of "ill-being" experienced by the person being assessed. Anti-oppressive assessments include an assessment of patients' "well-being" or "what is working," "what gives them strength," and "what gives them pleasure" [14]. Anti-oppressive practice assessments go beyond considerations of the "problem" by incorporating patients' strengths, coping strategies, personality, and life experience as well as the environmental resources available to patients [5].

Anti-oppressive assessments in psychiatric practice focus on patient engagement; understanding is developed through inductive rather than deductive processes. Assessment from this position requires unlearning and the re-understanding of assessment as an "art form" in which assessment becomes the skillful act of "question posing" and as a process of eliciting narratives from patients [1]. Questions remain a fundamental aspect of assessment; however, the questions asked are based on the information the patient shares with the clinician, rather than on a preconceived notion of the right questions to ask [10]. While closed-ended questions may make for a speedy assessment, they tend to be built on assumptions about "what is important" that were determined before the patient and the practitioner began their interaction. Open-ended questions may take more time, but they may lead the clinician to new insights and new understandings that are reflective of the needs of the patient. Patient narratives allow clinicians the opportunity to consider content, process, and context as holding shared importance in the making of meaning within the assessment. Most patients who have experienced previous assessments quickly become aware of the fact there are particular stories and particular answers that practitioners are looking for in order to complete their diagnostic assessment. The opportunity for the patient to share other kinds of information may be an opportunity for both the patient and the clinician to consider new possibilities [1, 15].

The social environment and the personal network surrounding the patient are important considerations when practicing from an anti-oppressive practice position. Intimate people in the older patient's life, family (including chosen family), friends, and neighbors should be encouraged to take an active role in care whenever possible. These allies can serve as consultants on the experiences of their loved one and the meanings these experiences hold [8].

Communication is a fundamental aspect of anti-oppressive practice and serves as a foundational aspect of the relationship-building process. Inclusive communication reduces a patient's experience of stigma and honors the perspectives and beliefs of the patient. This kind of approach to communication seeks to reduce power imbalances between the patient and the clinician and is the hallmark of anti-oppressive practice interventions [7, 13]. Within healthcare settings, jargon and "shorthand speech" can mean that clinicians may refer to patients as their symptoms (e.g., "paranoid delusions in emergency room ten"), their diagnosis (e.g., "schizophrenic in emergency room ten"), or stereotypes about the types of patients (e.g., "frequent flyer in emergency room ten"), and this kind of speech is harmful to patients [1]. Using plain language, avoiding jargon or acronyms, and providing supporting materials (e.g., pamphlets, fact sheets, website information when appropriate) that are available in multiple languages are ways to support patients' continued involvement in their care and to reduce power imbalances in access to information.

Teaching Point

Anti-oppressive practice is an approach to care that takes into account the social location/personal identities of the clinician as well as those of the patient. An anti-oppressive practice approach can improve a clinician's rapport with a patient as they feel more listened to and better understood than in many healthcare encounters that do not employ this method. Anti-oppressive practice aims to minimize power imbalances and promote patient empowerment.

30.1.2 Culture

An individual's perspectives and beliefs related to illness, health, and mental health are shaped by the individual's culture and community. The general population in North America is becoming increasingly diverse, and therefore, mental health practitioners who are committed to providing high-quality mental healthcare need to consider the significance of identity (and the intersections of identity) in order to achieve this goal. According to Abramson et al., to meet the needs of diverse populations, mental health clinicians need to understand the effect of culture on mental health [16]. The authors suggest, at times, a lack of understanding of cultural perspectives can create barriers to healthcare services and create issues or conflicts between patients and clinicians.

Culture plays a significant role in mental health, shaping the experiences and personal understanding of psychiatric illness as well as the way in which a patient responds to illness, copes with symptoms, and seeks support. Cultural mismatches explain lower levels of mental health service utilization by ethnically and racially diverse people; these mismatches result from a complex interaction of individual and systemic factors [16]. (For further details, see ▶ Chap. 32)

There is a lack of research focused on identity and diversity in mental healthcare, which means, in many instances, the reasons we use to explain why people do not use services are mostly speculative. However, consideration of the research that does exist suggests that individual, social, and systemic factors interact to result in low service utilization by racially and ethnically diverse patients. As a result, racialized patients (and patients who are marginalized due to other identities) may seek service only after their mental health issues have reached a crisis point, and therefore, the treatment they receive is often more invasive, less collaborative, and more expensive. (See ▶ Chap. 32)

For some older marginalized people, the fact that most medical professionals do not reflect their own identities, speak their language, or understand their values and beliefs is likely a deterrent to care. In some cases, the intersection of various identity positions may lessen the connections that can be made between healthcare professionals and patients, which in a mental health context may complicate the therapeutic rela-

tionship and reduce the effectiveness of some treatments. Abramson et al. suggest that clinicians working with older adults from a culture different from their own must demonstrate particular sensitivity with respect to using appropriate communication styles [16]. The authors advise clinicians to adjust their communication style (verbal and nonverbal) to better reflect the preferences of the patient [16]. When language poses a barrier, it is necessary for clinicians to utilize nonverbal communication strategies, including appropriate body language (e.g., eye contact, distance between two persons, body movements) [16].

The diversity among different cultural groups is often not as great as the diversity that can be found within each cultural group. When looking at any ethnic or cultural group, one must keep in mind the great amount of heterogeneity and diversity that exists within the group. An individual within a culture may not manifest attitudes or symptoms that are broadly characteristic of the specific ethnic or cultural group [17]. Abramson et al. suggest patients should be seen as unique individuals, rather than as static archetypes of a particular racial or ethnic group [16]. Talking to the patient and truly listening to their stories and the meanings that the patient ascribes to these stories is an important means of developing an appreciation for the ways in which the individual is both a member of a group with a shared identity and a unique individual who brings with them experiences, values, and beliefs that may reinforce and/or challenge group norms [1].

Culture must be considered, addressed, and understood by mental health professionals and researchers as the population of older adults becomes more ethnically and racially diverse. Culture influences the prevalence of psychiatric illness, how older adults interpret their environments, how they handle their daily life stresses, and how they cope with mental health problems; culture provides a context for treatment [16, 17]. Appreciating culture as a context for care is a necessary aspect of effective practice with geriatric patients who are an increasingly diverse population. Healthcare systems serving these patients need to provide individualized care that is culturally appropriate. Practitioners must understand the relationship between culture and mental health beliefs and practices. The planning of healthcare policies and programs for minority older adults must take the implications of cultural differences into account.

Table 30.3 contains information about how to build cultural competency/cultural safety skills and how to incorporate these into one's approach to assessment and treatment of diverse older patients.

Teaching Point

Clinicians must take into account the issue of culture in order to be able to provide high-quality care to older adult patients. Clinicians have a responsibility to learn how to incorporate cultural safety into their practice.

Table 30.3 Cultural competency/cultural safety [16, 57–59]

How to build cultural competency/cultural safety skills as an individual clinician	How to incorporate culturally sensitive practice at the agency/organization level
Become aware of culture and its pervasive influence on health	Attempt to provide patients with health-care workers of the same ethnicity/cultural background when possible. When such workers are not available, ensure the workers are sensitive to cultural differences
Learn about and understand your own cultural identity and share information about yourself to create a sense of equity and trust with your patients	Establish a focus for empowerment that builds strength and promotes community development
Recognize your own ethnocentricity (e.g., ways in which you stereotype, judge, and discriminate your emotional reactions to conflicting cultural values)	Teach patients how to navigate the system
Learn about other cultures you encounter and demonstrate respect for cultural forms of engagement	Develop policies that support appropriate services for minority patients (e.g., interpreter services, anti-discrimination policies)
Understand the impact of various forms of oppression on service delivery to minority populations	Solicit, promote, and utilize input from patients who belong to diverse communities
Appreciate that there is a lot of heterogeneity within various minority populations	Increase the agency's accountability to the diverse communities it may serve
Recognize the family's importance (or other important social supports: close friends, chosen family) as a potential source of support and point of intervention	
Understand cultural preferences in order to support patient self-determination. Ensure the assessment and treatment process yields appropriate outcomes for the patient according to that patient's values and preferences	
The patient defines whether an encounter/health-care experience is culturally safe. This is an intentional method to try to shift the power imbalance that is inherent in health service delivery from the clinician to the patient	

30.1.3 LGBTQ Communities

Health disparities related to sexual orientation have been identified as one of the most pronounced gaps in health research [18] with health research of LGBTQ older adults largely absent [19]. It is important to note that there is substantial diversity within older LGBTQ communities—they are not a homogeneous group. Diversity exists in terms of gender, ethnicity, educational attainment, income, levels of ability, socioeconomic status, and many other characteristics, all of which affect their mental health needs and influence their ability to access appropriate care and support.

Poverty among lesbian, gay, and bisexual people is shown to be as high or higher than among the heterosexual population [20]. Transgender people face high levels of employment and housing discrimination and consequently experience greater economic disadvantage and housing instability [21]. According to Chandavarkar and Khan, several factors compound the economic challenges faced by LGBTQ older adults, including unemployment, poverty, homelessness, lack of family support, and social isolation [20]. These social factors have a negative impact on LGBTQ people's mental health.

Previous research shows LGBTQ older adults are less likely to have children and less likely to be living with life partners than are older adults who identify as heterosexual [22]. Unfortunately, many LGBTQ older adults may be estranged from their families of origin due to a lack of acceptance of their identities by their families of origin. However, many LGBTQ older adults may have a strong social network of friends, networks that may be understood as "families of choice." Although prior research suggests LGBTQ older adults who rely upon friends to provide informal care may find themselves without adequate care when their needs become acute [23], some have suggested that LGBTQ older adults may have a social advantage over their heterosexual counterparts due to their well-developed social networks [24].

According to Brotman et al., in the limited research that does exist on LGBTQ older adults, repeated themes emerge, including profound marginalization experiences in all aspects of social and political life [25]. These lifelong experiences of marginalization and oppression can lead to a mistrust of health and social services; the invisibility of LGBTQ people exacerbates the lack of appropriate services, as their absence can obstruct any possibility of developing sensitive and appropriate health, social service, and long-term care services through ambient and evolutionary processes.

Generally, the sexuality of older people is not widely recognized. Price suggests that expressions of sexuality among older people are seen as problems to be managed or treated [26]. As such, older lesbians, gay, and bisexual people are understood to be "twice hidden" and to represent the most "invisible of an already invisible minority" [27]. Ageist assumptions are frequently combined with presumptions of heterosexuality [26]. Heterosexism is the assumption that all individuals are heterosexual and heterosexuality is more natural and normal than same sex attraction.

Older LGBTQ adults may experience various forms of discrimination, including ageism, heterosexism, and homophobia, which will lead to marginalization and invisibility [25]. Lesbian and gay older people can feel marginalized as ageism also exists within gay and lesbian communities. Isolation is likely to be a major threat to the well-being of older lesbian and gay people, placing individuals at higher risk of self-neglect, decreased quality of life, and increased mortality.

Past experiences of discrimination or fears of encountering further discriminatory practice appear to contribute to health risks as LGBTQ older people seek to avoid routine healthcare and fail to claim social and housing support when it is needed [28]. Lesbian and gay patients have reported negative reactions from healthcare practitioners, which include embarrassment, anxiety, rejection or hostility, curiosity, pity, condescension, ostracism, withholding treatment, detachment, avoidance of physical contact, and breach of confidentiality [25]. In a review of the literature by Addis et al., discrimination is seen as negatively impacting access to healthcare services by LGBTQ older people in a number of studies on LGBTQ health [29]. Similarly, LGBTQ people expressed hesitancy to disclose their sexual identity/gender identity to healthcare professionals. Given the historical role of healthcare systems in pathologizing LGBTQ identities, LGBTQ older people appear likely to continue to avoid disclosing their sexual orientation or gender identity, contributing to systemic failures of health and social care services to meet the needs of these groups, thereby sustaining discrimination and disparities in the quality of care they receive [29, 30].

Although it is difficult to get an accurate population estimate, recent data suggest that 0.3–0.5% of adults identify as transgender [31]. Transgender adults are at elevated risk of depressive disorders and attempted suicide [21, 32]. Fredriksen-Goldsen et al. found that transgender older adults have significantly poorer health in terms of physical health, disability, depressive symptomatology, and perceived stress than non-transgender LGBTQ older adults (when controlling for key background characteristics) [33]. These researchers found a strong association between concealment of gender identity and higher degrees of depressive symptomatology and perceived stress, while social support and feelings of belonging within the LGBTQ community were significantly associated with better physical health, lower likelihood of disability, and lower levels of depressive symptomatology and perceived stress.

Transgender adults risk discrimination, harassment, and victimization in healthcare settings [34]. More than a quarter of transgender adults have experienced discrimination by a physician or have been denied enrollment in a health insurance plan due to their gender identity [35]. Transgender older adults fear accessing healthcare services and are often hesitant to seek medical attention due to negative experiences in the past as well as fear of judgments by healthcare providers. Even now, many healthcare practitioners are inadequately prepared to address the needs of transgender older adults. Most clinicians lack knowledge concerning transgender health issues both in their training and in the lack of frequency in which they encounter openly transgender individuals [30, 34]. As a result, transgender individuals often incur significant time and travel costs in order to reach trained, gender-affirming clinicians.

Teaching Point

Clinicians need to be aware of the health disparities and the barriers to accessing healthcare services that exist for many LGBTQ older adults. Clinicians must educate themselves about how to best create an LGBTQ-affirming space ("positive space") where LGBTQ older adults will feel more comfortable accessing services.

30.1.4 Racialized and Immigrant Communities

Race matters in mental healthcare. Racism limits the life chances and life circumstances of seniors, but it is a factor that is often hidden from sight within the mental health literature. In their research on challenges and barriers to services for immigrant seniors in Canada, Stewart et al. discretely discuss the issue of racism [36]. In their discussion, they conclude that racism is a real issue experienced by many older adults. Seniors may experience racism in the community, in long-term care facilities, and in many other service contexts [36]. Race is a "social determinant of health" under the World Health Organization's population health approach, although it is one of the less discussed elements within this actuarial model. The effects of long-term stress resulting from racism leave significant traces on the bodies and minds of racialized seniors [37].

Jimenez et al. suggest race and ethnicity affect the meaning, type, and severity of psychiatric illnesses [38]. The authors argue that certain groups are more inclined to experience particular types of illnesses and to respond to these illnesses in particular ways. While their study suggests knowledge of particular ethno-racial tendencies may benefit standardized processes, the problem with standardization is that it holds the potential to foreclose other possibilities and to support diagnostic bias toward particular trends [15]. Their work also calls into question the use of standardized diagnostic scales and reveals the potential that these standardized tools may hold unacknowledged and unresearched biases. Knowing the validity of a scale with a non-mainstream patient group may help practitioners make informed decisions about which scales to avoid when working with marginalized populations. The authors suggest there is a need for more research and inquiry into mental healthcare with marginalized patients, particularly in relation to standardization. Practitioners may want to think critically about population health approaches that tend to lean on "big data" analysis for meaning making, as they may eclipse the experiences of minority populations who are underrepresented in healthcare uptake more generally and, therefore, are not well represented in research that studies very large populations of patients [37].

The work of Jimenez et al. raises questions about identity and the roles ethnicity, culture, race, and language play in shaping attitudes toward mental healthcare [38]. However, the challenge of studying this kind of nuanced factor means there are few definitive understandings. One significant variable in the provision of mental healthcare is the use of standardized measures or assessment tools as diagnostic instruments. Standardized measures need to be assessed in mental health practice with consideration of the composition of the population on which the scale/tool was tested and the manner in which this testing was undertaken. Several studies have demonstrated that this kind of testing may have a bias toward mainstream Western culture and Christocentric values [39]. Therefore, a practitioner may assist a minority group member patient by electing to refrain from using the standardized tool when the identity of the patient does not reflect the profile of the scale or measure and by noting in the chart when and why this has occurred.

As Jimenez et al. suggest, the greatest heterogeneity exists within what is described as a "homogeneous group" [38]. While cultural meanings, values, and beliefs may have an organizing principle within the context of psychiatric illness, much variation will still exist within and among the population. The patient receiving care may interpret, internalize, and perform these values and beliefs in unique ways, which is not necessarily the result of a psychiatric illness. Consulting with the patient about the meaning of their experiences, listening to the answers with openness, rather than seeking to check off certain predetermined ideas or symptoms, is very important; "wrong" narratives can help lead to the "right" diagnosis and intervention [1]. Ethno-cultural and linguistic seniors' services are available in many communities; however, in some cases, these services may be provided by small not-for-profit organizations and benevolent societies or as subsets of larger community service activities provided by organizations with much broader mandates [16]. Getting to know the services in the community and the nuances of these services is an important aspect of being able to provide effective referrals to members of marginalized groups. Here, interprofessional development activities may support a broadening of a clinician's knowledge of community resources and a deepening of a shared understanding of patient needs. Sharing knowledge of needs and resources may be the first step in ensuring that patients seeking services for mental health can be effectively linked to follow-up and complementary services. In this context, follow-up by social workers, recreation therapists, community support workers, and/or occupational therapists is likely necessary for the senior patient and will provide the team/service with valuable information about the qualities and limitations of the community services. Furthermore, in this context, discharge planning that includes linking and referral to community resources needs to mean more than simply providing a patient with a list of websites and telephone numbers; it may require follow-up and access to/support by psychiatric team members to ensure connections are made and rapport is established.

Stewart et al. suggest that for some seniors, the use of government services can be an emotionally triggering and stressful experience [36]. Immigrant seniors may bring historical

experiences of government corruption or state-sponsored violence to their interactions with the mental health system. Healthcare professionals have a duty to consider how these patient histories may shape their attitudes and beliefs toward mental health services. In these cases, work to resolve the underlying trauma may help to improve the situation, while consideration of the nature of referrals to the community and support for service access may also be required.

Stewart et al. also suggest immigrant seniors be assessed for post-traumatic stress disorder when considering mental health problems [36]. For many ethnically diverse seniors, migration may have occurred as a result of marginalization and oppression within their home country, leaving a legacy of trauma that may become acute in older age. (See ▶ Chap. 14) Challenges for practitioners may include patient attitudes about the receipt of care, particularly in contexts where mental health issues are highly stigmatized.

Translation/interpretation may pose another challenge for mental healthcaregivers and patients. For many people, the language of feelings, emotions, and psychological experiences is unfamiliar territory, and narratives around mental health can be difficult to translate. Whether one chooses to use professional, volunteer, or family members as interpreters, each of these choices brings its own challenges. Professional interpreters may alienate clients or rely too heavily on the interpretation of common phrases into technical assertions, while volunteers may lack the technical knowledge necessary to reflect treatment details accurately, and family members may interpret meaning in ways that reduce perceived stigma but, in doing so, may leave out key elements of a patient's story. Family violence (and other potential family "secrets") is a concern in family-based interpretation contexts, and, therefore, the use of family members as interpreters should be carefully evaluated [36].

Teaching Point

A patient's race, ethnicity, and history of immigration can affect various aspects of their experience of having a psychiatric illness, including access to and quality of mental healthcare services. Clinicians have a responsibility to take these issues into account when working with patients from potentially marginalized ethnoracial backgrounds as well as those who have lived experience with immigration.

30.1.5 People with Intellectual/Developmental Disabilities

People with intellectual disabilities are living longer than in previous generations. However, they often experience poorer health and earlier onset of age-related conditions [40] due to issues related to access to care and biological as well as lifestyle factors [41]. In addition, they experience greater health disparities in part due to lack of preventive health screenings [42, 43]. People with intellectual disabilities also experience a higher rate of mental health issues than the general population. In a study of 1023 adults with intellectual disability, the point prevalence of "mental ill-health" of any type was 40.9% (by clinical diagnoses), and if one excluded problem behaviors and autistic spectrum disorders, the percentage was 22.4% [44]. Point prevalence was 4.4% for any type of psychotic disorder, 6.6% for affective (depressive and bipolar) disorders, and 3.8% for any type of anxiety disorder.

Many programs for older adults and much of the research on seniors do not include any people with intellectual or developmental disabilities. People with intellectual or developmental disabilities should be included in programs and in research about seniors, but it is important to tailor interventions to incorporate the specific needs of this population. More education is needed for researchers and for healthcare practitioners regarding the use of universal design principles that are inclusive of people with disabilities [45]. Clinicians could better apply concepts of cognitive and physical accessibility to the growing population of people with major neurocognitive disorders or physical limitations using principles of universal design. Greater consideration of the desires and preferences of older adults could improve motivation and adherence.

Although older adults with developmental disabilities are living longer, they may demonstrate the signs of aging at an earlier age than the general population [40]. Unfortunately, older adults with developmental disabilities cannot access many generic services and supports for older adults because eligibility is generally based on the chronological age of 65 years and sometimes having an intellectual or developmental disability may be an exclusion criterion for accessing the service.

There is a significant gap in appropriate services for older adults with developmental disabilities and accompanying mental health concerns, including major neurocognitive disorders. Individuals who are "dually diagnosed" with intellectual disability and a major neurocognitive disorder are likely to either become "revolving patients" or experience "delayed discharge" in medical and psychiatric wards [46]. The prevalence of major neurocognitive disorder may be higher in people with developmental disabilities than in the general population (not just in those with Down syndrome) [40]. However, other conditions must be ruled out before a diagnosis of major neurocognitive disorder is given to someone with a developmental disability, including physical (e.g., hypothyroidism, hypercalcemia, vitamin deficiencies), psychiatric (e.g., depressive/anxiety disorder), sensory (e.g., hearing/vision impairment), and medication-related issues (e.g., overmedication, polypharmacy) [43].

According to Thorpe, behavioral problems are more common in those with intellectual disabilities, and behavioral issues are more common in this population than are core psychiatric disorders, such as depressive disorder or schizophrenia [47]. Some behaviors in people with intellectual disabilities are related to brain abnormalities (e.g., impulse control, attentional deficits, poor understanding),

but these may also be due to impaired learning of socially appropriate behavior or to learning of abnormal behaviors from others, especially in institutional settings. Additional stressors that are common in older age, such as bereavement or change of residential status, add a greater burden to an individual with an intellectual disability who has reduced cognitive and emotional coping skills and decreased or reduced social support networks.

Ironically, the move to deinstitutionalization may have worsened psychiatric care for adults with intellectual disabilities, because localized pockets of knowledgeable professionals, who were based in the institutions, dispersed. As a result, challenging patients with intellectual disabilities were spread across regions to be cared for by inexperienced community service providers. Meanwhile, inpatient psychiatric units that are used in periods of crisis are often aware of their inability to provide developmentally appropriate care [47].

In terms of treatment for individuals with intellectual disabilities, it is often even more imperative that a biopsychosocial approach be used in these cases. (For further details on approach to management, see ▶ Chap. 27) Although this is detailed elsewhere in this book, it is important to emphasize that a thorough assessment should be completed and that the diagnosis and factors contributing to the diagnosis should be identified. Particular disorders should be treated specifically rather than trying to treat symptoms more generically. If a medication needs to be initiated, the mantra of "start low, go slow" should be used. Individuals with intellectual disabilities should be monitored closely for response and for side effects because they do have an increased risk of side effects from many psychotropic medications [43].

Collaboration between the aging and the intellectual disabilities care systems could enhance service delivery to this population of older adults with intellectual disabilities who also have mental health issues. Although research and knowledge in this area is growing, there is still a lack of educational opportunities for healthcare practitioners in North America to increase their skills in working with this population. Unlike some countries such as the United Kingdom, no psychiatric specialist training stream exists for intellectual disabilities in North America, and there are few psychiatrists with special expertise, training, or interest in this area. Teaching and exposure to this patient population within most psychiatric residencies tends to be rather fragmented, if present at all, and is often confined to child psychiatry rotations [47].

Teaching Point

Older adults with intellectual disabilities have higher rates of various mental health issues when compared to older adults who do not have such challenges. Clinicians need to increase their comfort and their skills in working with this underserved population.

30.1.6 Homeless Populations

Although seniors constitute a small percentage of the total homeless population in North America, the absolute numbers are increasing [48]. There is difficulty inherent in detecting the "hidden homeless" and in obtaining accurate estimates of the population of homeless older adults. As a result of a variety of factors such as the poor economic climate, decreased availability of subsidized housing, decline in the amount of social assistance benefits, decrease in the number of social programs, weakened social supports, and rising rates of mental health problems and substance use, the proportion of homeless older adults in North America is increasing. These issues contribute to what has been called the changing face of homelessness [49].

The rise in older adult homelessness in North America has not led to a corresponding attention in the academic literature and in public policy statements; a knowledge gap remains in exploring the unique experiences and difficulties facing older adults who are homeless. There is debate over the age limit used to study homelessness in the older population. Some researchers argue defining geriatric homelessness as a category representing people "above age 50 years" is meaningful because homeless people resemble those in the community who are 10–20 years older from a physical health point of view. Between 14% and 28% of the homeless population using shelters in major cities in the United States are 50 years of age and older [48]. Research has noted a sharp increase in the proportion of homeless older adults in the United States in the past decade, from approximately 11% to 30% [50]. These prevalence rates are likely to be underestimates of the true proportion of older adults who are homeless, due to the vacillation of individuals from "homeless to housed" status, difficulty recruiting homeless older adults to participate in research studies, differing research definitions of homeless older adults (range from 40 to 65 years old age), and older adults' lack of attendance at public shelters and organizations [48].

The pathway into homelessness for older adults is multifactorial (as it is for younger homeless people) and includes deinstitutionalization, poverty, and lack of affordable housing [48]. Risk factors or triggering events in this group include evictions, loss of income, and the death of a spouse, relative, or significant other. Eviction from previous housing because of lack of adequate funds is another common reason for temporary homelessness. A variety of possible causes of homelessness is outlined in the literature, including structural issues, personal vulnerabilities, and the interaction of structural issues and personal vulnerabilities [51]. For older adults who have become homeless for the first time in later life, research highlights eviction, retirement and loss of income, difficulty with reentry into the labor force, and widowhood/widowerhood, as prominent causes [48, 52]. ◘ Table 30.4 examines some of the individual, relational, and structural/societal factors contributing to possible pathways to homelessness for older adults. Research studies estimate that among the aging homeless population, men outnumber

Table 30.4 Pathways to homelessness

Individual factors	Relational factors	Structural/societal factors
Alcohol abuse Substance abuse Psychiatric illness Systemic medical illness	Relationship difficulties/family dysfunction Loss of spouse/partner Difficulty maintaining employment Eviction Aggression	Various forms of oppression Discrimination Poverty Disenfranchisement Deinstitutionalization Unemployment/underemployment Lack of affordable housing

women by a ratio of approximately four to one, with older men reporting longer periods of homelessness when compared to older women [52].

Late-life homelessness is often associated with a host of physical and mental health problems. The most frequently cited physical health problems of homeless older adults include dental problems, arthritis, hypertension, circulatory problems, respiratory illness, gastrointestinal conditions, glaucoma, asthma, anemia, diabetes, and sensory impairment [52]. Neuropsychiatric disorders, including neurocognitive disorders and substance abuse problems, are highly prevalent among homeless older adults [48]. In spite of prevalent physical and psychiatric disorders, older adults who are homeless are less likely to utilize services for the homeless, including intervention and support programs, shelters, and soup kitchens, when compared to younger adults who are homeless [53]. Traditional community-based health service programs for seniors are not designed to serve the older adult homeless population. For these vulnerable people, several barriers impede access to such services, including a lifestyle that interferes with preventive measures and treatment of acute or chronic conditions, language and cultural barriers, lack of healthcare identification, and dissatisfaction with and perceived discrimination in existing services [54].

In a study by Burns examining the experiences of older adults using homeless shelters, participants spoke of challenges associated with shelter living as an older person [55]. Several mentioned tiring easily and being more sensitive to stress in general, which made adapting to shelter life particularly difficult for geriatric people. Shelter life was further complicated for those suffering from health and mobility issues, especially if this affected their ability to climb stairs or sleep on the floor. Further, one-half of the shelters surveyed close during the day, leaving individuals who need help with self-care and with planning daytime activities on the street at those times. This policy of being required to leave during the day was identified as a great source of insecurity for study participants. Several age-related challenges were reinforced by constraining shelter conditions, such as shelter design and rigid rules and regulations within the facilities. Neglecting to equip all shelters with elevators and in some cases forbidding mobility aids such as walkers limited participants' access to shelter spaces. Health and mobility issues made leaving the homeless shelter during the day particularly hazardous [55]. Shelter policies and the physical design features of homeless shelters need to be adapted to take into consideration the unique needs of older adult users. For psychiatric care providers, this indicates that referral to shelters does not necessarily mean that patients' housing needs are being met; these realities suggest the need for mental healthcare providers to consider how they can become involved in shelter boards and coalitions in an effort to advocate for their older patients at the systemic level.

Lack of privacy was one of the most important losses associated with homelessness as even the most intimate activities (such as showering) happened publicly. While some people found the lack of privacy constraining, others found comfort in the more communal type of living situation at shelters, given the opportunity to share meals and other social activities with other people [55]. Prior to coming into the shelter, most participants were suffering from social isolation and loneliness. The shelter setting provided opportunities to establish positive social ties with other homeless shelter users and staff.

Literature indicates a high prevalence of mood and psychotic disorders and cognitive impairment among homeless older people. Most experts now accept that approximately 1/3 of single homeless adults have a severe psychiatric illness and the prevalence of psychiatric disorders among homeless single women is higher than it is among men [48]. Statistics vary widely, but depression, psychosis, and cognitive impairment are the neuropsychiatric disorders most common in the homeless geriatric population. Older homeless people appear no more likely to drink alcohol than do younger homeless people. Older homeless women are less likely to drink than are their male counterparts. Illicit drug use is low among the homeless geriatric population [48].

In a study by Reynolds et al., participants ubiquitously described the challenges that they faced disentangling themselves from the recurring cycle of homelessness [56]. Factors impacting this challenge included the chronic nature of homelessness, difficulty obtaining treatment for mental health problems, alcohol and substance abuse, economic instability, housing instability, and problematic relationships. Participants also spoke about their difficulty finding and maintaining employment because of factors related to health and aging, intensifying their challenge of disentanglement from the cycle of homelessness. In order to decrease the shame homeless older adults feel and help them to become self-reliant, services that integrate an empowerment-based model are essential for teaching older adults the skills they need to thrive. In cases where they experience difficulty reintegrating into the

labor force, targeting employment better suited to older adults might serve as a beneficial strategy to help them disentangle from the recurrent cycle of homelessness.

Teaching Point
Homelessness in older adults is a growing problem, services for homeless people are (often) not designed to serve older adults appropriately, and most mental health services for older adults are not designed to serve those who are homeless. This contributes to the challenge of disentanglement from the cycle of homelessness for this population.

30.2 Case Studies

The following two case studies are used to illustrate some of the complexities and challenges inherent in providing mental healthcare for older adults who are from traditionally marginalized communities.

30.2.1 Case 1

Case 1 History

Ms. D. is a 66-year-old single woman who has a long-standing history of schizoaffective disorder and polysubstance abuse (alcohol, marijuana, and crack cocaine). She is supported financially by a basic age-related government pension. Ms. D. has had over 30 psychiatric hospitalizations since she had her first manic episode with psychotic features in her mid-20s. During her last psychiatric hospitalization, she was diagnosed with breast cancer, but she has repeatedly refused any treatment for this condition. She does seem to understand her cancer diagnosis and, when asked about treatment, states that she does not want any cancer treatment. Ms. D. has repeatedly told members of the mental healthcare team: "If I die from this disease, that's fine. I've died before in 1986, I'll just die again now." Ms. D. has a history of verbal and physical aggression when she is unwell and when she is under the influence of substances. She often shouts at co-residents and at staff members at her lodging home, calling them names and sometimes threatening them. As a result of this aggression, she was evicted from several lodging homes leading to periods of shelter use and absolute homelessness. Ms. D. is currently an inpatient on the psychiatric unit and was admitted due to deterioration in her mental status from nonadherence to her prescribed psychiatric medications. She has since been restabilized on her previous medications, and although her entire inpatient psychiatric treatment team agrees that she is now ready to be discharged from the hospital, the lodging home she was living at prior to the current hospitalization has refused to allow her return to their home due to concerns about her aggression. The social worker on the inpatient unit is trying to find her alternative housing, but many of the local lodging homes know of Ms. D.'s history and are refusing to take her into their home. The social worker contacted some of the homeless shelters in the city; however, Ms. D. was refused placement due to her history of aggression. Furthermore, many of the facilities have raised concern about her physical health, her refusal to accept treatment, and the potential liability these facilities may hold if she dies while living in the facility. The inpatient team does not believe that Ms. D. could be successful living alone in an apartment due to her history of nonadherence to medications, due to previous attempts at living independently that all ended in eviction (for aggression or drug use), and also due to her deteriorating health from untreated breast cancer.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What factors from Ms. D.'s history and what aspects of her identity might be contributing to making it difficult to find appropriate housing for her?

? Question 2. What are some possible solutions to her housing crisis at this point in time?

? Question 3. What are some possible strategies to try to prevent any further psychiatric hospitalizations for Ms. D.?

Case 1 Answers

Case 1 Answer 1 (Question 1—What factors from Ms. D.'s history and what aspects of her identity might be contributing to making it difficult to find appropriate housing for her?)

There are several factors likely contributing to the fact that Ms. D. is having difficulty finding appropriate housing. Ms. D.'s psychiatric diagnoses of schizoaffective disorder and substance use may result in psychiatric stigma, contributing to some refusals to provide housing to her. In addition to her psychiatric diagnosis, she also has a significant physical health issue (breast cancer) for which she is refusing treatment. Several lodging homes are refusing to accept her because of their fear about her dying in their facility and their potential liability in this situation. Certainly Ms. D.'s history of aggression is likely the most significant barrier to her finding appropriate housing with many lodging homes. Similarly, the homeless shelters refusing to house her are related to fear she will become aggressive with staff and coresidents.

Case 1 Answer 2 (Question 2—What are some possible solutions to her housing crisis at this point in time?)

One possible solution to Ms. D.'s current housing crisis is for her to attempt to live independently again, even though attempts at independent living were not successful in the past. Increased supports in the form of case management and/or Assertive Community Treatment Team involvement, which might include daily medication observation, may increase the likelihood that Ms. D. would be able to live independently in the community. A Community Treatment Order (Canada) or Outpatient Commitment (United States) could be another useful tool in ensuring she remains treatment adherent while in the community.

The case does not discuss what stage of change Ms. D. is currently in with respect to her substance use. If she is potentially ready to explore substance abuse treatment options, inpatient treatment programs could be considered, and if she is successful in completing such a program, this could open up more housing options for her upon discharge with the risk of aggression decreasing without substances being a significant issue anymore. Exploration of cancer care supports and homecare resources is also warranted. As Ms. D.'s physical health deteriorates, preparation for end-of-life care may also be required. The possibility that Ms. D. may require and may qualify for placement in palliative care needs to be considered.

If none of the housing options discussed above come to fruition, the inpatient treatment team may need to call a large-scale discharge planning meeting with representatives from all of the relevant local community agencies and housing providers present. A discharge plan for a complex patient like Ms. D. may need to involve some commitment from multiple community agencies.

Case 1 Answer 3 (Question 3—What are some possible strategies to try to prevent any further psychiatric hospitalizations for Ms. D.?)

There are several possibilities to explore in order to prevent future hospitalizations for Ms. D. One possibility to explore given her history of nonadherence to medications is the use of an injectable antipsychotic medication (if this has not yet been tried). Another possibility is to provide daily medication observation either by staff at her lodging home (once her housing is secured) or, if she is living independently, by mental health clinicians who visit her in the community (e.g., outreach program, Assertive Community Treatment Team, case management program). A Community Treatment Order (Canada) or Outpatient Committal (United States) may be required in order to improve Ms. D.'s adherence to the treatment plan.

Case 1 Analysis Ms. D.'s case illustrates some of the potential pathways to homelessness for older adults. In this specific case, Ms. D. has a long-standing history of a severe and persistent psychiatric illness (schizoaffective disorder) and ongoing harmful use of substances. A history of aggression had resulted in multiple evictions from various types of housing (independent, lodging home and shelter based). In addition, she has a significant physical health condition (breast cancer) for which she is not receiving any treatment. These factors interact to create a situation in Ms. D.'s case that may well lead to homelessness unless strategies are implemented by her inpatient treatment team to set up an appropriate discharge plan which would include significant, high-intensity psychiatric support in the community. Ms. D. has refused treatment for breast cancer, which is likely to result in deterioration in her physical health. Consideration must also be given to the likelihood that she has a palliative diagnosis, and therefore, referrals to palliative care resources, including end-of-life-care housing options, should be made.

30.2.2 Case 2

Case 2 History

Mr. S. is a 65-year-old widower who emigrated from Vietnam 13 years ago. His wife died in a motor vehicle accident 10 years ago when she was 40 years old. Following the death of his wife, Mr. S. became very depressed and experienced psychotic symptoms along with his depression. Mr. S. never sought any help for his mental health issues. Two years after his wife passed away, Mr. S.'s three children were apprehended by the local Children's Aid Society because of an assessment that Mr. S. was unable to provide appropriate care to his children due to his illness. All three children were placed in the foster care system, and Mr. S. was only allowed to have supervised visits with his children at the Children's Aid Society office. Mr. S. never learned how to speak English very well, and interpreters were not always available during these visits. After several years in the foster care system, Mr. S.'s children began to struggle to speak Vietnamese with their father, and although Mr. S. expressed that he wanted to see his children as much as possible and to have custody of his children returned to him, he became quite despondent regarding the visitation process and the fact that it was often so difficult to communicate with his children. Mr. S. stopped coming to the regularly scheduled visits. His psychotic symptoms persisted and worsened, and he also experienced intermittent depressive episodes. He became increasingly isolated and reclusive; his only visitors at this point are the Assertive Community Treatment Team workers who come to his home daily to ensure that he is taking his prescribed medications and provide some social support to Mr. S. None of the workers on the Assertive Community Treatment Team speak Vietnamese, and communication has continued to be an issue in the relationship between Mr. S. and his medical team.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. What factors in Mr. S.'s history and what aspects of his identity might be contributing to his current presentation?

? Question 2. What are some possible strategies to try to improve Mr. S.'s mental status and his social functioning at this point in time?

Case 2 Answers

Case 2 Answer 1 (Question 1—What factors in Mr. S.'s history and what aspects of his identity might be contributing to his current presentation?)

Ms. S. is an immigrant from Vietnam and he does not speak English very well. His lack of English language skills affects every aspect of his life, including his ability to communicate effectively with his children and with his outpatient psychiatric treatment team. The fact that interpreters were not always available to him when he was attempting to communicate with his children led to his increased frustration and eventual discontinuation of the

visits with his children. Mr. S. is now extremely socially isolated with his only visitors being his outpatient psychiatric treatment team (the Assertive Community Treatment Team). Unfortunately, none of the Assertive Community Treatment Team members speak Vietnamese, and they cannot hire an interpreter for every visit with Mr. S. so communicating with him at times is quite challenging, and this has negatively affected the therapeutic relationship. Mr. S. continues to miss his wife who died 10 years ago and he thinks about her every day. He blames himself for her death (he was driving the car when she died in the motor vehicle accident), and he has never forgiven himself for her death. He also misses his children every day and he believes that he is a terrible father. These thoughts and feelings contribute to his ongoing depressive symptoms.

Case 2 Answer 2 (Question 2—What are some possible strategies to try to improve Mr. S.'s mental status and his social functioning at this point in time?)

Mr. S. is very socially isolated at this point having lost his wife and his children. He has no other family. He is not currently connected to the local Vietnamese community. One potential strategy to reduce his level of isolation and potentially improve his functioning is for workers on the Assertive Community Treatment Team to try to connect him with some of the local Vietnamese organizations (e.g., social groups, associations, church communities). This may also require the assistance of an interpreter in order to have a conversation with Mr. S. about his interests and gauge which types of groups or organizations he may be interested in connecting with. Alternatively, connection with these organizations may support the provision of interpreter services (voluntary or formal services) to help the Assertive Community Treatment Team members to know the patient's social needs and wants better. In addition, a discussion with Mr. S. about his potential interest in improving his English language skills may be worthwhile. If he would like to do so, he could be connected with local English as a second language classes. This would be an opportunity to not only improve his English language skills but also potentially to connect with other immigrants (from Vietnam and elsewhere), also potentially expanding his social circle. In addition, given the relationship between Mr. S. and his children broke down, in the end due to language barriers, efforts could be made at this point (if all parties are willing to do so) to ensure that interpreter services were always available for visits with Mr. S.'s children. These relationships may be salvageable with priority being given to ensuring that good communication is made possible with the use of an interpreter. Here, the Children's Aid Society holds the responsibility as the guardian of the children to ensure these resources are forthcoming. In this context, it may be appropriate to investigate advocacy support to help Mr. S. obtain resources from the Children's Aid Society to ensure that his children are able to maintain connections with their father. Repairing his relationship with his children would likely improve Mr. S.'s mental status greatly and is also beneficial to the long-term mental well-being of the children.

Case 2 Analysis Mr. S.'s case demonstrates the potential for language and culture to pose a barrier to receiving appropriate services and access to needed care. Mr. S. has experienced multiple losses layered on top of one another. Analysis of his case requires healthcare workers to look at the influence of the institutional processes on his mental health. A lack of collaboration between services and resources has amplified Mr. S.'s experience of poor care. Mr. S.'s experiences of marginalization are magnified because of the limited availability of interpreters, which limits his practitioner's capacity to know him and to respond to his needs.

30.3 Key Points: Marginalized Geriatric Patients

- Mental health practitioners have a responsibility to educate themselves about traditionally marginalized populations and to understand the potential barriers that individuals who belong to one or more of these groups may face in attempting to access culturally appropriate mental health services.
- Clinicians need to keep in mind that their actions and the ways in which they practice can either reinforce or challenge oppressions and disadvantages faced by patients with marginalized identities.
- Practitioners need to think concretely about the importance of identifying and managing various forms of oppression in their practice, including ageism, sexism, racism, ableism, and homophobia, which can occur concurrently, as concerns that directly affect many older adults with psychiatric illness.

30.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Anti-oppressive psychiatric assessment utilizes an inductive approach to questioning. Which of the following does this type of questioning focus on?

A. Standardized assessment tools with closed-ended questions designed to build a definitive diagnosis
B. A "case history" approach considering the details of previous hospitalizations, previous treatment plans, and follow-up activities
C. Open-ended questions asked based on information the patient shares with the clinician and concern for understanding the patient experiences beyond "ill-being" and careful listening to the patient's narrative
D. Consideration of collateral knowledge of the patient's needs from friends, relatives, and primary healthcare providers as well as verification of the patients' status as marginalized

Answer: C.

Psychiatric assessments generally focus on "what's wrong" and the level of "ill-being" experienced by the person being assessed. In an anti-oppressive assessment, questions asked are based upon the information patients share with the clinician rather than on a preconceived notion of the right questions to ask. Anti-oppressive assessments include consideration of the patients' "well-being" or "what is working," "what gives them strength," and "what gives them pleasure" and inquire about strengths, coping strategies, personality, and life experience as well as the environmental resources available to the patient; thus, the correct answer is C. (See ► Sect. 30.1.1.)

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MCQ 2. Older adults experiencing homelessness are most likely to become homeless for the first time due to which of the following?

A. Substance use and abuse
B. Deinstitutionalization resulting from changes in government-funded mental healthcare resources
C. Financial issues tied to loss of income from sources such as employment and/or pensions as well as widowhood or separation
D. Psychosis resulting from nonadherence to drug therapy

Answer: C.

Although all of the answers above could potentially lead to homelessness, for older adults who have become homeless for the first time in later life, research highlights eviction, retirement and loss of income, difficulty with reentry into the labor force, and widowhood/widowerhood as prominent causes [48, 52]. (See ► Sect. 30.1.6.) Therefore, the correct answer is C.

MCQ 3. Psychiatric practice with patients from marginalized groups is enhanced through critical reflexivity. Critical reflexivity allows healthcare practitioners to enhance their practice through which of the following?

A. A deeper understanding of the power relations at play within the interaction between the patient and the practitioner, including those at the personal level that might produce biases
B. Acknowledgment of power relations at play between members of the healthcare team and community-based resources and supports
C. An awareness of the importance of standardized tools and resources in facilitating and supporting a definitive diagnosis
D. Reflection on the things that went wrong within the interaction between the patient and the practitioner during assessment and treatment

Answer: A.

In order to mitigate the potential barriers between patients and healthcare practitioners, as the more powerful parties in the process, healthcare practitioners have a responsibility to engage in critical reflexivity. This means that practitioners must understand their own social location and how this affects their relationship to their practice and their behaviors and approaches to practice [1]. Anti-oppressive practitioners develop a deep understanding of who they are as an individual, who they are as a professional, and their role in the specific intervention they are undertaking in the moment [2]. The correct statement is A.

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Sexuality and Sexual Dysfunction in Later Life

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31.1 Background

31.1.1 Sexual Functioning and Sexual Rights

Phases of Sexual Response Cycle

The human sexual response cycle can be divided into four phases: *excitement*, *plateau*, *orgasm*, and *resolution*. Physiological changes during the *excitement* phase include vascular congestion, generalized muscle tension, and increased cardiorespiratory activity [1]. In males, the excitement phase involves penile erection due to increased blood flow to the genitals. For females, increased blood flow contributes to variable erection of the clitoris, enlargement of the labia minora, and swelling of the vaginal wall. This stage is generally consistent with vaginal lubrication, breast swelling, and nipple erection. In the *plateau* phase, there are enlargement of the testes and scrotal contraction to bring the testes closer to the perineum. Also, there continues to be a minor increase in penile erection and secretion of semen and seminal fluid into the urethra. For females, there is continued enlargement of the vaginal wall and labia minora, as well as increased clitoral sensitivity. The *orgasm* phase is the climax of the sexual response cycle and is the shortest phase. In males, ejaculation occurs due to rhythmic contraction of the muscles in the perineum, and orgasm occurs simultaneously. For females, the uterus and the perineum also undergo rhythmic contractions, and orgasm is achieved via release of general skeletal muscle tone. Females differ as they lack an ejaculatory response, and the length of time of an orgasm could be longer. There is a release of sexual tension for both sexes. In the *resolution* phase, there are decreased blood flow to the genitals, relaxation of muscles in the perineum, decrease in cardiorespiratory rate, and a potential sense of fatigue. There is also a psychological feeling of well-being and intimacy. For males, the penis returns to a flaccid state in two stages. During the first stage, the penis is half its erect size and is in an absolute refractory state, meaning penile stimulation will not lead to initiation of the sexual response cycle. In the second stage, the penis returns to its flaccid size over a longer length of time and enters into a relative refractory state meaning penile stimulation could potentially lead to initiation of the sexual response cycle [1]. Some females can return to the orgasm phase with minimal refractory time and, therefore, may experience multiple orgasms.

Sexual Rights

All humans have a presumptive and fundamental human right to engage in sexual activity. As individuals age they can become susceptible to specific neuropsychiatric disorders impacting their ability to make independent decisions; in turn, some may find themselves residing in a hospital setting or supervised long-term care (LTC) facility where privacy to engage in sexual activity is limited. Nonetheless, living with a neuropsychiatric disability in a hospital or LTC facility should not be automatically equated with a restriction on one's right to engage in sexual activity. The *UN Convention on Rights of Persons with Disabilities* reminds State Parties, for example, of the critical aim to combat stereotypes, prejudices, and harmful practices relating to persons with disabilities, including those based on sex, in all areas of life (Article 8) [2]. Where possible, individuals with disabilities should be provided the same range, quality, and standard of free or affordable healthcare and programs as offered to other persons, which can include sexual and reproductive health (Article 25). Some healthcare providers offer their patients specific programs addressing sexual health so that they can fully understand their fundamental rights to freedom of sexual expression and sexual privacy.

Normative Age-Associated Changes in Sexual Functioning

In males, decreased libido with advancing age can be due to several etiologies, not solely due to decreased testosterone. Older males require more physical penile stimulation, longer time to achieve erection, and the duration of orgasm may be shorter and less intense [3]. Another factor is that erectile dysfunction is the most common sexual dysfunction in males. The incidence of erectile dysfunction increases with age, and its etiologies may be multifactorial including causal factors related to cardiac, neurological, endocrine, oncologic, neuropsychiatric illnesses, and medication side effects.

In females, there are postmenopausal hormonal changes that account for changes in sexual functioning. Older females can expect to have fewer and less intense orgasms. Decreased vaginal lubrication, itching, soreness, and thinning of the tissue are a consequence of lower levels of estrogen which leads to urogenital atrophy [3]. This thinning of tissue causes increased susceptibility to infection and may cause dyspareunia. As for males, the aforementioned medical conditions can also contribute to sexual dysfunction. For both sexes, there are also age-related changes in physical appearance such as decrease in skin elasticity and firmness and changes in hair pigmentation. These signs of biological aging can be added stressors that contribute to a decrease in sexual desire. Table 31.1 summarizes common age-related physiological changes in sexual functioning [3].

31.1.2 Epidemiology

Demographic Factors

Aside from the role of healthcare professionals who care for older adults, the reality is that we will all reach a stage later in our lives where issues of changed sexual function are prevalent.

Table 31.1 Normative age-associated changes in sexual functioning [3]

Females	Males
Fewer and less intense orgasms Thinning of vaginal mucosal membranes ↓ Vaginal lubrication Vaginal itching/soreness Dyspareunia ↑ Susceptibility to infections	Shorter and less intense orgasms ↓Libido ↑ Physical penile stimulation to achieve orgasm ↑ Duration to achieve erection Erectile dysfunction

From a demographic standpoint, the life expectancy of males and females has increased; it is estimated that the number of adults greater than 65 years of age will more than double by 2050 [4]. Thus, older individuals will represent a larger proportion of the population. Associated with this is the concept of "active life expectancy." This term reflects the number of years without health-related difficulties in performing instrumental activities of daily living. Active life expectancy at age 65 is estimated to increase by 2.5 years by 2022 [4]. Later life also leads into new stages of life that not only includes retirement but also an "empty nest" where there are no longer dependents to care for. Adapting to this greater level of independence for older adults coincides with increased privacy, which can translate into more opportunities to engage in sexual expression. Lastly, the positive impact on psychological and physical well-being cannot be understated. Several surveys have found a positive correlation between sexual activity and physical health, along with a positive correlation between sexual expression, mental health, and overall quality of life [4].

31.1.3 Diagnostic Evaluation

Assessing Sexual Health

Discussing sexual health at any age can be a sensitive topic. There are some basic elements that clinicians should consider when having this type of conversation with their patients. First, some patients may prefer discussing sexual issues with a physician of the same sex and as close to their age range as possible. At times, this may necessitate a referral to a medical colleague. Second, such a discussion should always be held in a private setting to respect the individual's dignity. Third, one should allow adequate time for the conversation. It can be difficult to even start such a dialogue on the topic; therefore, it does not typically need to be the sole focus of one's first encounter but should be assessed in the early stages of care to foster trust, openness, and respect. It may also be useful to begin such a conversation by asking permission to discuss more personal issues. Examples of questions that may help the dialogue include "What is your current experience with sexual intimacy?" "How do you express sexual interest?" "What would you like to tell me about your sexual life?" or "How do you find your level of sexual interest?" [5].

There are a handful of assessment tools that can be used to assess sexual behavior, knowledge, and attitudes. The PLISSIT model was developed by Jack Annon in 1976 to discuss sexual health among all age groups and to help guide intervention. PLISSIT is an acronym for *Permission* (P), *Limited Information* (LI), *Specific Suggestions* (SS), and *Intensive Therapy* (IT) (see Fig. 31.1) [3]. The first level of intervention involves asking *permission* to speak about sexual activity, which ultimately gives the individual a sense of control. Additionally, you are providing the patient with reassurance that his or her sexual expressions are normal as long as they do not inflict harm on others [3]. The second level of intervention involves providing the individual with accurate *information* about basic anatomy and physiology necessary to understand normative patterns of aging and sexual functioning. At this stage, a discussion of lifestyle factors, medical conditions, and medications that could affect sexual functioning should be held. Common medical conditions that contribute to sexual dysfunction include

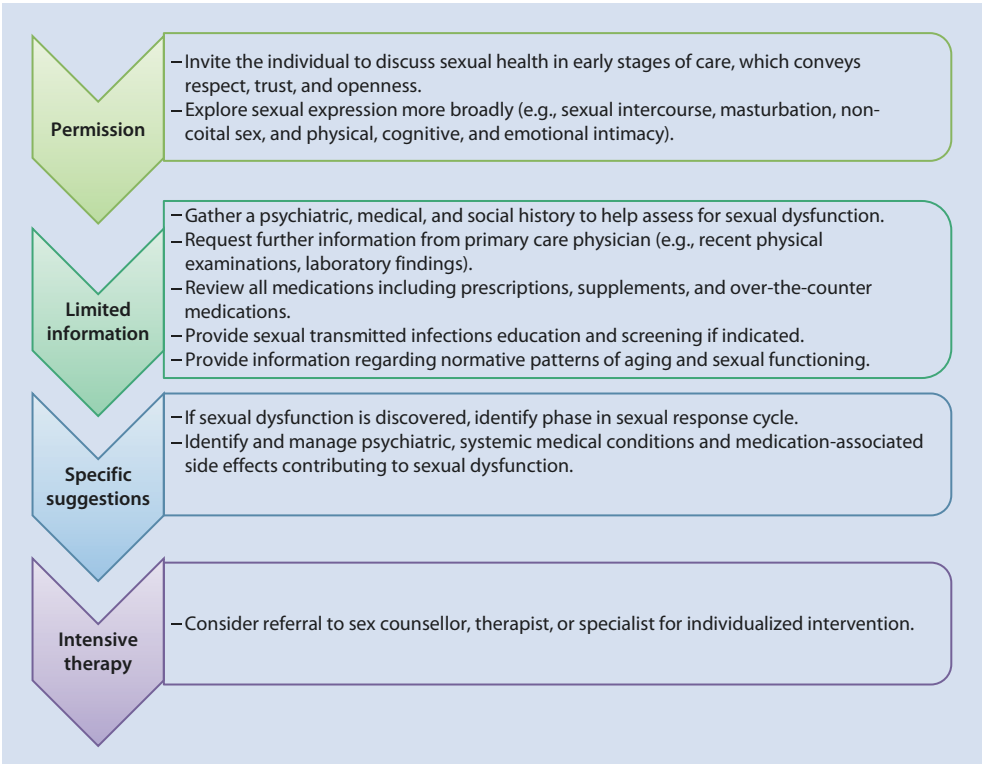

Fig. 31.1 Strategies for assessing sexual health [3]

hypertension, diabetes mellitus, hyperlipidemia, smoking, spinal cord injury, Parkinson disease, prostate cancer, prostatectomy, benign prostatic hypertrophy, and excessive alcohol intake. Psychiatric illnesses, particularly depressive and anxiety disorders, and medications, such as antidepressants, antipsychotics, anticonvulsants, antihistamines, antihypertensives, antispasmodics, and antiestrogens, can lead to sexual dysfunction. The third level of intervention involves *specific suggestions* to improve sexual health, which may require a referral to professionals including a counselor, sex therapist, or specialist physician to help design an individual intervention. The fourth level of intervention involves long-term *intensive therapy*, which is generally required only if there are issues in the relationship beyond sexual activity. Questionnaires such as the Sexual Behavior Questionnaire (SBQ) can be used to help give an indication of current and past sexual behavior, along with the Aging Sexual Knowledge and Attitude Scale (ASKAS), which is conducted in a "true-false-I-don't know" format that has been used in several studies involving nursing home residents [6]. The Staff Attitudes about Intimacy and Dementia (SAID) questionnaire is also helpful in stimulating discussion topics for staff education.

Assessing, Diagnosing, and Managing Sexual Dysfunction

The most recent edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) has included sex-specific sexual dysfunctions [7]. Table 31.2 lists the DSM-5 diagnostic entities of sexual dysfunctions [7]. Except for substance/medication-induced sexual dysfunction, the diagnoses of sexual dysfunctions require a minimum duration of approximately 6 months and have more exact severity criteria (i.e., mild, moderate, severe specifier). Subtypes for all diagnoses of sexual dysfunctions include specifiers of *lifelong* versus *acquired* and *generalized* versus *situational*. Lifelong sexual disorders have been present from first sexual experiences, whereas acquired sexual disorders develop after a period of relatively normal sexual function [7]. The generalized subtype applies to sexual dysfunctions not limited to context, whereas the situational subtype applies to sexual dysfunctions that only occur with certain types of stimulation, situations, or partners [7]. Sexual dysfunctions are a heterogeneous group of disorders characterized by a significant disturbance in one's ability to respond sexually and/or to experience sexual pleasure. A person can have multiple sexual dysfunctions at the same time, in which case, all the dysfunctions must be diagnosed.

Table 31.2 DSM-5 diagnoses of sexual dysfunctions [7]

Sexual dysfunctions	Delayed ejaculation Erectile disorder Female orgasmic disorder Female sexual interest/arousal disorder Genito-pelvic pain/penetration disorder Male hypoactive sexual desire disorder Premature (early) ejaculation Substance-/medication-induced sexual dysfunction Other specified sexual dysfunctions Unspecified sexual dysfunction

A sexual dysfunction may occur during one of the stages of the sexual response cycle, in both females and males. The first step is to identify the phase in the sexual response cycle at which the dysfunction arises. With respect to etiology, there are two broad categories—physical and psychological causes. Potential physical illnesses leading to sexual dysfunction are hormonal changes and cardiac, vascular, metabolic, neurological, renal, hepatic, or systemic disease [8]. Substance use or medication side effects can lead to sexual dysfunction. Potential psychological causes can include acute or chronic stressors, anxiety or depressive disorders, history of traumatic sexual experiences, body image problems, and negative attitudes toward sex. For females, the most common issues with sexual dysfunctions are inhibited sexual desire, inability to become aroused, anorgasmia, and dyspareunia. Erectile dysfunction is the most common sexual dysfunction in males and the incidence increases with age [9]. Other common sexual dysfunctions in males are ejaculation disorders and inhibited sexual desire.

A complete medical workup would include a review of the history of presenting illness, past medical history, family history, medications, substance use, social history, and physical exam with genitourinary pelvic examination, as indicated, to help narrow potential etiologies. Medication classes that contribute to sexual dysfunction are antidepressants, antipsychotics, anticonvulsants, antihistamines, antihypertensives, antispasmodics, and antiestrogens [5]. Additional preliminary diagnostic tests may include a complete blood count, liver associated enzymes, renal function tests, fasting blood glucose, lipid profile, thyroid function tests, prostate specific antigen, nocturnal penile tumescence and rigidity testing, and a pap smear.

Once a potential etiology has been identified, the underlying cause is treated, and management strategies may include pharmacological, surgical, and psychotherapeutic interventions. It is also important to provide patients with education regarding normative patterns of aging to help alleviate any misconceptions. Education on healthy lifestyle factors like physical exercise, smoking cessation, and minimal substance use (including limiting alcohol intake) may also help treat underlying causes. Encouraging other forms of intimacy such as physical, cognitive, emotional, commitment, and interdependence may help foster the sexual experience. Use of water-based personal lubricants, low-dose topical estrogen creams, or estrogen-based vaginal suppositories may treat symptoms caused by urogenital atrophy in females, a cause of dyspareunia [3]. Treatment of erectile dysfunction for males can involve phosphodiesterase enzyme type 5 inhibitors, vacuum pump devices, intraurethral suppositories, penile injections, and penile prostheses [3]. Where possible, it may be necessary to refer the patient to an appropriate specialist for further management.

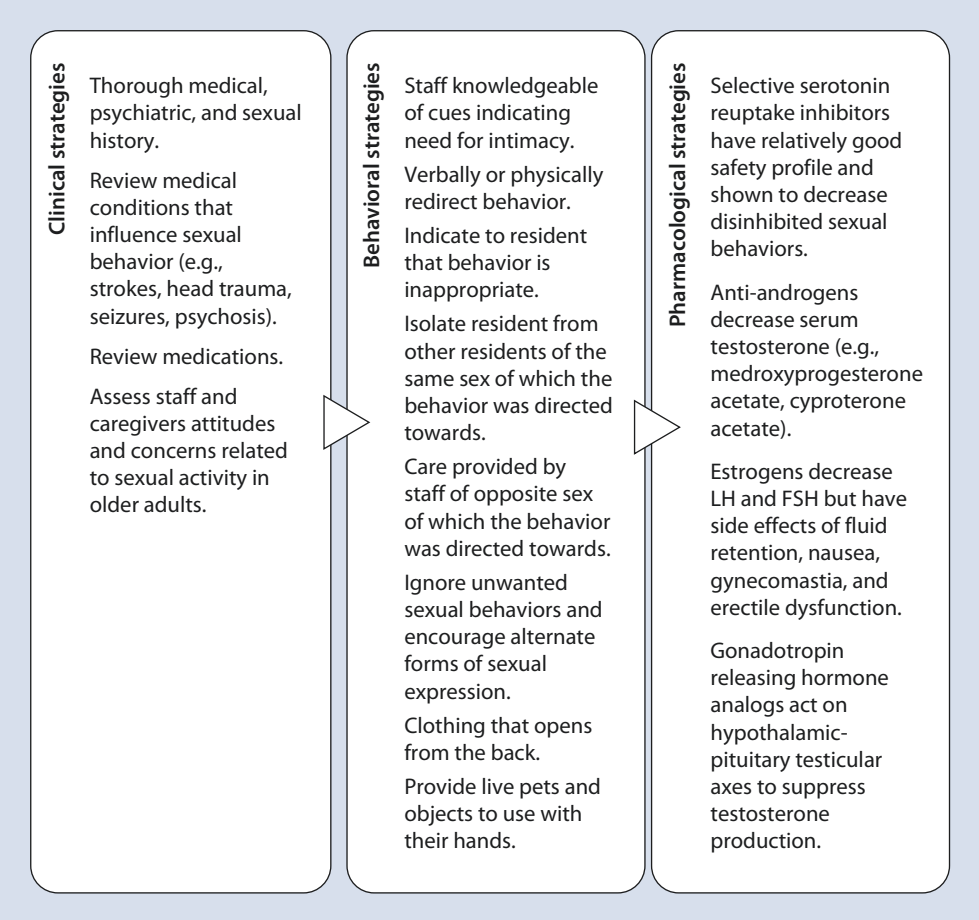

Fig. 31.2 Management of sexually disinhibited behaviors in long-term care facilities [13]

Sexually Disinhibited Behaviors in Patients with Major Neurocognitive Disorders

Some healthcare providers may view residents' sexual behaviors in LTC facilities as somehow problematic rather than expressions of intimacy. One survey found that approximately 60% of LTC staff members felt it was unnecessary for residents to remain sexually active, despite approximately 80% of them believing residents experienced sexual desires [10]. The first step involves assessing staff member attitudes toward sexual activity in older adults to determine biases and misconceptions. This will allow for creating a nonjudgmental space in which to tease apart what may be considered appropriate versus inappropriate sexual behaviors. A culture should be created that fosters and maintains residents' dignity while achieving sexual expression. However, sexual activity with another partner should always be consensual.

Inappropriate sexual behaviors in LTC facilities are more likely to occur in patients with major neurocognitive disorders. In one study examining behavioral issues in Alzheimer disease patients, researchers found that 7% exhibited sexual disinhibition and this increased with the clinical severity of the disease [11]. Males with a major neurocognitive disorder are also more likely to display sexually disinhibited behaviors than women with the same condition [12]. Of the major neurocognitive disorders, those with frontal and temporal lobe pathologies are more likely to display sexually disinhibited behaviors [13]. One should keep in mind that some patients with major neurocognitive disorders may not be aware of their surroundings and may therefore display public behaviors that are typically done privately. In a similar vein, residents may misidentify another person as their loved one and behave in a manner that is inappropriate in the context of that personal relationship. If the sexually inappropriate behavior is of acute onset, this may point to an episode of delirium, and the underlying cause should be identified and treated. Figure 31.2 enlists management strategies of sexually disinhibited behaviors in LTC facilities [13].

Teaching Point

A key point in addressing disinhibited behaviors in LTC residents with major neurocognitive disorders is to recognize their desire for intimacy and determine ways to safely achieve this natural desire for sexual expression.

31.1.4 Sexual Expression in Later Life

Asexuality in Later Life: Fact or Myth?

Limitations on previous research studies into sexual activity among older adults led to a common misperception that there may be decreased intimacy in later life. Some of these

studies inadequately described the population being studied (e.g., cultural groups, socioeconomic status, education level) making it difficult for the research findings to be generalizable [3]. Second, there is a paucity of good quality research into sexual activity in later life, often due to embarrassment associated with one-to-one interviews, self-reporting biases, and poor response rates of postal questionnaires [14]. Third, there is a lack of standardized measures, and therefore consistency across studies cannot be assessed. Fourth, many studies were cross-sectional in nature which makes it difficult to tease apart the cause and effect. Fifth, most of the studies' representative samples were heterosexual populations, and there is limited published research on patterns of sexual expression in the lesbian, gay, bisexual, and transgender (LGBT) older adult population [4]. In addition to these limitations, we cannot disregard the fact that we live in a youth-oriented culture where there is a perceived notion that sexual desirability and aging are separate entities.

Current data on sexual behavior in later life debunks the myth of geriatric asexuality. Surveys that helped to debunk this myth include the American Associations of Retired Persons Survey (AARP 2010), the National Social Life, Health, and Aging Project (NSHAP 2009), and the National Survey of Sexual Health and Behavior (NSSHB 2010) [15–17]. These more recent studies are also limited by their reliance on cross-sectional data and lack of standardized measures. Having a satisfying sexual relationship was found to be important for older adults with a partner [15]. The NSHAP survey found that 39% of men and 17% of women between 75 and 85 years of age reported being sexually active [16]. Another study found that 43% of men aged 70 years or older reported engaging in vaginal intercourse, while 22% of women aged 70 years or older reported the same. This sharp contrast was primarily related to relationship status for women. A study in Perth, Australia, found that older men by age group were sexually active in 40% of cases in the group aged 75–79, 27% in the group between 80 and 84, 19% in the group aged 85–89, and 11% in the group between 90 and 95 years [18]. There does appear to be a decline in sexual activity with aging. For example, a Swedish postal survey of men aged 50–80 years found that there was a decrease in interest in sex with age but even among the oldest men (aged 70–80 years), 46% reported orgasm at least monthly [19].

Teaching Point

Sexual needs in later life appear to be similar to those in adult life with variations in frequency, intensity, and mode of expression.

For older adults who are sexually active, partner availability greatly predicts sexual activity. Good health is another predictor of increased sexual activity. The 1999 AARP Survey found that older adults with chronic medical conditions (e.g., hypertension, diabetes mellitus, prostate enlargement, cancer) engage in less sexual activity than their healthier counterparts. Better physical health was also found to be associated with more liberal sexual attitudes. Closely linked to this is stable mental health, specifically the absence of depression, which leads to increased sexual activity. Better cognitive functioning and moderate alcohol consumption also contribute as positive predictors. The AARP study also found that women's attitude toward sex, partners' characteristics, and personal self-concept determined satisfaction in sexual activity. For men, a belief that their partner was romantic and sensitive to their moods determined their satisfaction in sexual activity. Thus, having a positive attitude toward sex can increase sexual activity. Figure 31.3 summarizes the predictors of increased sexual activity in later life [6].

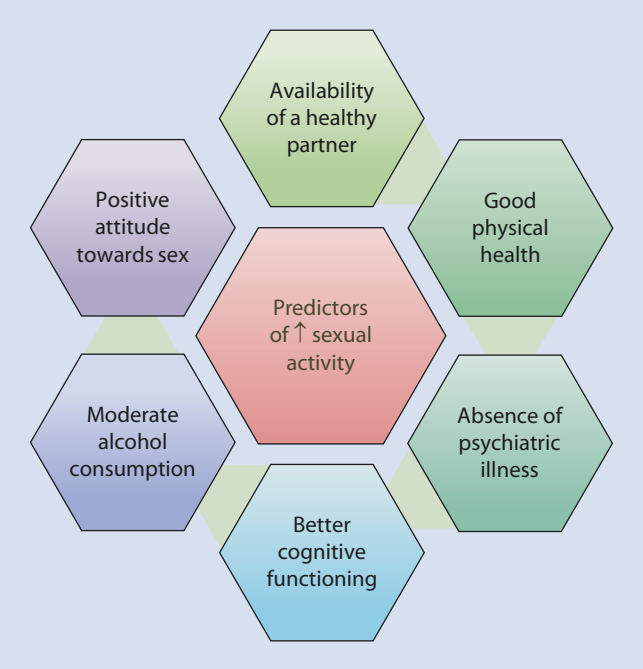

Fig. 31.3 Predictors of increased sexual activity in later life [6]

Barriers to Achieving Sexual Expression in Later Life

There are a number of societal, ideological, institutional, and physiological factors that can create barriers for adults in later life to achieve sexual expression. Most older adults were raised in the first half of the twentieth century, a time that reflected a western world of conservative norms. The ideologies during this time fostered a general viewpoint that pleasurable sexual activity was for men, while sexual activity for women was a means for procreation and marital satisfaction [3]. This is demonstrated in the 1999 AARP study in which older adults felt that sex between non-married people was inappropriate. The AARP study provided further evidence of this negative attitude vis-à-vis the correlation that women aged 75 years or older are less likely to have a partner than older males, and women have a less positive attitude toward sexual activity than males of the same age. Another study in Finland showed that even among older adults who are sexually active, there was a viewpoint that sexual activity in older adults was improper [20]. There is also a reported gender

difference in views toward masturbation as being seen as an acceptable form of self-pleasure in males but not in females [6]. This general attitude can also extend to family members and healthcare staff members who may unintentionally or inadvertently impose such viewpoints on older adults and foster this negative stereotype.

Teaching Point

Many studies now highlight the role of noncoital sexuality as having an increasing importance in older adults. It is therefore important to acknowledge the changing nature of sexuality as one ages and not to pathologize it.

For some older adults, the lack of opportunity for sexual expression can be a real barrier. As mentioned previously, availability of a partner is a strong predictor of sexual activity. In a study of LTC residents, it was reported that 30% of men and 40% of women cited the lack of a partner as the main reason for sexual inactivity [21]. Single females in later life also report lack of sexual activity due to the absence of a socially sanctioned partner. Across most cultures, women typically live 5–7 years longer than men, and in LTC homes, the ratio of females to males aged 65 years or older is approximately 3:1 [4]. Therefore, there is a very real demographic factor placing heterosexual females at a disadvantage. Lack of opportunity could also indicate the physical or mental incapacity of a partner. This suggests that poor health in general can be a barrier. Sexual activity was positively correlated with good health and a prior active sexual history in men and sexual desire and a healthy partner for women [4]. Anxiety has been associated with decreased sexual activity in both sexes [16], while depression and its pharmacological treatment were associated with poor sexual functioning in all age ranges [22]. Adverse side effects of medications in general could lead to sexual dysfunction and consequently decreased sexual activity.

For older adults who are residents in LTC facilities, there is the additional barrier of lack of privacy in one's physical environment. The environment plays a significant role in the resident achieving his or her sexual goals as the structured setting can leave residents in a situation where control over most aspects of their lives is decreasing. These institutions are structured for communal living with an open and public space that is created for ease of visibility for staff members to care for residents. Unfortunately, an environment with open doors and multiple beds per room does not foster privacy for sexual intimacy. Some individuals in later life choose to live with their families, which may also decrease their level of privacy. Another barrier in LTC facilities is the lack of privacy of information. Staff members at these facilities have access to residents' medical records and therefore are aware of sexually related medical issues. This could be a deterrent for some residents in seeking out information or opportunities for sexual expression. They may also refrain from such activity if they fear it will become public knowledge [6]. Figure 31.4 shows the barriers to sexual expression in residential and institutionalized settings [6].

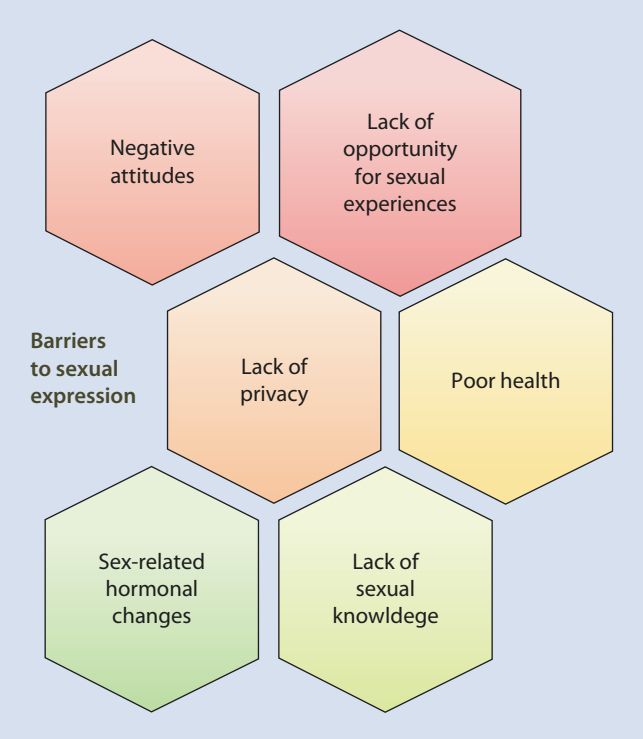

Fig. 31.4 Barriers to sexual expression in institutionalized settings [6]

Lack of sexual knowledge is another challenge that some older adults can face. During their youth, sex education may not have been a part of the standardized curriculum. Therefore, societal misconceptions may play a significant role in assumptions regarding sexual function that lead to lowered expectations for sexual fulfillment. There is also misinformation regarding normative patterns of aging and sex-related hormonal changes. Evidence for this is seen in the rising rates of infection with human immunodeficiency virus and acquired immune deficiency syndrome (HIV/AIDS) diagnosed in those greater than age 50 years old [4]. Finally, there is also a lack of knowledge of lifestyle factors that could contribute to sexual dysfunction. Figure 31.5 shows strategies for enhancing sexual expression in later life [6].

31.1.5 Legal and Ethical Issues

Clinicians and other healthcare personnel working with older populations need to remain abreast of legal and ethical issues related to the right to consensual sexual activity. There is a need to balance autonomy rights of patients, while avoiding paternalism, and all the while ensuring the safety of patients and other sexual partners. Some older individuals experience neuropsychiatric illness, which can limit their knowledge and comprehension of what constitutes appropriate sexual conduct. Some older individuals reside in supervised residential or other institutional settings, such as LTC facilities or hospitals, where their privacy rights are curtailed and there may also be institutional policies dealing with sexual activity.

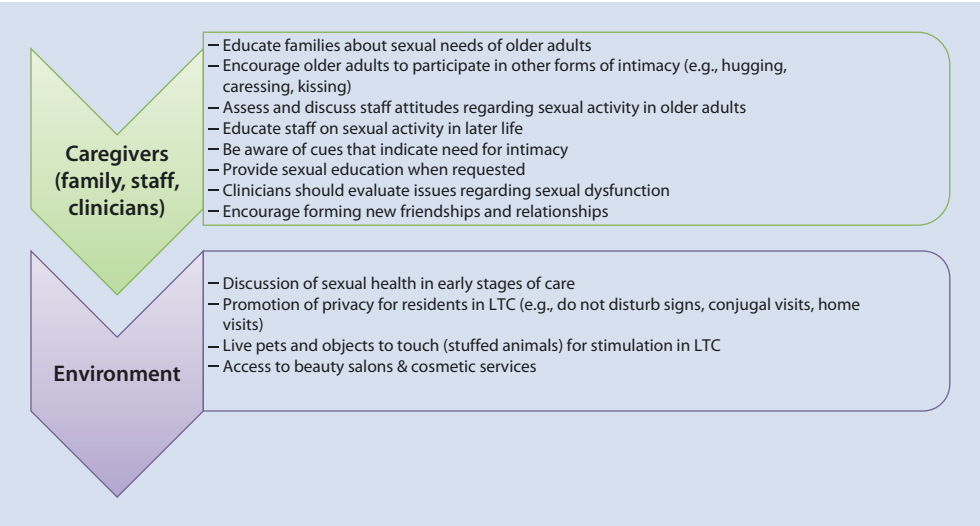

Fig. 31.5 Strategies for enhancing sexual expression in later life in long-term care (LTC) facilities [6]

All individuals are presumed at baseline to be mentally capable to make independent and autonomous decisions. Yet, it may become evident to a clinician that a patient has lost cognitive function and requires assistance from others in making important decisions. The fact that someone is older does not automatically imply a lack of or diminished decisional capacity; indeed, a presumption of cognitive capacity is independent of age or type of neuropsychiatric diagnosis. Older individuals may express a desire to engage in sexual activity but require assistance in ensuring they have the appropriate social context or setting. If, on the other hand, one's decisional capacity is truly in question, a clinician may choose to conduct a formal decisional capacity assessment. And even where an individual may be found incapable for certain decisions (e.g., treatment, finances), he or she could still be capable for other decisions (e.g., sexual activity).

A sexual decisional capacity assessment to determine if the individual can understand and appreciate the consequences of sexual activity may be warranted. Legislative changes to standardize sexual decisional capacity assessments could ensure that all patients of hospitals and residents of LTC facilities are treated equally and that there is less subjectivity associated with the assessment [23]. Even with standard practices in place, it may be challenging to determine if an individual has the capacity to consent to sexual relations and, if so, to what extent does that consent reach. Generally speaking, in order to consent to sexual relations, one has to have sufficient knowledge and understanding of the nature of the activity, the reasonably foreseeable consequences, and the capacity to choose whether or not to engage in sexual activity without coercion [24]. Given the fact that a person may have capacity to make some decisions and not others, the type of question being asked becomes very important. That is, even if one is deemed capable to consent to sexual relations, there will be situations where the issue of decisional capacity may still remain that raises the distinction between "issue-specific" and "situation-specific" tests.

From an *issue-specific* perspective, a sexual decisional capacity assessment would examine whether the person understands, at a general level, the nature of sexual relations, whereas a *situation-specific* perspective would explore whether a person has the capacity to consent to sexual activity with a particular person at a particular time [24]. On the one hand, it can be argued that an individual consents to sexual relations generally and that there is no reason why a patient can consent to sexual relations with one person and then not have the capacity to consent with another. On the other hand, it can be argued that one does not consent to sexual relations in general but that one consents to "this act of sexual activity with this person at this time and place." On a practical level, however, it may be that there is no authority that can evaluate situation-specific contexts in all circumstances and thus issue-specific capacity may prevail by default.

Aside from the distinction between issue-specific and situation-specific cases, one must also consider an older individual's fluctuating capacity to consent to sexual relationships. That is, age, the nature of a neuropsychiatric illness, and compliance with medication can all impact an individual's capacity to consent at various times. Therefore, an individual may be capable to consent to sexual relations at one point in time but be incapable at another, even merely hours apart. If the transition from capable to incapable materializes too quickly, then there may not be an opportunity for staff members or other individuals to notice any changes in the decisional capacity of the patient. If the transition from capable to incapable occurs gradually, then it is possible that there will be indicators which healthcare staff members can observe and can reassess the question of capacity at that time [25]. In either case, the fluctuating decisional capacity of individuals poses serious problems for healthcare providers in assessing decisional capacity.

Given the fact that an individual may have capacity to consent in one area and not another, there may be instances where one has the capacity to consent to sexual intercourse but does not have the decisional capacity to consent to contraception [25]. That is, an individual may indeed understand the consequences of engaging in sexual intercourse (e.g., pregnancy, sexually transmitted infections) but may

not fully understand that there are options available that may decrease the chances of unwanted or adverse results. This raises the question as to whether there should be a separate test for capacity to decide on contraceptive treatment, and if so, what happens if one has the capacity to consent to sexual relations but not contraceptive treatment.

A test for decisional capacity for contraceptive treatment can include assessing one's understanding of the reasons for contraceptives, how common types of contraceptives work, rates of effectiveness, and the advantages and disadvantages of each [25]. The threshold of understanding for each of these components would need to be determined. Even if this threshold was not met, there is no simple remedy to balance the rights of the individual with the incapacity to consent to contraceptives. It would be impractical to attempt to require an individual to use contraceptive methods when engaging in sexual relations.

Issues with decisional capacity will need to be further researched and standardized so that there is an appropriate balance between one's right to expression while protecting vulnerable populations. The protection of vulnerable populations is no more apparent than in cases of unwanted sexual advances by one resident toward another vulnerable resident of the same facility, who may lack the full cognitive capacity to understand the consequences of the actions. Indeed, research has shown that adults with intellectual disabilities were significantly less knowledgeable about almost all aspects of sexual expression and appeared significantly more vulnerable to abuse [26]. Training, education, and prohibitive actions may be required to protect others. Indeed, it can and has occurred that some older residents have preyed on those who are more vulnerable and at risk for exploitation. Criminal liability can ensue where if a sexual assault takes place and those responsible for protecting the vulnerable resident, whether the institution or treatment team members, may come under legal scrutiny. As a preemptive action, it may be useful to conduct regular risk assessments with residents known to be of moderate to high risk of engaging in sexual aggression. This is particularly the case with forensic psychiatric patients, older patients with aggression associated with major neurocognitive disorder, and those known to have a criminal record for sexual activities in the past who may be sharing living accommodations in close proximity to others, even where staff members are supervising [27].

In cases where a complaint of sexual impropriety has been filed to the hospital or LTC facility, there will be unique issues that arise with older individuals when investigating the complaint. Indeed, there are already several barriers investigators face when investigating issues of sexual assault, and it is likely that some of these barriers will be amplified in the context of older patients. For example, memory recall, delusional thoughts, indicators of consent or non-consent, and general misinterpretations can all be called into question when dealing with complaints of sexual impropriety in an older population [23].

It should never be assumed that sexual complaints are illegitimate or delusional; these will require a comprehensive investigation to understand the full context of what events occurred.

If that investigation leads to a reasonable belief that sexual misconduct occurred, the police may need to be contacted. If the complainant suffers from a major neurocognitive disorder, court processes will need to be explained so that, if the police proceed with a formal charge, the complainant is aware of the subsequent legal stages. These stages may include providing a formal statement, testifying in open court, and being cross-examined. This process may be burdensome to some older individuals and could negatively impact their mental health. Those with progressive neurocognitive disorders may have an increasingly limited decisional capacity over time, creating further barriers during an ongoing and usually lengthy court process.

The myriad of legal issues which apply to protecting older patients and avoiding legal liability for the LTC facility speak to the importance of outlining clear and uniform guidelines and policies across healthcare institutions and LTC facilities as it relates to sexuality in older adults [23]. While broader issues of capacity to consent to sexual acts, police reporting procedures, and criminal penalties for sexual assault will need to be modified at a broader level, many other policies related to sexuality in older adults can be implemented at the institutional level. Some of these policies may address issues related to privacy, confidentiality, same-sex wards, family involvement, and sex education.

Older individuals who are residing in a hospital or LTC facility have a reduced level of privacy by virtue of living with others. Not all residents are permitted overnight passes into the community to stay with a loved one—what reasonable accommodations can be made for such residents and their partners who find themselves in such a situation? Where privacy is limited, some institutions have attempted to address the issue of conjugal visits by allowing coresidents or residents with partners living in the community to access a private room in the LTC facility or hospital. In this case, the level of monitoring needs to be reasonably appropriate and reflective of the amount of autonomy the resident would otherwise expect.

Related to privacy, an individual may wish to engage in sexual relations with a spouse or with a coresident without fear of being judged, labeled, or suffer reputational damage. How then can a healthcare institution protect the privacy and confidentiality of those who wish to engage in sexual relations? In LTC homes, for example, the residential population may be relatively small and all residents may know each other. If a private room is offered to residents, the location of the room and its visibility to others will need to be taken into consideration to protect the identity of individuals entering and exiting the room. This may pose barriers to smaller LTC homes or wards with limited resources to alter structural components of the setting.

Some healthcare and LTC institutions may attempt to protect their residents by implementing same-sex wards. Presumably, this would reduce the opportunity for unwanted sexual abuse to coresidents. This type of policy, however,

may have the opposite effect in some situations. Without acknowledging the fact that older populations continue to engage in sexual relations, these institutions are forcing consenting individuals to keep any sexual activities hidden from staff or other residents. This behavior can lead to unintended consequences as complainants of sexual impropriety will be fearful to come forward or to obtain sexual health checkups by a physician. Instead, some have argued that mixed-sex wards should be promoted for the ongoing social health and well-being of the residents, including the right to sexual expression and autonomy [27].

Teaching Point
Protective practices need to be in place in healthcare and LTC institutions to ensure those who have a demonstrated history of sexual harassment are monitored and secluded where necessary.

Family involvement is another complex aspect to consider as it relates to sexuality in older adults. Should families or surrogate decision-makers be made aware of ongoing relationships between their loved ones and other residents and, if so, to what extent? This will depend on a number of factors. Most importantly, if the patient is capable to consent to sexual activity and does not wish their family to know, he or she retains the right to confidentiality. If, however, the patient has diminished decisional capacity, then the wish to engage in sexual relations will need to be discussed with their substitute decision-maker, guardian, or legal representative.

The most important and likely most effective method of protecting patients and the institution, while ensuring compliance with safe practices, is through sex education. Ongoing sex education can assist patients in learning about consent, decisional capacity, the nature of sexual acts, contraceptives to protect against pregnancy, sexually transmitted infections, and other issues related to sexuality [26]. If patients are aware of the sexual nature of their activities and the policies established by the institution, they can better comply with the policies while reporting any violations they observe. Residents need to be acutely aware of their own abilities, including diminished cognitive abilities, and how those may affect their ability to protect themselves from unwanted sexual contact. Some of these diminished abilities may include weakened muscular strength to resist acts, limited mobility, as well as speaking, hearing, and visual impairments [23]. Furthermore, by demonstrating openness to sexuality, older residents will be able to ask questions and provide suggestions as it relates to policies surrounding sexual practices.

Healthcare administrators may also need to revise or create policies and practices surrounding sexuality in older adults while staying up-to-date with changes in law. Older individuals have a right to express themselves sexually and are presumed capable unless it is otherwise assessed. When decisional capacity is called into question, standardized sexual decisional capacity assessments should be conducted to reduce subjectivity and bias in the evaluation. Where sexual impropriety is suspected, patients should be made aware of their legal rights and the processes in place to protect them from future abuse.

Teaching Point
Institutional policies can play a significant role in promoting legal and safe sex practices while respecting issues related to privacy, confidentiality, mixed wards, and family involvement. Patient education will be the most important factor in promoting sexuality in older adults while protecting vulnerable populations.

31.2 Case Studies

31.2.1 Case 1

Case 1 History

Mr. J. was a 68-year-old, single male with a long-standing history of paranoid schizophrenia, hypertension, mild neurocognitive disorder, and a recent stroke for which he was admitted to the hospital. After becoming medically stable, he was transferred to a psychiatric ward because of bizarre behavior and agitation occurring in a clear sensorium. He has been a psychiatric inpatient for 6 weeks now. Prior to hospitalization, he lived independently and was neither in an intimate relationship nor did he have children. His primary care physician indicated to the inpatient psychiatrist that Mr. J.'s schizophrenia was stabilized on a long-acting injectable antipsychotic, haloperidol, and an oral antipsychotic, chlorpromazine, approximately two decades ago. He had not been seen or followed by a psychiatrist in the past 10 years. He had led an active lifestyle prior to having the stroke. Mr. J. thrived on his independence at home and demonstrated his capacity to attend to his basic activities of daily living, but he did have difficulty with instrumental activities of daily living, particularly managing his finances. Throughout this hospitalization, he continued to display some impulsivity and disinhibited behavior, but there were no delusions or hallucinations present. For example, he eloped from the ward to search for renting an apartment in another town. He made sexually suggestive comments to female staff members and requested sexual activity with a 44-year-old female co-patient. After consultation with a geriatric psychiatrist, it was suggested to try escitalopram 10 mg daily to help decrease Mr. J.'s disinhibited behavior, which proved to be beneficial as his sexually inappropriate behavior has ceased on the ward. His other medications included hydrochlorothiazide 25 mg daily and aspirin 81 mg po daily. Over the previous week, Mr. J. has been increasingly irritable and agitated. His nurses noted that this was more common in the morning, especially when checking in on Mr. J. in his room for a reminder of breakfast. Mr. J. eventually disclosed to his nurse that he is having issues lately with his "morning routine," specifically masturbation

and achieving orgasm. The staff member became aware that Mr. J. masturbates in his room but felt that masturbation while in hospital is inappropriate and attempted to divert his attention by suggesting he focused instead on his health.

Case 1 Questions and Answers

Case 1 Questions

Question 1. In what other ways could the healthcare team address Mr. J.'s concern?

Question 2. As Mr. J.'s most responsible physician in the hospital, how would you assess his concern?

Question 3. Based on Mr. J.'s medical history, psychiatric history, and current management strategies, what are the interventions you would suggest that could ameliorate any underlying etiologies to his sexual dysfunction?

Case 1 Answers

Case 1 Answer 1 (Question 1—In what other ways could the healthcare team address Mr. J.'s concern?)

Firstly, the staff member should take a moment to address Mr. J.'s concern with the interdisciplinary team. This would provide an opportunity for staff members to assess their own biases regarding sexual intimacy in later life. Using the Staff Attitudes about Intimacy and Dementia (SAID) questionnaire may be useful in such a situation where the patient had a mild neurocognitive disorder. Staff members should encourage an open dialogue with Mr. J. rather than shame him for wanting to engage in sexual intimacy. Open dialogue will help find additional ways in which Mr. J. could minimize his frustration and irritability. Other modes of physical stimulation (e.g., pet therapy [6]) may be beneficial. Mr. J. may also feel respected if there are ways to help promote his privacy, such as a do not disturb sign. The team should also provide Mr. J. with education regarding normative patterns of aging and safe sex practices in general.

Case 1 Answer 2 (Question 2—As Mr. J.'s most responsible physician in the hospital, how would you assess his concern?)

Allocating the appropriate time to discuss such a sensitive topic and finding a private setting in which to do so convey respect for Mr. J.'s concerns. It is important to foster an open dialogue so that Mr. J. feels comfortable. If Mr. J. is experiencing a sexual dysfunction, then determining the phase in the sexual response cycle when this issue arises will help guide the assessment. A complete medical workup including a history of presenting illness, past medical history, family history, medications, substance use, social history, and physical exam may help to clarify potential etiologies. A preliminary discussion of the potential of vascular, psychological, and medication-induced etiologies may help Mr. J. better understand the cause of his sexual dysfunction and thereby lead to increased cooperation in diagnostic evaluation. Although Mr. J. had only a mild neurocognitive disorder, Alzheimer-related behavioral disturbance can manifest as sexual disinhibition; this increases with the clinical severity of the disease [11]. As previously discussed, male patients with major neurocognitive disorders are more likely to display sexually disinhibited behaviors than women with the same conditions [12]. Medications that could have contributed to sexual dysfunction in this case included the antidepressant (escitalopram), antipsychotics (chlorpromazine and haloperidol), and diuretic (hydrochlorothiazide). Potential physical illnesses leading to sexual dysfunction in Mr. J. included age-related hormonal changes, cardiac, vascular, neurological, or possible systemic medical disease [8]. As mentioned before, erectile dysfunction, ejaculation disorder, and inhibited sexual desire are common sexual dysfunctions in males, where the former is the most common with an incidence that is expected to increase with age [9].

Case 1 Answer 3 (Question 3—Based on Mr. J.'s medical history, psychiatric history, and current management strategies, what are the interventions you would suggest that could ameliorate any underlying etiologies to his sexual dysfunction?)

Upon reviewing Mr. J.'s past psychiatric history, he was diagnosed with schizophrenia but had not exhibited any psychotic symptoms (e.g., delusions, hallucinations) for many years; therefore, this diagnosis should be reevaluated with further collateral history. Tapering or discontinuing Mr. J.'s oral antipsychotics, chlorpromazine and, possibly, haloperidol, would help treat a potential underlying etiology to his sexual dysfunction. Antipsychotics can cause sexual dysfunction through cholinergic receptor antagonism and/or elevation of prolactin. The prolactin-sparing antipsychotic, aripiprazole, can be considered to proactively manage the medication-induced sexual dysfunction, thus improving sexual side effects in patients with schizophrenia [28]. Randomized, double-blind controlled studies in patients with schizophrenia with antipsychotic-induced sexual dysfunction have shown that adjunctive treatment with aripiprazole and sildenafil led to improvement of sexual dysfunction and decrease of prolactin levels [29]. Furthermore, there are also metabolic side effects with antipsychotic treatment that can adversely affect cardiovascular health. Another medication to consider discontinuing in Mr. J.'s case is his antidepressant escitalopram as this can also contribute to sexual dysfunction. For Mr. J., there is a risk-benefit analysis given that escitalopram has improved his impulsivity and sexual disinhibition. Lastly, he has been an inpatient for several weeks, and there may be an element of physical decompensation, and encouraging physical activity would improve his overall physical health and possibly his sexual health.

Case 1 Analysis A barrier noted in Mr. J.'s case was the lack of privacy in his physical environment. The structured inpatient setting likely has led Mr. J. to a situation where control over some aspects of his life, including sexual expression, was decreasing. Moreover, adverse side effects from both antipsychotics and an antidepressant could have led to his sexual dysfunction. Noncoital sexuality appears to hold significant importance in his life. Having a need to balance his autonomy

rights with ensuring his safety and safety of other potential sexual partners, while avoiding paternalism by staff members, is crucial. Moreover, clarifying what the institutional policies dealing with sexual activity on the inpatient ward are is essential. Because his schizophrenia and mild neurocognitive disorder could potentially limit his knowledge and comprehension of what constitutes appropriate sexual conduct, his decisional capacity may have been in question by his clinician who may choose to conduct a formal decisional capacity assessment if any explicit concerns arise.

31.2.2 Case 2

Case 2 History

Mr. D. was a 70-year-old single male with a major neurocognitive disorder who was a resident in a long-term care (LTC) facility for the past 3 years; there were approximately 450 other coresidents at the same facility. Since arriving at the LTC, Mr. D. had become overly familiar with many of the other female residents. Several residents and family members of other residents have complained to the management about Mr. D.'s behavior. Others reported to staff that he made unwanted sexual advances to residents and touched other coresidents inappropriately; occasionally, he was spotted in the computer room, which is publically open to all, and viewed pornographic websites. Mr. D. did not have any family who visited him, but he did have another male coresident friend with whom he was often found in the lounge with making sexual jokes and innuendos toward younger female staff. One day, a staff member entered the room of a 70-year-old female resident who also suffered from a major neurocognitive disorder. When the staff member found Mr. D., he pulled his pants up, and the female resident was observed to be crying and trying to yell for assistance. Mr. D. brushed the incident off as consensual sexual activity and told the staff member not to be concerned. The staff member decided not to report the incident, but a few weeks later, senior management of the LTC received a letter from the female resident's daughter demanding an explanation, which she heard firsthand from her mother. In the letter, the daughter stated that she would file a criminal lawsuit against Mr. D. and a civil lawsuit against the LTC facility for failing to protect her mother if an explanation was not forthcoming; the letter also reported that they had evidence that Mr. D.'s behavior had been going on for a while.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. Prior to the observed sexual encounter, Mr. D. was observed making unwanted sexual advances, touching other coresidents inappropriately, and watching pornography in the public computer room, all of which led to complaints by others. What could have been done by the LTC facility staff at this time to promote a safe environment for all residents?

? Question 2. What could the nurse have done immediately after observing the sexual interaction between Mr. D. and the female coresident in the room together?

? Question 3. How could the LTC facility have responded to the daughter in a manner that protected her mother and other residents from unwanted sexual contact in the future?

Case 2 Answers

Case 2 Answer 1 (Question 1—Prior to the observed sexual encounter, Mr. D. was noted to make unwanted sexual advances, touching other coresidents inappropriately, and viewing pornography in the public computer room, all of which led to complaints by others. What could have been done by the LTC facility staff at this time to promote a safe environment for all residents?)

Staff at the LTC facility should have created written reports of all incidents observed and complaints received. If inappropriate sexual conduct continued after an initial warning, privileges could have been limited or removed depending on the extent of noncompliance. For example, the use of time spent on the computer could have been supervised or limited; similarly, contact with other patients, especially female patients, could have been better monitored or limited. If such behaviors continued or were of an egregious nature, the LTC facility would have had an obligation to contact the police and possibly may have needed to explore having Mr. D. transferred to another LTC home that could have better accommodated and supervised his needs.

Case 2 Answer 2 (Question 2—What could the nurse have done immediately after observing the sexual interaction between Mr. D. and the female coresident in the room together?)

The nurse should have reported the incident to the manager of the LTC. This would likely have triggered an internal investigation leading to the determination of whether this sexual encounter was consensual or not. If it was, then this could have been explained to the daughter once the complaint was filed, and if not, then the LTC facility could have taken the appropriate action including contacting the authorities.

Case 2 Answer 3 (Question 3—How could the LTC facility have responded to the daughter in a manner that protected her mother and other residents from unwanted sexual contact in the future?)

The LTC facility should have issued a formal apology for the staff member having not reported the incident. The LTC facility should have launched a full internal investigation to determine the sequence of events and whether the sexual acts were consensual or not. Upon completion of the investigation, new procedures should have been put in place to protect all residents from unwanted sexual contact while at the same time training LTC staff to look for and report any inappropriate sexual behavior. Several practices could have been put in place to prevent unwanted sexual contact in the future. Some examples include:

- A formal reporting process for patients to report sexual impropriety
- Staff training to look for, respond, and report inappropriate sexual behavior
- Policies and practices for breaking rules related to inappropriate sexual practices
- Patient education relating to sexuality in older adults
- Speciality programs for challenging patients to better manage their sexual behaviors

Case 2 Analysis Several issues arose in this case regarding how to deal with nonconsensual sexual activity. The first is that expectations around prompt reporting of sexual assault, sexual abuse, or sexual misconduct by staff members needed to be explained by managers so staff was fully aware of the appropriate steps to take. Was it possible the staff member in this case was not fully informed or prepared to deal with Mr. D.'s behavior due to a lack of procedures or policies having been established? It was clear that the staff member failed to document this incident in the medical chart in a timely manner, which could have additional legal repercussions. Second, it was critical that coresidents be educated by staff members about the implications of nonconsensual sexual behavior, especially within residential settings where there was already a high degree of supervision or monitoring for vulnerable patients. Patients should know to whom they can report unwanted sexual advances in residential settings. Ongoing education about policies and procedures is particularly relevant for vulnerable older patients living with major neurocognitive disorders. Although LTC facilities and other residential institutions with older patients may be concerned about the possibility of lawsuits, there may be situations where a staff member has not fulfilled their professional obligations and a formal apology may be appropriate.

31.3 Key Points: Sexuality and Sexual Dysfunction in Later Life

- There are four phases of the sexual response cycle: excitement, plateau, orgasm, and resolution.
- Education regarding normative age-associated changes in sexual functioning is important for adults in later life to help dispel misconceptions.
- Current data demonstrates that adults in later life are sexually active with changes in mode of sexual expression.
- Predictors of sexual activity in later life include the availability of a healthy partner, good physical health, absence of a history of psychiatric illness, better cognitive functioning, moderate alcohol consumption, and a positive attitude toward sex.
- Barriers to sexual expression in later life include negative attitudes held by the individual themselves, family or healthcare staff, lack of opportunity of sexual experiences, poor health, lack of privacy, lack of sexual knowledge, and age-related hormonal changes.
- The PLISSIT model can be a helpful way to approach and organize discussion regarding sexual health.
- Sexually disinhibited behaviors are generally observed in patients with major neurocognitive disorders and can be managed through enhanced clinical assessment, behavioral strategies, and pharmacological strategies.

31.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Mr. K. is a 65-year-old male presenting to his female primary care physician, Dr. Knott, of 10 years requesting transfer to another physician colleague, possibly a male. Mr. K. was diagnosed with major depression 1 year ago with the precipitating factor being life transition into retirement. His wife, who is 53 years old, continues to work and is physically active, and Mr. K. finds that he is unable to connect with his wife physically. Upon further exploration of Mr. K.'s request, Dr. Knott discovers that Mr. K. feels his depression is not well managed despite being on sertraline 150 mg po daily. What would be the most reasonable course of action?

A. Facilitate Mr. K.'s request without delay as a physician colleague may provide a new set of eyes and other management strategies.
B. Offer to optimize Mr. K.'s sertraline and explain that he is at a subtherapeutic dose.
C. Ask Mr. K. if there is marital discord and offer to speak to his wife separately.
D. Dr. Knott focuses on Mr. K.'s presenting complaint, ongoing depressive disorder and determine what aspects of his depressive disorder are unresolved and how it is impacting his functioning.

Answer: D

As Mr. K. is a long-time patient, Dr. Knott requests the remainder of the appointment be taken as time to help understand his issues and offer a transfer of care if he continues to feel there is a break in the therapeutic alliance. Understanding that Mr. K.'s depression may have evolved over time is important for Mr. K. to be more forthcoming with personal details. The key is attempting to understand the impact of his symptoms on his functioning. Mr. K.'s inability to connect with his wife physically indicates that they are having intimacy issues. Further exploring this will help tease out whether physical and/or psychological issues are the cause. This also helps foster an open dialogue regarding Mr. K.'s sexual health. Therefore, the correct answer is D.

MCQ 2. Both female and male geriatric patients have a decline in sexual activity clearly related to:

A. Lack of time and interest in sexual activity
B. Decreased substance use
C. Increased widowhood and divorce
D. Fear of disease and injury

Answer: C

Previous studies into sexual activity indicated that there remains a continued interest in intimacy among older adults in their retirement phase, and therefore, statement A is incorrect. Increased substance use including medication side effects can lead to sexual dysfunction, which makes statement B incorrect. Anxiety and depressive disorders, history of traumatic sexual experiences, and negative attitudes toward sex are several plausible causes for decline in sexual activity in older adults; however, fear of disease and injury (as in statement D) could also potentially indicate an underlying psychological stressor. However, for older adults who are sexually active, partner availability greatly predicts sexual activity, and, therefore, the most plausible answer is C.

31

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Aging and Mental Health in the Era of Globalization

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32.1 Background

An unprecedented population shift in age distribution is unfolding globally, with longevity and the global proportion of older adults well surpassing historical levels. For the first time in history, the number of adults 60 years and older will outnumber children under the age of 15 by 2045 [1]. Most of the increase is projected to occur in developing countries, many of which have significant resource constraints, inequitable distribution of these limited resources, and occurrences of civil unrest, particularly protracted civil wars, relative to developed nations [2, 3]. These factors underpin migratory phenomena, by way of displacement and voluntary immigration to the relatively wealthy global north. The global population aging trend is evident in both migratory groups, with voluntary immigrants aging in their host nations and an increasing proportion of displaced persons aging in displacement [4]. As such, recognition of the mental health needs of these vulnerable older adults constitutes a growing priority. For health practitioners in western nations encountering an increasingly diverse patient population, the need to provide culturally informed care is ever greater. Similarly, public health planners must also adapt health services to the globalization trend by delivering culturally appropriate healthcare. This chapter will focus on specific aspects of mental health in the era of globalization including:

- Public health perspectives on global aging
- Displacement and the associated burden on mental health
- Globalization at the local level: resettlement and culturally informed care

32.1.1 Public Health Perspectives on the Aging Population

The population is aging rapidly across the globe, with the proportion of people aged 60 years and older projected to almost double from an estimated 900 million or 12% of the global population in 2015 to 2 billion or 22% by 2050 [5, 6]. This reduction in old-age mortality is unexpected and unprecedented, with the result that the infrastructure in many nations, both developed and undeveloped, are inadequately prepared for this population shift. While the increased longevity of older adults creates new opportunities for both individual and societal development, there also need to be concurrent socioeconomic policies and services to enhance the well-being of older adults, prolong their ability to reside independently in the community, facilitate access to culturally and linguistically appropriate resources, and minimize marginalization [7]. The chief challenge is to establish physical and social infrastructure that can foster better health and well-being in older age [8] while at the same time identifying and minimizing the marginalization of older adults.

Marginalization of older adults often commences on exiting the labor market. Certain groups are more susceptible to social devaluation, notably ethnic and racial minorities, immigrants, women, and older adults with disabilities [8]. Addressing the issue of marginalization and age-related discrimination is a weighty task but an essential one given the rapidly rising proportion of older adults and the strong links between such adverse experiences and health, well-being, and self-efficacy [5, 6]. The World Health Organization defines healthy aging as "the process of developing and maintaining the functional ability that enables wellbeing in older age" [5]. Adverse experiences are linked with poor health, which is in turn linked with functional ability and self-rated well-being. As such, optimizing healthy aging requires healthy environments and healthy policies to address the population shift.

The population shift has far-reaching socioeconomic and political implications, particularly with respect to the oldest-old age group (i.e., aged 85 years and older) who over the past few decades have been the most rapidly expanding segment of the population in developed countries [9]. In social welfare states, this poses significant challenges in that the old-age dependency ratio (defined later in the chapter) is growing ever larger with the aging population [9]. While most of the young old will have a number of years lived without disability, the oldest of the old are more likely to live with infirmity and disability. Notably, the prevalence of major neurocognitive disorders (dementia) will rise considerably [5], although it is as yet unknown whether the incidence of the disorder is also increasing [9]. In terms of overall rate of aging, most of the increase is projected to occur in developing countries, most of which have significant resource constraints, thus underscoring the importance of an organized global mental health response.

Teaching Point

The old-age dependency ratio is the number of people above retirement age divided by the number of people of working age and constitutes a crude measure of fiscal pressure associated with supporting old-age security. In reality, increasing numbers of older adults are working well past retirement age, and as such, the dependency ratio is not entirely accurate for social service planning.

As noted above, the reduction in old-age mortality has been unexpected, with inadequate infrastructure and mental health resources for this population shift. From a global mental health perspective, this is concerning, as the gap in mental health resources between and within nations is alarmingly wide. While 80% of the global population resides in low- and middle-income countries, less than 20% of the share of mental health resources is consumed in low- and middle-income countries, and even then, treatment is often well below minimum acceptable standards, with many undergoing inhumane treatment [10, 11]. This treatment gap is substantial and raises ethical questions, notably the role of developed nations in transferring knowledge, skills, and evidence-based treatment strategies to low- and middle-income countries.

Teaching Point
The treatment gap for neuropsychiatric disorders in low- and middle-income countries ranges from 60% to 90% [11].

While global mental outreach programs are rapidly taking root, particularly in disaster settings, the geriatric age group is generally overlooked by such efforts. Both the physical and mental health status of displaced older adults is infrequently and poorly measured in humanitarian emergencies [2, 12, 13]. This represents a failure of public health given that there can really be no health without mental health [11]. Globally, communicable diseases are beginning to account for a reducing proportion of the global burden of disease, while chronic conditions including neuropsychiatric disorders concurrently account for a greater proportion of disease burden, particularly in older age. In fact as a group, neuropsychiatric disorders are the leading causes of disability worldwide although health expenditure does not match the burden [14–17] as illustrated in Fig. 32.1. Neuropsychiatric disorders, including substance use disorders, accounted for 10.4% of global disability-adjusted life years in 2010 [14, 15]. Furthermore, 28.5% of global years lived with disability are attributed to neuropsychiatric disorders, making them the leading cause of years lived with disability [14, 15].

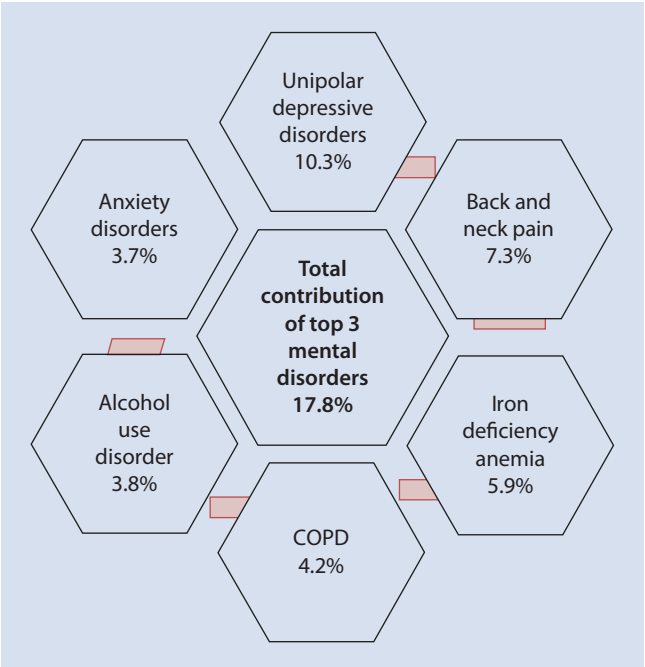

Fig. 32.1 Global top six contributors to years lost to disability in 2012 [16]. *COPD* chronic obstructive pulmonary disorder. Data obtained from the World Health Organization's global burden of disease estimates for 2000–2012. The top six conditions are illustrated, with the percentages reflecting the proportion of years lost to disability from each condition

Teaching Point
Neuropsychiatric disorders account for the most sizeable proportion of the global burden of disease.

Given the substantial global magnitude of neuropsychiatric impairment, an organized global public health response is required to address the burden of mental illness, as mental health strongly influences productivity, physical health, and the management of non-neuropsychiatric comorbidities. Currently, even in the wealthiest of nations, mental health is allocated a very small portion of health spending as illustrated in Fig. 32.2 [17]. This disparity persists despite prominent and reliable metrics showing that mental illness should be integrated into the chronic disease agenda at all levels and across multiple domains of government [18]. The disparity between funding for mental and physical illness is perhaps most stark at the research level where noncommunicable disease research funding still predominantly favors cancer and cardiovascular disease [18], conditions that are undoubtedly important but carry a lower burden of disease than psychiatric illness.

Neuropsychiatric disorders are associated with complications in the management and prognosis for non-neuropsychiatric conditions, such as cardiovascular disease and diabetes mellitus. Mental illness is also associated with increased risk of acquiring other conditions (e.g., infectious diseases like human immunodeficiency virus and hepatitis) [19]. In this instance, added to the increased risk of contracting such diseases, nonadherence with medication promotes microbial drug resistance, which in turn has profound public health implications in the globally [18]. As such, mental health transcends mind-body dichotomies and transcends national borders in this era of globalization, requiring a coordinated global mental health strategy.

In terms of the economic burden of mental illness, in individuals with chronic mental illness there is an associated reduction in economic productivity that in turn increases the risk of poverty and homelessness. This negative cycle is quite concerning in the aging adult as physiological reserves begin to wane with age and the ability to tolerate harsh conditions such as poverty and homelessness also declines.

Teaching Point
In global regions with limited economic means and limited mental healthcare resources, aging with a neuropsychiatric disorder presents a notable risk for inhumane treatment and human rights abuses [20].

Even for those without a history of mental illness, socioeconomic deprivation and aging-related marginalization impart susceptibility to both physical and mental illness, yet

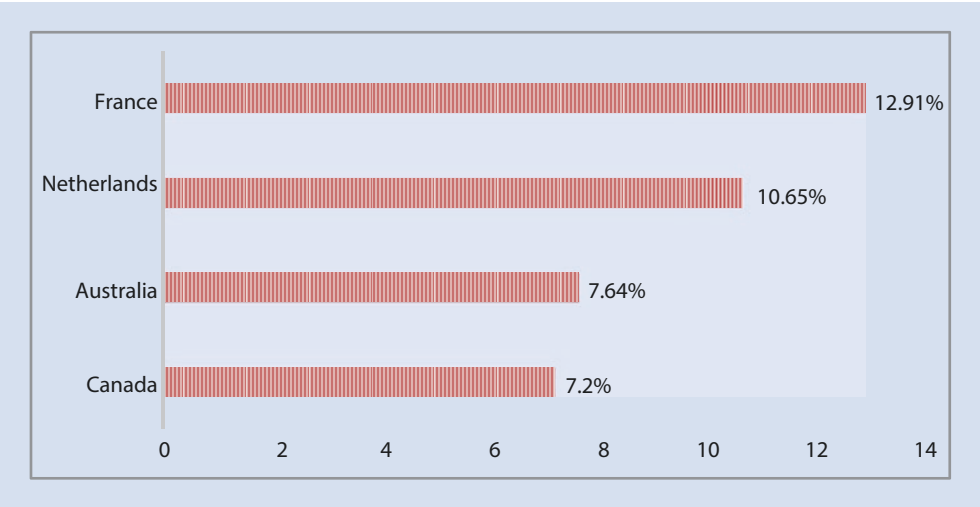

Fig. 32.2 Public mental health expenditure as a percentage of total national health expenditure in select high-income countries in 2011 [17]. Data was obtained from the World Health Organization global survey data (no data was made available for the United Kingdom and the United States)

there are limited resources available for treatment, and the stigma associated with mental illness may prove to be too great a deterrent to seeking treatment. Stigma constitutes an adverse and pervasive factor in mental illness. Stigma in itself should be considered a condition requiring public health intervention and serves as a key feature in Case Study 1 described later.

32.1.2 Displacement and the Associated Burden on Mental Health

Global trends in human movement that were previously viewed as distant events are increasingly becoming a reality at the local level. Recent escalations in civil wars, genocide, and dwindling resources in developing nations have resulted in an unprecedented increase in the number of displaced persons, who are increasingly seeking refuge in developed nations. As the population of displaced persons has grown exponentially, so has the duration of displacement, with displacement becoming an increasingly protracted experience [2]. Consequently, generations of displaced persons are aging in displacement [2].

Almost two-thirds of the global population of older adults (aged 60 years and more) reside in developing countries, where they are more vulnerable to poverty, isolation, poor health, and the adverse effects of disaster and conflict [6, 21]. Thus, the number of older adults at risk of displacement and the number in displacement are significant; they reside in displacement for prolonged periods and are rising as a proportion of the global displaced population [2].

Teaching Point

To appreciate the phenomenon of aging in displacement, one needs only to compare the relative duration of displacement across the years: in 1993, the average duration of displacement was 7 years, but by 2004, this had quickly risen to 17 years [4].

Prolonged displacement or suspension in an indeterminate state presents a psychologically distressing experience for older adults who may never regain the opportunity to age in place. Depending on the underlying reasons and conditions of displacement, aging in this setting may prove to be so unsettling as to be fundamentally disintegrating [2]. The phenomenology of aging in displacement is a troubling one as the associated burden of illness is largely weighted toward chronic conditions including chronic mental illness, yet this is little recognized or addressed in displaced older adults [2].

Older adults are more vulnerable to the deprivation, stressors, and adverse health outcomes associated with displacement, as illustrated in Table 32.1. In older adults, adverse conditions including displacement, relocation (particularly forced relocation), economic deprivation, disability, and isolation have all been linked with depressive disorders, anxiety disorders, and other forms of neuropsychiatric disorders [22]. Regrettably, displaced older adults have largely been overlooked in humanitarian emergencies, added to which their physical and mental health status is poorly measured [2].

Teaching Point

Depressive disorders among older adults are associated with chronic illness, neurocognitive impairment, and disability; comorbid depressive disorders may independently exacerbate these conditions [23].

Given the links between poor mental health, morbidity, and mortality, it is essential that clinicians working with displaced older adults attempt to screen, identify, and offer treatment for mental disorders. The assessment and treatment may be complicated by cultural factors that influence the interpretation of symptoms, the importance attached to symptoms, and the likelihood that a diagnosis of a mental disorder will be accepted. Anxiety and depressive symptoms may be misinterpreted as systemic medical symptoms [24] as

Table 32.1 Aging in displacement: Factors associated with adverse health outcomes

Factor	Detail
Biological	History of neurological and psychiatric disorders, including substance use disorders Chronic medical conditions: depression, cardiovascular disease, diabetes mellitus, physical disability Nutritional deprivation
Psychological	Displacement-related trauma or history of other trauma Identity destabilization, sense of anomie in extremely displaced persons Lack of control over living environment and fate Prolonged state of physiological stress
Physical	Material deprivation: lack of basic living amenities Lack of security Harsh physical environment: inhospitable shelters and settlements
Social	Isolation: family losses and family network disintegration Loss of social capital: disrupted social networks and poor social supports Inability to identify with displacement community
Spiritual	Perceived helplessness and hopelessness over circumstances Lack of a sense of purpose

this may be more culturally acceptable, particularly if cultural beliefs hold that mental illness is a personal weakness, a moral failing, or a form of punishment and thus constitutes a loss of face for the individual and their family. In this setting, identifying and subsequently reducing the duration of untreated mental illness requires the development of culturally sensitive tools [18].

In displaced older adults that migrate to western nations, the barrier is doublefold, as they must overcome internalized and culturally shaped stigma and then contend with the stigma associated with mental illness in their host nation. Despite much concerted effort to address the stigma of mental illness in a number of western nations, it is still a palpable problem, which, in combination with internalized culturally shaped stigma, presents a barrier to health-seeking behavior as demonstrated later in Case Study 1. The development of culturally informed methods to eliminate the stigma, discrimination, and social exclusion associated with mental illness across cultural settings is well recognized as a Grand Challenge, a global mental health initiative launched in search of solutions to barriers faced by those with neuropsychiatric conditions [18].

As the wealthy global north continues to receive more refugees and immigrants, it will be important to refine and redevelop assessment tools given the western ethnocentric bias inherent in the majority of current tools. Sociosomatics, or the social construction and course of illness, is arguably as important as the sociocultural norms of western psychiatry in any approach to intervention [25]. The use of a cultural formulation interview guide may be useful, with an example provided in the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5) [26].

Teaching Point

Beyond exploring the patient's immediate psychosocial context, the mindful clinician should also question the broader context of illness by considering ethnocultural factors that may affect the encounter in addition to considering their own personal assumptions.

The process of displacement presents a significant stressor, the effect of which is not entirely ameliorated by resettlement as discussed later in ▶ Sect. 32.4. Experiences of trauma and psychological deprivation in the course of displacement are multifold and far reaching, with reported intergenerational transmission well beyond the index trauma [27] and well beyond resettlement in a stable host nation. Furthermore, the psychosocial pressures of displacement are associated with increased risk of mental disorders and chronic physical conditions [2]. As such the psychological needs of displaced older adults cannot be overlooked. Suffering may be occurring in silence, particularly in the older adult who may prefer to suffer in silence than to suffer stigma.

32.1.3 Globalization at the Local Level: Resettlement and Culturally Informed Care

Global migration trends, transcultural factors, and deprivation represent increasingly important factors for consideration by clinicians providing care to older displaced persons whether on global missions or at home to refugees and new immigrants in a westernized context. The latter presents an important area for local global intervention. This phenomenon of local level globalization is perhaps most evident in the increasingly culturally and linguistically diverse population of westernized nations. While much of this migration is voluntary, there is also the resettlement of displaced persons. Displacement is classically seen as a phenomena defined by a life in transit in refugee camps, with enclaves of non-naturalized individuals awaiting further migration or alternately awaiting a return home. However, the lived experience of displacement also continues after such individuals reach a place of asylum and are granted residency. Displacement then becomes a state of mind beyond a state of geography and circumstance. It is important to recognize this continued state of displacement as it can have profound effects on mental and physical health.

For older adults who face the challenge of reintegration in a foreign environment, it is essential to have access to culturally and linguistically diverse health and social services [2, 25, 28]. Studies repeatedly show distinct differences between such populations and the naturalized population [29, 30], and these differences can persist across successive generations. In one such study of older Somali refugees in Finland, clinically significant differences were identified with Somalis faring worse across the board on measures of psychological distress, depressive symptoms, sleeping difficulties, self-rated health status, subjective quality of life, and functional capacity relative to their age and education-matched Finnish counterparts [30]. As observed elsewhere, exposure to trauma prior to immigration was associated with higher levels of psychological distress, poorer health status, and poorer subjective quality of life among Somalis [30]. These findings are not unique and emphasize the vulnerability of displaced older adults, particularly those with a history of migration-related trauma.

The concept that trauma is transmitted across generations is central to the historical trauma discourse and is increasingly being recognized [27]. The potential for intergenerational transmission of trauma places added importance on efforts to recognize and address the burden of mental illness among displaced older adults. Persisting distress associated with traumatic displacement experiences likely also shape interactions with mainstream care, particularly health-seeking behavior as mental health is viewed with a lens of moral failure by a number of ethnocultural groups. To this end, psychological distress may take the form of somatic presentation, and mental health services may be utilized with reluctance.

Teaching Point
Persisting effects of trauma may not only worsen individual health and quality of life, it may also influence the health and well-being of family members across successive generations.

Studies consistently report a lower likelihood of mental health service usage by East Asian immigrants in North America when they experience levels of psychological distress comparable to European Americans [28, 31]. Furthermore, studies of psychiatric illness presentation among Asian refugees seeking medical care report a tendency to articulate somatic rather than affective complaints [28, 29, 31]. The somatization may reflect culturally shaped notions of disease etiology, disease legitimacy, treatment, and appropriate help-seeking behavior [29]. Although non-psychiatric medical conditions must be ruled out, failure to consider somatization after initial investigations may result in further unnecessary and potentially invasive tests as demonstrated later in Case Study 1. Culturally responsive frameworks for psychoeducation and mental health literacy are required to address the ethnoculturally diverse illness behavior that is increasingly encountered in western clinical care [28, 29]. Similarly, there is a need for instruments that can assist clinicians in recognizing culturally specific symptom presentation [24].

Host countries must account for the above noted factors in health and social service planning for resettlement, and mental health clinicians must become more proficient at ethnoculturally and geosocially informed evaluations. Clinical competence in this area is regarded as the ability to consider the patient in the context of the patient's own culture as well as from the perspective of the clinician's cultural values and prejudices [32]. Furthermore, the geosocial aspect requires that clinicians working with such populations be sociopolitically informed in order to enrich their understanding of their patients and improve the validity of their assessment. These skills are particularly essential for clinicians evaluating victims of torture.

32.2 Case Studies

The following cases demonstrate the complexity of culturally shaped illness behavior and the role of persisting displacement following resettlement. Key concepts to consider with each case include (i) distress generated by encounters of illness in a framework at odds to the patients' sociocultural construction of illness and (ii) the role of internally held stigma.

32.2.1 Case 1

Case 1 History

Mrs. Z. is a 67-year-old married Chinese-Canadian woman who has resided in Canada for 18 years. She immigrated to Canada with her husband and two daughters and has permanent residency status. Neither Mrs. Z. nor her husband is fluent in English; however, their daughters act as translators when required. Mrs. Z. has seen her family physician on multiple occasions in the past 2 years for mild cardiorespiratory symptoms; however, investigations to date have been negative. At her insistence, her family physician referred her to a cardiologist for a second opinion. The cardiologist conducts an extensive workup that is negative, but Mrs. Z. fails to be reassured. Mrs. Z. remains preoccupied with her heart rate although she has been told that it is within normal limits despite her experience of palpitations and chest tightness. The cardiologist and the family physician both suggest an outpatient psychiatric referral as Mrs. Z. is noted to be increasingly preoccupied with her symptoms and has extensively limited her physical activity level contrary to medical advice.

Mrs. Z. and her husband are quite distressed by the suggested psychiatric referral and stop attending appointments

at their family physician's clinic. Instead, they take two expensive trips to the United States to seek more intensive and invasive cardiovascular procedures, but all investigations have been negative to date. Despite experiencing an adverse reaction during one of the diagnostic procedures, Mrs. Z. is undeterred and continues to seek further evaluations. Mrs. Z. and her husband also begin utilizing their local emergency department whenever Mrs. Z. has symptoms. During one such visit, she is admitted to the general medical ward due to febrile neutropenia, hypotension, and anorexia. The general medical ward team treats Mrs. Z. for pneumonia and identifies no other physical illnesses, although Mrs. Z. continues to report palpitations and chest discomfort. Mrs. Z. and her husband are both adamant that the hospital has not investigated her symptoms adequately and refuse to engage in discharge planning. Mrs. Z. is constantly fretful, tearful, and increasingly withdrawn. She refuses to engage with the ward's physiotherapist, stating that she will faint or have a heart attack if she leaves the bed. The psychiatric service is consulted and an interpreter is booked to facilitate the assessment.

On the psychiatrist's arrival, Mrs. Z. and her husband express surprise and anger that a psychiatrist has been consulted. They eventually relent and consent to engage in an assessment. Mrs. Z. endorses a 21-month history of feeling stress and fatigue, although she is unable to identify stressors other than the cardiovascular symptoms and worrying about her heart. She endorses a 9-month history of poor short-term memory, anorexia accompanied by a 16-pound weight loss, and early morning waking with panic symptoms which has led to a reduction in her usual morning activities due to concern about further "stressing her heart". Prior to becoming sick, she enjoyed tai chi in the mornings and walks through Chinatown in the afternoons with her husband. Since her cardiac symptoms began, she has discontinued her evening meditation practice as she is unable to focus. Her husband notes that she has become subdued and no longer seems to get enjoyment out of her hobbies or friends. Her husband expresses concern that there is an untreated cardiac problem that is interfering with their shared role as caregivers for their active grandchildren. A review of her history also reveals a history of panic disorder in her twenties; however, Mrs. Z.'s understanding of her symptoms is that she had a condition called neurasthenia, a form of "stress overload" which resolved with stress management.

When the psychiatrist shares the diagnostic impression of a current episode of major depressive disorder comorbid with an underlying anxiety disorder, Mrs. Z. and her husband become upset again and state that "that is for crazy people" through the interpreter. Mrs. Z. states that she knows of people with madness in China, and she is not one of them. Mrs. Z.'s husband goes on to say that no one wants to do the appropriate tests to determine what is wrong with Mrs. Z.'s heart and that the only way the psychiatrist can be of assistance is to tell the internal medicine physician to do more tests. The interpreter herself is of a similar age group to Mrs. Z. and advises the psychiatrist that she concurs with the patient and that the diagnosis of depressive disorder is "not valid". Mrs. Z. declines any discussion of medication or follow-up with psychiatry but eventually relents to try brief cognitive behavioral therapy with a psychosocial support worker on the ward when it is explained to her that it can help reduce the stress that her symptoms are causing her. The psychosocial support worker is typically a social worker with some basic training in brief psychological support.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What additional information about Mrs. Z.'s history would be helpful?

? Question 2. What is your differential diagnosis?

? Question 3. How else can the psychiatrist further the dialogue with Mrs. Z.?

Case 1 Answers

Case 1 Answer 1 (Question 1—What additional information about Mrs. Z.'s history would be helpful?)

It would be helpful to understand Mrs. Z.'s illness in the context of her background. Additional details that should be elicited on history include her educational and occupational background, migration history and experience of resettlement, circumstances surrounding the past history of neurasthenia (notably, personal losses), home life predating the onset of her symptoms, and degree of mental health literacy. This information will be infinitely helpful toward a more valid formulation.

Case 1 Answer 2 (Question 2—What is your differential diagnosis?)

The differential diagnoses should be broad but informed by the preceding medical workup, Mrs. Z.'s prior history of neurasthenia and the psychosocial context in which Mrs. Z.'s symptoms are occurring. The history of extensive cardiovascular workup suggests that the likelihood of an anxiety or depressive disorder secondary to another medical condition is of low likelihood. Based on the history provided above, the differential diagnoses according to the DSM-5 would include:

- Major depressive disorder with anxious distress.
- Somatic symptom disorder.
- Panic disorder.
- Illness anxiety disorder.
- Culturally bound expression of psychological distress affecting another medical condition; however, this is of low likelihood given that no other medical conditions have been identified so far despite repeat investigations of Mrs. Z.'s symptoms.

Teaching Point
The extensive cardiovascular investigations that Mrs. Z. has sought place her at risk of adverse sequelae associated with each diagnostic test. Despite these risks, she continues to pursue further diagnostic tests and only gains momentary reassurance with each normal test result, consistent with a somatic symptom disorder. Given the chronology of symptoms, the somatic symptom disorder likely precipitated the anxious depressive disorder.

Case 1 Answer 3 (Question 3—How else can the psychiatrist further the dialogue with Mrs. Z.?)

Given the degree of resistance to psychiatric involvement, it would be important to gain a better understanding of Mrs. Z. and her family's explanatory model for her symptoms and their culturally shaped impressions of mental illness. It appears that the interpreter is not only interpreting language but is in fact also reformulating the psychiatrist's questions and feedback with a cultural lens which is problematic. To this end, the first order should be to provide feedback to the interpreter to this effect, then subsequently attempt to conclude the assessment with another interpreter. Enlisting a cultural broker to formulate a treatment plan may also be helpful. Finally, Mrs. Z.'s daughters may prove to be allies in the treatment plan, so it may be beneficial to contact them to gauge their degree of mental health literacy. With Mrs. Z.'s consent, the ward's psychosocial support worker may find it beneficial to provide some psychoeducation prior to discharge.

Teaching Point
Mental health literacy is associated with help-seeking behavior and service utilization. It may play a role in help-seeking on behalf of others, thus eliciting family members may be particularly helpful in formulating an acceptable treatment plan and facilitating mental health service usage by older adults.

Case 1 Analysis Case 1 demonstrates the deeply entrenched presence of stigma regarding neuropsychiatric illness. Mrs. Z. and her husband likely hold some culturally shaped notions of neuropsychiatric illness which are likely further shaped by the stigma regarding neuropsychiatric illness in their current social environment. Mrs. Z.'s distress in response to her family physician and her cardiologist's suggestion of a psychiatric referral is not entirely unexpected as it poses her illness in a framework at odds to her sociocultural construction of illness, which is reflected in the interpreter's opinion that a depressive disorder is not a "valid" illness. The high intensity use of acute care services like the emergency department is unnecessary and concerning given the reality of limited healthcare resources. As such, psychiatric intervention has an added important role to play here beyond addressing Mrs. Z.'s morbidity.

Mrs. Z.'s use of the emergency department reflects the oft noted pattern that a small proportion of patients consume a relatively large proportion of healthcare resources, added to which these heavy resource consumers frequently have a comorbid neuropsychiatric illness. In Mrs. Z.'s case, refusal to acknowledge and receive appropriate treatment for her depressive disorder and somatic symptom disorder underscores the concept that stigma in itself should be considered a condition requiring intervention, both as an individual and public health good. Given that Mrs. Z. finds her prior diagnosis of neurasthenia to be acceptable, it may present an avenue through which to approach her current episode of illness. Specifically, addressing her symptoms as potential manifestations of "stress overload" may allow her to begin engaging in some basic cognitive behavioral therapy, with the goal of subsequently addressing her depressive disorder in a more fulsome manner. Identifying local, culturally grounded mental health programs with clinicians fluent in Mrs. Z.'s language and attempting to identify allies among her family members may also be beneficial in improving Mrs. Z.'s health literacy, including mental health literacy.

32.2.2 Case 2

Case 2 History

Mrs. G. is a 66-year-old Ethiopian woman who resides with her son and his family in Toronto, Canada. She migrated to Canada 16 months previously, having spent the preceding 6 years in an East African interim camp for refugees. During her first year in the camp, she received medical aid through a humanitarian organization and was diagnosed with human immunodeficiency virus (HIV) infection. Treatment was initiated, and she did well, achieving undetectable HIV viral levels and favorable CD4+ counts. On arriving in Canada to join her son's family, she did not initially disclose her HIV status, but she did continue to take the antiretroviral medications she had brought with her. She eventually disclosed the infection and subsequently saw an infectious disease specialist 12 months ago. Her antiretroviral medications were switched as the regimen that was initiated in the refugee camp was thought to be outdated. She stopped the new regimen within 3 months of starting it but did not disclose this and failed to attend her 6-month follow-up appointment at the infectious disease clinic.

Recently, Mrs. G. has become withdrawn, more religious with daily mass attendance, fasting, and all-night prayer vigils once a week. She has stopped attending her immigration friendship group which she previously enjoyed. She now exclusively keeps to the local Ethiopian community, particularly the church community; however, they have become

concerned about her religious fervor, dysphoric affect, paranoia about "the Canadian people", and newly acquired amulets even though this is discouraged by her church. Although not required by her church or previously worn by her, she has taken to wearing a veil even when she goes to bed. Her son has begun to worry about her hyperreligiosity, forgetfulness, and recent onset of productive cough.

She eventually presents to her family physician at her son's urging, with a productive cough, low-grade fever, weight loss and is noted to have declined considerably since her last appointment 4 months previously. She is noted to be somewhat confused and internally preoccupied and refuses to remove the veil she has wound around her face, leaving just her eyes, nose, and lips exposed. Mrs. G.'s son reports that she began wearing the veil at all hours approximately 9 months ago. Aside from being HIV positive, Mrs. G. has no other known medical problems. She receives a weekly blister pack of antiretroviral medications and does not take any other medications. The family physician considers Mrs. G.'s presentation to be a medical emergency; thus, she calls an ambulance and sends Mrs. G. to the emergency department for further workup and a medical admission. Her son is advised to go home and gather some of her belongings for the admission.

On returning home to gather some of Mrs. G.'s belongings, her son discovers a stockpile of antiretroviral medications in her room. Mrs. G. has a stack of unopened blister packs of antiretroviral medications dating back 6 months. Her son is alarmed and on arriving at the hospital, he alerts the admitting physician of Mrs. G.'s nonadherence. An extensive medical workup is initiated on admission to the hospital. Laboratory investigations reveal a chest X-ray in keeping with a *Pneumocystis jiroveci* pneumonia (previously known as *Pneumocystis carinii* pneumonia), a negligible CD4+ count, some mild to moderate electrolyte abnormalities, and a grossly abnormal arterial blood gas. As expected, she has an alarmingly high viral load.

Mrs. G. responds quickly to treatment for pneumonia. Despite the robust clinical response to treatment, there is no appreciable improvement in her mental status; thus, the psychosomatic medicine (consultation-liaison psychiatry) service is consulted. Mrs. G. is also seen by the psychosomatic medicine service because she is refusing to resume highly active antiretroviral therapy and it is not clear whether she has the capacity to make this treatment decision. She has also continued to refuse to remove her veil, many times draping it over her whole face and appearing to be in prayer for extended periods which has raised concerns about the possibility of a psychotic disorder or psychotic symptoms due to a major neurocognitive disorder. The psychiatric consult is significant for depressive symptomatology for the past 6–9 months, profound abnormalities in neuropsychological testing, and significant impairment in her ability to perform some instrumental activities of daily living. Mrs. G. scores 21/30 on the Montreal Cognitive Assessment, and the MRI of her brain is unremarkable.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. The family physician sent Mrs. G. to hospital in an ambulance. What medical emergency is the family physician likely concerned about?

? Question 2. What other conditions are on your differential diagnosis?

? Question 3. What are potential reasons for Mrs. G.'s facial concealment?

? Question 4. What displacement-related factors are prominent in this case?

Case 2 Answers

Case 2 Answer 1 (Question 1—The family physician sent Mrs. G. to hospital in an ambulance. What medical emergency is the family physician likely concerned about?)

Delirium is a medical emergency. An older adult presenting like Mrs. G. with inattentiveness, confusion, and preoccupation with internal stimuli should be evaluated for delirium so that the underlying cause can be treated. Delirium is an important risk factor for major neurocognitive disorder and death.

Case 2 Answer 2 (Question 2—What other conditions are on your differential diagnosis?)

The differential diagnosis includes:

- Major depressive disorder, rule out psychotic features.
- HIV-associated neurocognitive disorder (dementia).
- Depressive disorder due to another medical condition (HIV, opportunistic infections).
- Psychotic disorder due to another medical condition: in keeping with the discussion in ▶ Chap. 23, it would be important to rule out HIV coinfection with syphilis and other opportunistic CNS infectious disorders.

Teaching Point

HIV infection is associated with a number of coinfections and opportunistic infections that must be ruled out, particularly in patients with antiretroviral medication nonadherence, high viral loads, and poor CD4+ counts.

Teaching Point

Recognition and treatment of psychiatric disorders such as major depressive disorder are important as psychiatric disorders in HIV-positive individuals are associated with significantly increased morbidity and mortality as illustrated in ◘ Table 32.2 [19].

Table 32.2 Risks associated with untreated mental disorders in HIV-positive individuals [19]

Issue	Impact of untreated psychiatric disorder
Quality of life	Poorer quality of life, healthful behavior and self-care
Treatment adherence	Poorer HIV treatment adherence and increased risk of drug resistance with subsequent treatment failure
Disease progression	Faster disease progression and complexity
Other comorbid medical conditions	Reduced adherence with treatment of other medical comorbidities and reduced help-seeking behavior
	Increased risk of acquiring other medical conditions, notably blood-borne infections
	Bidirectional increase in recreational drug use
Mortality	Significantly increased

Case 2 Answer 3 (Question 3—What are potential reasons for Mrs. G.'s facial concealment?)

HIV infection and certain HIV medications may cause lipodystrophy, with some older antiretroviral medications presenting a higher risk. Mrs. G.'s facial concealment should be evaluated to determine whether this is associated with a psychotic disorder or is in fact due to objective facial disfigurement. In Mrs. G.'s case, facial concealment stems from facial lipodystrophy associated with the outdated antiretroviral medication regimen she was taking in the refugee camp. She noted the facial lipodystrophy after arriving in Canada and beginning a new antiretroviral medication regimen; thus, it would not be surprising if she attributed the lipodystrophy to her new medication regimen and erroneously discontinued it as a result of this.

Case 2 Answer 4 (Question 4—What displacement-related factors are prominent in this case?)

Mrs. G.'s case demonstrates some important factors associated with displacement, most notably exposure to traumatic incidents as she disclosed later that she was sexually assaulted in the course of fleeing her village. Late life displacement with transit through a refugee camp exposed Mrs. G. to a number of adverse circumstances including deprivation, isolation from family, sexual trauma, and the acquisition of a highly stigmatized chronic infectious disease. Combined together, these factors predispose Mrs. G. to a complex course during the resettlement process in Canada. Furthermore, her internalized stigma about HIV and poor health literacy likely acted as a barrier to help-seeking behavior when she initially began to observe lipodystrophic facial changes.

Case 2 Analysis The stigma of living with HIV is significant and may in fact result in avoidance of clinical care. In Mrs. G.'s case, being HIV positive is an intense source of shame in her home country and would likely result in her being shunned socially. Furthermore, the migration process can exacerbate internal shame about having HIV as host nations tend to seek the most healthy and economically productive persons for immigration in order to minimize the burden to the host nation's healthcare systems. Mrs. G. initially did not disclose the infection to her son due to shame and fear that he would ask her to leave the family, a common fear that persists today despite the advances in public understanding of blood-borne infections. The shame and stigma of HIV are not solely due to the infection itself; the mode of acquisition may be a significant contributor, particularly when acquisition stems from traumatic sexual exposure. In Mrs. G.'s case, she had unknowingly contracted the infection when she fled the military rampage of her native village and was assaulted. She blamed herself for not being devout enough in her worship and sees the HIV infection as divine punishment for something bad she had done. The concept of the wages of sin certainly continues to exist in tension with scientific understanding of the infection.

Mrs. G. started antiretroviral treatment in the refugee camp. However, she chose to stop antiretroviral medications on arrival in Canada because she rejoined a church and became quite devout given her belief that "prayer is the most potent treatment." She reports that she also knew that prayer was the right choice because the antiretroviral medications had disfigured her. She took to wearing the veil to hide the facial lipodystrophy which has been quite distressing. She reports that she cannot look at her face in the mirror when grooming herself because she is horrified by the visage she encounters. Given the importance of religion to Mrs. G., it would be helpful to involve a cultural broker and a spiritual leader from her community in her treatment and in psychoeducation about the likely origins of the facial lipodystrophy.

32.3 Key Points: Aging and Mental Health in the Era of Globalization

- The global population is aging rapidly, with the proportion of people aged 60 and older projected to almost double from 12% in 2015 to 22% by 2050.
- As a group, neuropsychiatric disorders are the leading causes of disability worldwide.
- Despite the sizeable burden of disease, even in the wealthiest of nations, mental health is allocated a very small portion of the health spending budget.
- Stigma in itself should be considered a condition requiring public health intervention as it presents a significant barrier to help-seeking behavior.
- Clinicians and healthcare institutions in western host nations are facing an increasingly diverse patient population and need to develop a degree of cultural competence.
- Public health planning must also adapt to globalization trends and incorporate standards for the delivery of culturally appropriate healthcare.

- The mental health treatment gap is substantial: while 80% of the global population reside in low- and middle-income countries, less than 20% of the share of mental health resources is consumed in low- and middle-income countries.
- As the global population ages, displaced populations are also aging, and increasingly, many are aging in displacement.
- The traumatic effects of displacement are often not ameliorated on resettlement and may in fact be transmitted across generations.
- The intergenerational transmission of trauma places added importance on efforts to recognize and address the burden of mental illness among displaced older adults.
- Global mental health outreach programs are rapidly taking root, but the geriatric age group is generally overlooked by such efforts.

32.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following categories of disease account for the largest global burden of disease?

A. Cancer
B. Cardiovascular disease
C. Neuropsychiatric disorders
D. Infectious diseases
E. None of the above

Answer: C

Neuropsychiatric disorders account for the most sizeable global burden of disease, with a significant burden of disability, loss of productivity, and lack of self-actualization; therefore, statement C is the correct answer.

MCQ 2. Which of the following statements is correct?

A. Neuropsychiatric disorders are associated with relatively modest disability.
B. Neuropsychiatric disorders are associated with increased risk of nonadherence with treatment for other medical conditions.
C. Intergenerational transmission of trauma can occur among displaced families but is usually mitigated by relocation to a politically stable host nation.
D. The global mental health treatment gap is substantial: only 20% of the global population reside in high-income countries, but as much as 60% of the share of mental health resources is consumed in high-income countries.

Answer: B

Option A is incorrect as evident in MCQ 1. Option C is incorrect as relocation to a stable host nation does not reliably ameliorate trauma. Intergenerational effects of trauma are increasingly recognized after displaced persons relocate to stable host nations. Option D underestimates the global mental health gap in mental health resource consumption between low- and middle-income countries and high-income countries. While 20% of the global population resides in high-income countries, an estimated 80% of the share of mental health resources is consumed in high-income countries. Therefore, option B is correct.

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Palliative Care for Geriatric Psychiatric Patients with Life-Limiting Illness

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33.1 Background

33.1.1 Description of Palliative Care

Palliative care is specialized, multidisciplinary medical care for patients with serious illness that focuses on symptom management and explores with patients and families how to improve quality of life in the face of often progressive and life-limiting illnesses. As the aging population experiences increasing medical comorbidities that result in organ failure and frailty, a palliative care approach from the time of diagnosis, rather than toward the end of life, supports patients to live as well as possible in the course of the disease trajectory. It emphasizes what medical, psychological, and spiritual care is needed to help patients and families achieve an acceptable quality of life. Palliative care plays an increasingly prominent role as debility increases and disease-modifying management decreases and therefore is distinct from hospice care and end-of-life care. Patients receiving palliative care can continue to pursue curative treatment such as chemotherapy. If conditions decline, patients may forgo curative or life-prolonging treatments and opt for hospice care instead. Hospice care is an interdisciplinary care that offers aggressive comfort care for patients from the medical, emotional, and spiritual standpoint while providing bereavement services for families. For geriatric psychiatric patients who often have lived with chronic psychiatric illness most of their lives or who are beginning to develop late-life psychiatric symptoms, palliative care promotes the delivery of patient-centered medical care to this vulnerable population. Geriatric care with its detailed examination of patient's physical functioning, cognition, social support, and living environment overlaps considerably with a palliative care approach.

33.1.2 Establishing Goals of Care with Advance Care Planning

Advance care planning is one of the cornerstones of quality palliative care. Advance care planning is a process of patients communicating their values and goals regarding their medical care. Providers discuss with patients their life-limiting disease, the natural disease trajectory including prognosis, and potential treatment decision with a balanced realism of "hoping for the best, and preparing for the worst" [1]. Some patients prefer to have detailed information about their illness, while others prefer a broad overview. In some cases where patients lack decision-making capacity, families and/or designated medical decision-makers will need to represent how they think the patient would respond and act to potential complications of illness, not their own personal wishes. (See ▶ Chap. 9). Often in these discussions, patients and families despair that talking about the uncertainties of illness takes away hope and emphasizes death and dying. A reframing of how the medical team can best support patients to not just live but more importantly *live well* using the patient's metric of how they define quality of life can change the tenor of the discussion to redefining hope while acknowledging worries. Based on patient goals, clinicians can then provide treatment recommendations that align with those goals. Treatment plans include what will be done (e.g., aggressive symptom management or limited trial of life support) and what will not be done (e.g., artificial nutrition or rehospitalization). The Serious Illness Conversation Guide provides guided questions for clinicians to engage in these often difficult conversations while conveying empathy and hope [2].

The importance of defining and documenting patient wishes and goals of care is underscored in cases of patients diagnosed with cognitive impairment. Early palliative care involvement at the time of diagnosis can help the patient formulate preferences for medical care as well as assign a durable power of attorney to represent patient's interest in the event the patient lacks capacity. Advance directives or living wills identify surrogate decision-makers and can include explicit instructions on the patient's preferences for care. In the USA, a Physician's Order for Life-Sustaining Treatment (POLST) is a medical order recognized by paramedics and hospitals regarding what level of care a patient desires around resuscitation, level of invasive treatment (e.g., ICU-level care versus comfort-focused care), and artificial nutrition.

Teaching Point

Palliative care incorporates the patient's values into medical care planning during a critical period where life-limiting illness redefines how the patient can live well for as long as possible. Geriatric patients with psychiatric illness are a particularly vulnerable population that benefit from early palliative care to ensure that advance care planning can accommodate for situations when things go well and when they do not.

33.1.3 Major Neurocognitive Disorder as a Terminal Diagnosis

Psychiatrists most frequently encounter patients with major neurocognitive disorder (NCD) in the mild to moderate stages of disease where patients experience memory loss, personality changes, and difficulties with activities of daily living. Patients with advanced NCD are often too physically incapacitated to attend clinic visits and may often be seen in more acute settings such as hospitals. Because major NCD is often under-recognized as a terminal diagnosis, psychiatric providers can play an important role in helping patients and families prepare for advance care planning at different stages of NCD, especially in advanced stages.

In the disease trajectory of major NCD, potential complications arise that compromise not only cognitive function but also portend a functional decline. Complications such as infections, falls resulting in fractures (especially of the hip), and inability to ambulate leading to pressure wounds can accelerate a downward decline in overall health. In advanced

major NCD, pneumonia, fevers, and eating problems accounted for the most frequent complications with an association of a 6-month mortality rate of 47%, 46%, and 38%, respectively [3]. Patients with advanced major NCD, especially those living in nursing homes, have unmet palliative care needs often resulting in treatments or interventions that do not result in increased survival and more importantly do not improve the quality of life for this population. Treatment for urinary tract infections does not increase survival [4]. Treatment for pneumonias increases survival but not comfort in advanced major NCD [5].

Without advance care planning or palliative care involvement, patients with major NCD are often subjected to increased number of hospitalizations, episodes of restraint use, laboratory testing, and tube feeds compared to patients with advanced cancer [6, 7]. The burden of hospitalizations, particularly resulting in intensive care, not only creates a heavy financial cost of care at the end of life but may also result in unwanted care for patients whose goals of care may be more comfort focused. Advance care planning is imperative for patients diagnosed with early major NCD to ensure that their goals are articulated and addressed before they lose decisional capacity and/or communication ability in the future. At some point in the disease process especially in cases where there is decline in functional status, such as when patients are minimally verbal or spend more than half of their time in a chair or bed, a do-not-hospitalize order may be one aspect of care that can be documented in the medical record.

Families commonly struggle with the decision to either place a feeding tube or forgo artificial nutrition as dysphagia progressively worsens during an acute illness or when malnutrition is diagnosed. Families often mistakenly believe that feeding tubes are safe, prevent future aspirations and pressure ulcers, and improve nutrition and survival. To the contrary, eating difficulties often reflect the natural part of end-stage major NCD. Artificial nutrition is associated with increased risk of aspiration, discomfort, tube malfunction, physical and chemical restrains, and pressure ulcers [8–10]. Nearly two-thirds of patients with tube feed placements died within a year with a median survival of 56 days [11]. Artificial nutrition does not improve with tube feeds, as patients with chronic illnesses and poor oral intake often have advanced malnutrition that cannot be corrected with artificial nutrition [12]. The American Geriatrics Society does not recommend feeding tubes in advanced major NCD and instead recommends careful hand-feeding [13].

Unlike other chronic medical conditions such as cancer or heart failure, predicting mortality within 6 months in advanced major NCD remains under debate. This challenge can limit patient access to hospice, as, in the USA, Medicare stipulates coverage for end-of-life care for patients with a 6-month mortality. Numerous diagnostic scales have been developed, including the Functional Assessment Staging Tool (FAST) [14], Mortality Data Set [15], and Mini-Suffering State Examination Scale [16] although there remains a lack of agreement in prognosticating reliably and sensitively a 6-month mortality in this population [17] (See ◘ Table 33.1). In the USA, Medicare has specific criteria to qualify patients for hospice services who have a 6-month or shorter prognosis for survival. The National Hospice and Palliative Care Organization uses FAST to qualify patients with major NCD for hospice. The FAST scale assesses functional performance and activities of daily living on a 16-item schedule designed to parallel progressive activity limitations associated with Alzheimer disease. Patients with at least a score of stage 7 or greater and have secondary conditions related to major NCD such as pressure ulcers, urinary infections, or dysphagia qualify for hospice care.

Symptoms of pain, dyspnea, and agitation are most common in end-of-life care [7, 18–20], and the former two symptoms are especially underdiagnosed and undertreated in cases of major NCD since cognitively impaired patients are often unable to self-report. Older adults may present not only with acute pain but may also have chronic pain from conditions such as osteoarthritis, claudication, postherpetic neuralgia, and spinal stenosis. The Pain Assessment in Advanced Dementia (PAINAD) and Pain Assessment Checklist for Seniors with Limited Ability to Communicate (PACSLAC) assess pain based on screening and direct observation [21]. PAINAD and PACSLAC use facial expression, vocalizations, body language and movement, and behavioral changes to assess pain. Caregivers are also an invaluable source in incorporating their observations into the patient's pain assessment. Dyspnea, the subjective sensation of breathlessness that can vary in intensity and sensation, can change over the course of major NCD especially if patients have other chronic diseases like chronic obstructive pulmonary disease that can present with episodic exacerbations. The prevalence of dyspnea in the last week of life substantially increases. Finally, patients with advanced major NCD are more vulnerable to agitation. An important assessment is to determine if agitation is terminal and thus irreversible in the dying process, for which treatment is focused on treating the agitation, or if there are other modifiable factors such as pain, constipation, or infection, which, when treated, can relieve agitation. A discussion of pain and dyspnea management at the end of life is beyond the scope of this chapter. References to palliative care textbooks can provide specific pharmacological and non-pharmacological management of these symptoms. Management of agitation in the palliative care setting will be addressed later in this chapter under delirium subsection.

Teaching Point

Major NCD is both a cognitive and physical disease that is terminal. Medical complications related to advanced major NCD include recurrent infections, swallowing difficulties, pain, and dyspnea. Hospice care can play an important role in caring for patients with advanced major NCD.

Table 33.1 Comparison of major neurocognitive disorder rating scales and predictors of mortality [14–16]

Scale	Predictors
Functional Assessment Staging Tool (FAST) [14]	Stage 1: No difficulty, either subjectively or objectively Stage 2: Complains of forgetting location of objects; subjective work difficulties Stage 3: Decrease job functioning evident to coworkers; difficulty in traveling to new locations Stage 4: Decreased ability to perform complex tasks (e.g., planning dinner for guests, handling finances) Stage 5: Requires assistance in choosing proper clothing Stage 6: Decreased ability to dress, bathe, and toilet independently Substage 6a: Difficulty putting clothing on properly Substage 6b: Unable to bathe properly; may develop fear of bathing Substage 6c: Inability to handle mechanics of toileting (i.e., forgets to flush, does not wipe properly) Substage 6d: Urinary incontinence Substage 6e: Fecal incontinence Stage 7: Loss of speech, locomotion, and consciousness Substage 7a: Ability to speak limited (1–5 words a day) Substage 7b: All intelligible vocabulary lost Substage 7c: Nonambulatory Substage 7d: Unable to sit up independently Substage 7e: Unable to smile Substage 7f: Unable to hold head up *Note:* To be eligible for hospice, beneficiaries with Alzheimer disease must have a FAST scale of ≥ 7
Minimum Data Set [15]	Activities of Daily Living (ADL) Scale Male sex Cancer Congestive heart failure O_2 therapy in last 14 days Shortness of breath < 25% of food eaten Unstable medical condition Bowel incontinence Bedbound Age > 83 years Not awake most of day *Note:* Each category is assigned points. ADL score refers to rating on a 5-point scale functional ability in seven functional domains such as dressing and eating. A higher total risk score predicts a higher-risk estimate of death within 6 months. A score of 0 predicts an 8.9% risk, a score of 5 predicts a 23.2% risk, and a score ≥ 12 predicts a 70% risk
Mini-Suffering State Exam [16]	Not calm Screaming Pain Decubitus ulcers Malnutrition Eating disorders Invasive actions (e.g., blood tests, mechanical restraints, hemodialysis) Unstable medical condition Suffering according to medical opinion Suffering according to family opinion *Note:* Each item is assigned one point. Total scores from 0 to 3 indicate low level of suffering, 4 to 6 intermediate level, and 7 to 10 high level

33.1.4 Delirium in the Palliative Care Setting

Delirium is a common yet often under-recognized and underdiagnosed serious neuropsychiatric complication in geriatric patients and especially at the end of life, often referred to as "terminal delirium," "terminal restlessness," or "terminal agitation." (Please see ▶ Chap. 17 for in-depth discussion of delirium). The hallmarks of delirium include abrupt onset of disturbances in awareness, attention, cognition, and perceptions that fluctuate over the course of the day. In some cases, delirium may be reversible, depending upon etiology and proximity to the time of death, with diminishing likelihood of reversibility in the final hours to days of life, and is often a harbinger for predicting impending death. In one study of geriatric patients admitted to skilled nursing facilities 3 months following a hospital admission, the prevalence of delirium approached 55% at 1 month and 25% at 3 months and persisted until death in 72% of those patients [22]. Other studies in terminally ill cancer patients in palliative care settings report rates of 28–42% on admission to 88%

1 week prior to death [23], with reversible delirium rates as low as 27% [24].

The psychiatrist is often called upon to evaluate and provide recommendations for insomnia, sleep-wake cycle disturbances, depression, anxiety, apathy, major NCD, or psychotic symptoms. Often times these neuropsychiatric sequelae are attributable to one of the various subtypes of delirium (i.e., hyperactive, mixed state, or hypoactive) that can interchangeably fluctuate on a continuum and be superimposed upon other premorbid neuropsychiatric disorders (including major NCD and depressive disorders) and/or systemic medical conditions (including strokes, hypertensive and atherosclerotic vessel changes, and primary or metastatic tumors). Delirium is highly distressing for patient, family, and staff members [25] and interferes with the recognition and control of other physical and psychiatric symptoms, including pain [26, 27].

Pathophysiology, Reversibility, and Workup of Delirium

With a diverse phenomenology leading to a global brain dysfunction, delirium is generally thought to be attributable to a decreased cholinergic function, sometimes referred to as "reduced brain reserve," but also involves dopamine, noradrenergic, GABAergic, glutaminergic, serotonergic, and opioid circuits, with various proposed mechanisms ultimately leading to a common pathway [28, 29]. Clinical workup for terminal delirium should focus on identifying precipitating factors and the underlying pathology to alleviate symptoms. The workup for potentially reversible causes should closely align with the goals of care and involve discussions with the patient and family, generally favoring less invasive procedures. Goals of care guide the level of invasive workup and treatment, such as favoring a urinalysis that is relatively less burdensome compared to lying in an MRI machine. In some cases, delirium may be irreversible because (i) of the underlying etiology of the disease such as end-stage organ failure or imminent death, (ii) a diagnostic workup did not reveal an etiology, or (iii) a time-limited treatment trial failed to reverse the delirium. A prospective study of 237 hospice inpatients who developed delirium and were followed until the time of death had a mean number of 1.8 plausible delirium etiologies identified with the most common being hepatic failure, medications, prerenal azotemia, hyperosmolality, hypoxia, disseminated intravascular coagulation, organic damage to the central nervous system, infection, and hypercalcemia. Manifestations of hyperactive delirium and the requirement for symptomatic sedation closely correlated with hepatic failure, opioids, and steroids, while dehydration-related etiologies were significantly associated with hypoactive delirium. Cases attributed to medication and hypercalcemia-induced delirium typically resolved, whereas a low remission rate was associated with hepatic failure, dehydration, hypoxia, and disseminated intravascular coagulation [30]. Screening tools such as the Memorial Delirium Assessment Scale and the Confusion Assessment Method have been used in the palliative care setting [31, 32].

Management of Delirium

Frequently non-pharmacologic interventions are not effective for controlling the symptoms of delirium particularly in the dying phase, often necessitating reliance upon psychotropic medications despite the lack of approval of any medication by the US Food and Drug Administration for the treatment of delirium. Haloperidol remains the gold standard for treatment of delirium in geriatric patients with or without cancer [33, 34]. The risks of QTc prolongation and torsades de pointes associated with intravenous haloperidol should be discussed with patients and families in light of their goals of care. Chlorpromazine may be considered as an alternative to haloperidol, when increased sedation is required. In cases of irreversible delirium or delirium refractory to antipsychotics, benzodiazepines and other sedatives may be adjuncts while acknowledging the risk of potentially worsening delirium. Benzodiazepines may be particularly helpful in status epilepticus. Opioids while sedating should be avoided in treating delirium unless pain is the primary cause of delirium. ◘ Table 33.2 provides a list of common medications used to treat terminal delirium. In nearly all cases, aggressive management of delirium in the dying process promotes comfort. In some cases, patients experience pleasant and comforting hallucinatory experiences that may not need pharmacological intervention. A formidable clinical challenge arises when a dying patient is unresponsive to standard pharmacological interventions for delirium which can occur in 15–52% of dying patients [35, 36]. In such cases, palliative sedation which uses proportionately higher levels of sedation to help relieve otherwise intractable and distressing physical symptoms at the end of life may be indicated as a therapy of last resort to relieve suffering [37]. When alternative means of relieving symptoms are ineffective or produce intolerable side effects even with expertise from palliative care, the goals of palliative sedation are not to intentionally hasten a patient's death but rather to provide the lowest level of sedation to relieve symptoms. Apprehension that use of sedating medications would hasten death in the palliative care setting has not been supported in the literature [38–40].

Teaching Point

Delirium is common in the palliative care population. A limited workup depending on the goals of care may identify reversible causes. Often terminal delirium portends the beginning of the dying process, and the goal of management at that point is comfort.

33.1.5 Depression in the Palliative Care Setting

Patients faced with a life-limiting illness have a spectrum of normal responses reflective of the way they have coped, bringing in both their strengths and vulnerabilities [41]. There is a dynamic tension between adjusting to and

Table 33.2 Medication management for terminal delirium

Medication	Administration availability	Initial starting dose (maximum daily dosage)	Notes
Haloperidol	PO (tab, liquid), PR, SC, IM, IV	1 mg PO or 0.5 mg IV or SC q1 hour PRN and then every 6–12 hours in divided doses (20 mg)	In emergent cases, give IV every 15 minutes until symptoms resolved. Once symptoms resolved, take total amount used in 24 hours, and divide over 24-hour period Parenteral doses twice as potent as oral doses Useful in treating nausea
Chlorpromazine	PO, PR, SC, IM, IV	25–50 mg PO or IV or PR q1 hour (2000 mg)	Consider if more sedation needed Monitor for anticholinergic effects and hypotension
Olanzapine	PO (ODT), IM	2.5 mg qday (40 mg)	Useful in treating nausea
Quetiapine	PO	25 mg PO q12 hours (800 mg)	Monitor for anticholinergic effects and hypotension
Lorazepam	PO (tab, liquid), PR, SC, IM, IV	0.5–1 mg any route (40 mg)	
Midazolam	PO (liquid), SC, IM, IV	0.1–0.2 mg/kg IV/SC loading dose, then repeat every 30 minutes PRN agitation Maintenance dose: 0.02–0.2 mg/kg/hour (240 mg)	Give 25% of total dose needed to control symptoms as continuous infusion Medication most frequently used for palliative sedation
Phenobarbital	PO (tab, liquid), PR, SC, IV	50–100 mg IV loading dose every 10–15 minutes until comfortable Maintenance: 60–800 mg divided over 24 hours (800 mg)	Used primarily for palliative sedation

Note: IM intramuscular, *IV* intravenous, *ODT* oral disintegrating tablet, *PO* per oral, *PR* per rectum, *PRN* pro re nata (as needed), *SC* subcutaneous

defending with a crisis stressing coping capabilities. A psychological adjustment is hopefully made to preserve equilibrium. Defenses, especially denial, can be adaptive in the first part of crisis and should be supported. Maladaptive defenses can impair functioning and care. Illnesses pose a threat to the sense of self physically and psychologically through loss, change relationships, disrupt economic circumstances, and may alter how patients rely on spiritual resources. Depressed and anxious feelings therefore are part of a normal spectrum of responses, but which must be repeatedly assessed by psychiatrists among this vulnerable population.

The prevalence of depression in patients with advanced illness varies from 3 to 42% [42]. A number of factors may account for the discrepancy among studies including settings of where studies take place (e.g., inpatient vs outpatient, cancer clinic vs general palliative care clinic), inclusion or exclusion of diagnosis of adjustment disorder, differences in defining "normal" distress from psychiatric illness, and inclusion of somatic symptoms. Cultural factors may also play a role including the acceptance among patients and medical providers that depression is a normal reaction to a patient's terminal illness. Despite the prevalence of depression in the palliative care population exceeding that in the general population, depression remains profoundly underdiagnosed even when patients are at the end of life [43, 44]. Untreated depression in patients with life-limiting illness has adverse implications including being an independent early predictor of death in patients with advanced cancer, requests for hastened death, symptom exacerbation with sometimes difficult to treat cases, and impaired quality of life [45, 46].

Diagnostic Challenges of Depression

Because advanced physical illness and its associated treatment often cause fatigue, lack of appetite, loss of energy, and poor concentration, symptoms also found commonly in the physical manifestations of depression, the psychological symptoms of depression are given more weight when assessing for depression in the palliative care population [47, 48]. Symptoms such as dysphoria, depressed mood, tearfulness, lack of pleasure, guilt, and hopelessness may therefore help to distinguish depression in this population, though these symptoms may also be interpreted realistically and in context of being aware of the finitude of a terminal illness. Demoralization has been closely identified with depression with its overlap of hopelessness, helplessness, meaninglessness, and existential distress as core features [49]. The distinguishing features differentiating demoralization from depression include a sense of incompetence but preservation of reactivity of mood compared with depression marked by anhedonia, lack of reactive mood, and loss of drive.

Grief must also be distinguished from depression [47, 50]. Grief is a normal and expected response involving feelings,

emotions, and behaviors stemming from a loss. It can mimic depression with somatic symptoms and social withdrawal. Whereas depression is a psychiatric illness characterized by a denigrating self-worth, hopelessness, and anhedonia with a constant and unremitting quality, grief has a preserved sense of self-worth. Grieving patients can enjoy pleasure and hope with symptom intensity diminishing over time. Grief is also characterized by yearning, desire to reunite with the lost loved one, and intrusive or preoccupying thoughts about the deceased. Pathological or complicated grief occurs when feelings of grief are prolonged and lead to significant functional impairment and difficulty in finding meaning and purpose in life [51]. DSM-5 lists persistent complex bereavement as a disorder under other specified trauma- and stressor-related disorder and excludes bereavement in the diagnosis of a major depressive disorder, meaning that patients may have a diagnosis of major depression in the context of bereavement. Emerging research supports a distinction between bereavement and non-bereavement-related depression [52]. (Please refer to ▶ Chap. 14, for further discussion on distinguishing elements among major depression, normal grief, and complicated grief).

The clinical interview remains the gold standard in diagnosis of depression. Various screening tools have been tested in the palliative care population including the Beck Depression Inventory, Patient Health Questionnaire-2, and Hospital Anxiety and Depression Scale [53–55]. For terminally ill patients, a single-item asking "Are you depressed?" was found to have both a specificity and sensitivity of 1 [53]. Medical causes of depression are discussed in ▶ Chap. 10. Psychological and spiritual causes may include grief, existential distress, family dynamics, and guilt.

Management of Depression

Goals of care and prognosis in patients with life-limiting illness guide management of depression. Goals of care outline how to optimize care including the level of invasive treatment such as determining whether to identify potentially reversible causes or alternatively control symptoms. In patients with a survival prognosis of days to weeks, pharmacological use of psychostimulants (e.g., methylphenidate) with a faster response rate frequently outweigh the use of standard antidepressants like selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) that can take weeks to take full effect [56]. Moreover, methylphenidate also has the added benefit of treating fatigue, enhancing cognitive dysfunction in patients with brain tumors, and improving sedation associated with opioid use [57].

Patients who are expected to live for several months or longer may benefit from antidepressants (◘ Table 33.3). Treatment with standard antidepressants is well tolerated in the palliative care population and is superior to placebo [58]. Comorbid symptoms such as insomnia, neuropathic pain, or poor appetite will affect the selection of an antidepressant. For example, tricyclic antidepressants (TCAs) and SNRIs are often used currently to treat depression and neuropathy, whereas mirtazapine (a noradrenergic and specific serotonergic antidepressant or NaSSA) is frequently used for insomnia and anorexia. Monoamine oxidase inhibitors are generally discouraged because of dietary restrictions as well as numerous drug interactions. Drug interactions should also be considered as specific chemotherapeutic and pain medications (e.g., methadone) can alter cytochrome P450 metabolism. As patients have increasing difficulties with swallowing, formulations of medications can be changed from tablets and capsules to liquid or crushing tablets or orally disintegrating tablets. At some point, psychiatrists may want to consider tapering off medications while monitoring for discontinuation syndrome, if the burden of taking medications outweighs the benefits.

Psychotherapy plays a fundamental role in treatment, even for patients with a prognosis of days to weeks who may benefit from supportive psychotherapy that validates worries and feelings, reflects, explores fears, and shares in the experience of being ill [41]. The patient-therapist relationship changes when working with terminally ill patients who are well enough to engage in therapy: therapy is time limited and determined by the patient's ability to physically participate in psychotherapy and prognosis, goals are more limited such as foregoing insight as an essential therapeutic task, and patients rather than the therapist set the frame of where and when psychotherapy is to take place [59]. A number of evidence-based, brief, semi-structured psychotherapies in the palliative care population have demonstrated improvement in overall well-being. Cognitive behavior therapy is well established. (See ▶ Chap. 8). Dignity therapy focuses on enhancing dignity structuring and interviewing around the psychological, existential, and spiritual challenges of a life-threatening illness and creating a written generativity/legacy document [60]. The outcomes for improving depressive symptoms are mixed but suggest that dignity therapy is beneficial in patients with psychological distress [61, 62]. Meaning-centered psychotherapy was founded on the principles of Viktor Frankl who emphasized finding meaning in times of great suffering. The goal of this psychotherapy is to increase patients' sense of meaning and spiritual well-being by highlighting their choice of attitudes, engaging in life, and defining a legacy [63]. Similar to dignity therapy, outcomes for depression with meaning-centered psychotherapy were mixed, but spiritual suffering, desire for death, and anxiety improved over time [64, 65]. Finally, Managing Cancer and Living Meaningfully (CALM) addresses four areas in patients with advanced disease with the goals of decreasing death anxiety and depressive symptoms and improving attachments and spiritual well-being: (1) symptom control and communication with medical providers, (2) self-concept and changing relationships with close others, (3) spiritual well-being and sense of meaning and purpose in life, and (4) preparing for the future [66]. CALM has demonstrated success in decreasing death anxiety and depression [67].

Table 33.3 Medication management for depression in palliative care

Medication	Administration availability	Initial starting dose (maximum daily dosage)	Notes
SSRI			Well tolerated with fewer drug interactions and side effects than TCAs Usually takes 6–8 weeks to take effect
Fluoxetine	PO (tab, liquid)	20 mg/day (40 mg)	Numerous drug-drug interactions (e.g., methadone)
Paroxetine	PO (tab, liquid)	20 mg/day (40 mg)	Numerous drug-drug interactions Has significant anticholinergic side effects Short half-life so risk for discontinuation syndrome if stopped abruptly
Sertraline	PO (tab, liquid)	50 mg/day (200 mg)	Few drug-drug interactions Well tolerated
Citalopram	PO (tab, liquid)	20 mg/day (maximum 20 mg in patients older than age 60, 40 mg for others)	Few drug-drug interactions Well tolerated
Escitalopram	PO (tab, liquid)	10 mg/day (maximum 10 mg in patients older than age 65, 20 mg for others)	Few drug-drug interactions Well tolerated
SNRI			Often used concurrently to treat neuropathic pain Usually takes 6–8 weeks to take effect
Venlafaxine	PO (tab, capsule)	75 mg/day (225 mg)	May have stimulating effect, increase blood pressure Monitor for discontinuation syndrome
Desvenlafaxine	PO (tab)	50 mg/day (100 mg)	Limited data in palliative care setting
Duloxetine	PO (capsule)	30 mg/day (120 mg)	Frequently used in fibromyalgia and neuropathic pain Monitor for discontinuation syndrome
Miscellaneous antidepressants			Used to augment SSRI or SNRI
Bupropion	PO (tab, capsule)	Slow release: 150 mg/day (400 mg) Extended release: 150 mg/day (450 mg)	Avoid in seizures and eating disorders
Mirtazapine	PO (tab, ODT)	15 mg/day (45 mg)	Useful in insomnia and anorexia in lower doses
TCA			Cautiously use in patients with cardiac history Has significant anticholinergic effects Useful in neuropathic pain at doses lower than those used to treat depression Usually takes effects in 4–8 weeks Dose at night because of sedating effects
Desipramine	PO (tab)	25 mg qhs (150 mg)	Less anticholinergic than amitriptyline or imipramine, so preferred agent
Imipramine	PO (tab, capsule)	25 mg qhs (100 mg)	
Amitriptyline	PO (tab)	25 mg qhs (150 mg)	
Nortriptyline	PO (capsule, solution)	25 mg qhs (150 mg)	Less anticholinergic than amitriptyline or imipramine, so preferred agent
Doxepin	PO (capsule, liquid)	25 mg qhs (300 mg)	Useful for pruritus Extremely sedating
Psychostimulant			Effective within a few days Use in patients with prognosis of days to weeks
Methylphenidate	PO (tab, capsule, liquid)	2.5 mg BID (second dose no later than 1–2 pm) (20 mg)	Monitor for use in patients with cardiac history May cause anorexia and insomnia
Wakefulness promoter			
Modafinil	PO (tab)	200 mg (400 mg)	Use often limited by cost Used primarily for cancer-related fatigue

Note: BID twice a day, *ODT* oral disintegrating tablet, *PO* oral, *qhs* bedtime

Teaching Point
Depression in the palliative care setting is easily confused with a normal reaction to living with a terminal illness, grief, and the disease itself. Physical symptoms of depression should be excluded in the diagnosis and emphasis placed instead on psychological symptoms. Selection of medications to treat depression will depend on the prognosis of the patient.

33.1.6 Anxiety in the Palliative Care Setting

Similar to depression, the range of anxiety in the palliative care setting varies from study to study from 3 to 25% and depends on the specific anxiety disorder [41, 68]. Anxiety often coexists with major depression.

Diagnostic Challenges of Anxiety

Medical, psychosocial, and existential factors contribute to heightened feelings of anxiety. Physical symptoms such as shortness of breath, pain, tachycardia, nausea, and diaphoresis may be related to the disease itself or associated treatments. For example, poorly treated chronic obstructive disease causing the sensation of breathlessness or restlessness may lead to suspicions of panic attacks. Side effects from medications (e.g., steroids, beta-adrenergic agonists) may also mimic anxiety symptoms. Anticipatory nausea/vomiting is a well-documented phenomenon of classical condition among patients undergoing chemotherapy who experience anxiety based on past experiences with chemotherapy [69]. Disruptions to family relationships, finances, uncertainty about the future, and fears of dying or loss of independence also contribute to anxiety.

Specific phobias, panic disorders, generalized anxiety disorder, and post-traumatic stress disorder may have been treated in patients prior to being diagnosed with a life-limiting illness, whereas some patients are first diagnosed as they undergo treatment. Among older patients, a lifetime accumulation of traumatic events and newly created traumas can create challenges in addressing post-traumatic stress disorder at the end of life. (See ▶ Chap. 14). They may not only reexperience a traumatic reaction such as reliving their loved ones' illness and death when diagnosed with their own life-limiting illness but may also undergo intensive medical treatments that can be experienced traumatically [70]. For example, an older patient with advanced lung disease may have a prolonged stay in the intensive care unit requiring invasive treatments such as mechanical ventilation, restraints, and prolonged sedation, often complicated by delirium. All those situations can be experienced as traumatic; therefore, a trauma-informed approach should be used. (See ▶ Chap. 26).

Numerous screening tools have been used in patients with advanced illness including the Hospital Anxiety and Depression Scale, Rotterdam Symptoms Checklist, Brief Symptom Inventory, and Profile of Mood States, although the clinical interview remains the standard diagnostic technique [68].

Management of Anxiety

Management of anxiety overlaps considerably with depression. Goals of care, prognosis, and urgency of symptom relief influence the approach to care from the invasive to noninvasive/comfort-oriented approach. A thorough review of the patient's medical history, medications, and psychosocial stressors may identify potentially reversible factors. Patients with mild anxiety symptoms may benefit from supportive measures. Most often though, patients will require pharmacological treatment (◘ Table 33.4). For rapid relief of symptoms and patients with a shorter survival prognosis of days to weeks, benzodiazepines are the first line of treatment. Caution is used when prescribing these medications as patients may already experience preexisting cognitive impairment. The preferred benzodiazepines for patients with liver disease are lorazepam, oxazepam, or temazepam. For patients with a prognosis of months or longer, SSRIs are the preferred medications to manage chronic anxiety. Other adjunctive treatments including gabapentin, propranolol, and trazodone have also been used to treat anxiety.

Psychotherapies are also effective with the palliative care population. Ideal candidates for psychotherapy are those who decline medication management, desire for improved self-control, and acknowledge the efficacy of such an approach [41]. Patients with delirium, major NCD, or other cognitive impairment have limited success in psychotherapy. Psychodynamic approaches are less useful than behavioral and psychoeducational approaches. In addition to cognitive behavioral therapy, CALM which specifically addresses death anxiety is effective in reducing anxious symptoms [67], as did dignity therapy [61]. Meaning-centered psychotherapy did not decrease anxiety but did improve spiritual well-being and quality of life [64]. Alternative therapies such as progressive muscle relaxation, guided imagery, music therapy, and hypnotherapy have also been found to be effective in this population. A psychoeducational approach can allay, anticipate, and normalize fears patients may have about their prognosis, symptoms, and treatment expectations.

Teaching Point
Evaluation of anxiety should include a biopsychosocial assessment. Disease progression and treatment-related complications can mimic many somatic symptoms of anxiety. Pharmacological management will depend on the urgency of symptom relief, goals of care, and prognosis.

Table 33.4 Medication management for anxiety in palliative care

Medication	Administration availability	Initial starting dose (maximum daily dosage)	Notes
SSRI refer to Table 33.3			
SNRI refer to Table 33.3			
Benzodiazepines			Avoid alprazolam because of short half-life Cautious use because of risk for sedation and falls
Lorazepam	PO (tab, liquid, IM, IV, SC)	0.25–1 mg q60 minutes PRN anxiety Titrate to effect	Preferred use in liver disease Useful in status epilepticus Can be scheduled or given PRN
Diazepam	PO (tab, liquid, rectal gel, injection, IM)		Minimize use given active metabolite can extend half-life
Clonazepam	PO (tab)	0.25–2 mg/day Titrate to effect	Consider scheduling given slow onset
Other medications with anxiolytic properties			
Propranolol	PO (tab, liquid, capsule, IV)	10 mg BID or TID	Often used in palliative care to help with tremors Monitor vital signs
Gabapentin	PO (tab, capsule, liquid)	100 mg BID or TID (3600 mg)	Often used to treat neuropathic pain Decrease dose in renal failure
Trazodone	PO (tab)	25 mg (500 mg)	Risk for sedation, priapism, orthostasis

Note: BID twice daily, *PO* oral, *PRN* pro re nata (as needed), *TID* thrice daily

33.1.7 Substance Use Disorders in the Palliative Care Setting

While substance use disorders have become increasingly widespread in the general population with prevalence estimates ranging from 6 to 15% [71, 72], there are few studies evaluating the prevalence of substance use disorders in patients in the palliative care setting. Positive screening of cancer patients at risk for alcohol and other substance use disorders varies from 17 to 43% [73, 74]. Unremitting substance use disorders in the palliative care population can render them vulnerable to absent or compromised social support in the setting of advanced disease and treatment, hinder treatment and adequate pain management, and increase risk of hastening morbidity and mortality [75, 76]. A therapeutic approach that simultaneously addresses substance use disorders while targeting medical treatment and pain management affords opportunities for promoting adherence to medical treatment and potential recovery. Pain continues to be undertreated at the end of life especially among ethnic minorities, women, elderly, and substance abusers [77–79]. Undertreated pain can become a barrier for the treatment of substance use disorder and increases the risk of substance and prescription abuse [80]. (See ▶ Chap. 16).

Aberrant drug use behavior, pseudoaddiction, and undiagnosed and/or undertreated comorbid psychiatric illnesses raise significant concerns for substance use disorder. The degree of aberrant drug behavior can vary from mild, such as requesting early refills or reporting losses of prescription, to severe such as forging prescriptions or diverting prescription medications. Aberrant drug use behavior does not always indicate a substance use disorder. A risk stratification approach distinguishing less serious from highly aberrant behaviors may help guide clinicians in identifying inadequately treated pain which includes both physical and psychological elements. Pseudoaddiction refers to aberrant behavior mimicking substance use disorder as a result of inadequate pain management with the resolution of the concerning behavior when adequate pain relief is provided [81]. Finally, psychiatric illnesses that have not been diagnosed or optimally treated in palliative care patients can further exacerbate substance use disorder, especially as these are highly comorbid with substance use in the general population.

Clinical Approach and Management of Substance Use in the Seriously Ill Population

As advanced illness progresses, the context of serious illness changes and can often result in worsening physical pain while further exacerbating anxiety and challenging coping strategies patients have developed. A harm/risk-reduction approach with an emphasis on safety rather than a risk-elimination or punitive approach facilitates a meaningful engagement between patients and clinicians to discuss openly

the challenges of providing appropriate pain management. Close collaboration and coordination with an interdisciplinary team of the primary care physician, medical specialists, nursing, social work, and pain/palliative care providers can create a treatment plan to meet the evolving needs of the patient, family, and team. Listed below are some strategies to assess and treat pain for palliative patients who may be at risk for substance use disorder or are actively misusing [82]:

1. Obtain a thorough substance use history, distinguishing between those who have active substance use disorders from those who are at risk or in recovery. Screening tools that have been used in the palliative care population include the Opioid Risk Assessment Tool, CAGE (*C*ut down-*A*nnoyed-*G*uilty-*E*ye opener), and Screener and Opioid Assessment of Patients with Pain [73, 74, 83].
2. Access Prescription Monitoring Programs (PMPs) that collect data on controlled substances dispensed in each US state. PMPs can identify evidence of drug abuse or diversion such as when multiple providers are writing prescriptions for controlled substances for a given patient. Caution however must be exercised when interpreting information from the PMPs as there can be misinformation such as not knowing if medications are dispensed for symptoms such as in the hospice setting and potential time lag when PMPs are updated.
3. Consider implementing a written opioid contract, carefully defining patient and provider expectations which may motivate contemplative patients toward a sense of control over their comorbid substance use disorder. Components of an opioid agreement should establish a single prescriber, designated pharmacy, and random pill counts (e.g., at office visits or home health visits). Opioid contracts are controversial with weak evidence supporting the efficacy in reducing opioid misuse [84].
4. Obtain periodic urine drug screens. Interpretation of results can vary depending on whether the goal is to screen for illicit drug use or confirm the use of prescribed medications. Some urine toxicology results may not indicate the presence of prescribed drugs because (a) the drugs may have been taken outside of the detection window or interacted with other medications, (b) there may be variations in patient pharmacogenetics, (c) there are variable thresholds of detection, and (d) there are false negatives [85].
5. Optimize pain management with non-opioid analgesics and non-pharmacologic measures. Consider TCAs, SNRIs, and other agents such as gabapentin for neuropathic pain [86]. Minimize benzodiazepine prescribing due to age-related risks (e.g., cognitive impairment/delirium, fall/fracture risk) and increased risk for serious or lethal overdose when coadministered with opioids [87]. Utilize non-pharmacological treatments such as relaxation techniques, acupuncture, acupressure, distraction, biofeedback, and cognitive behavioral therapy for pain.
6. Initiate opioids at appropriate doses and intervals. Titrate long-acting opioids to minimize the use of short-acting or breakthrough opioid medications. Opioid-tolerant patients may require higher doses to satisfy pain requirements. In high-risk patients, methadone may be the preferred opioid to provide satisfactory analgesia while reducing the risk for diversion and abuse but usually requires substantial changes in therapy including dose increases and multiple daily doses compared to once-a-day dosing for opioid dependence. Dispensing of abuse-deterrent drugs that combine an opioid with naltrexone may be limited by costs.
7. Schedule frequent follow-up visits with patients, prescribing opioids in very limited quantities while monitoring for adequate pain management, substance use, and disease progression.
8. Encourage participation in recovery (e.g., Smart Recovery, 12-step) programs. Consider consultation with an addiction specialist. As many recovery programs set abstinence as an imperative, this may not be a realistic goal for terminally ill patients who are receiving opioid-based therapies. Further, as illness progresses, patients may be too physically weak to attend these meetings.

Teaching Point

Substance use disorder is challenging in patients who may be suffering both physically from their illness and emotionally in living with a terminal illness. Pain should be optimally treated while closely following with patients who have had a prior history or current substance use.

33.1.8 Off-Label Use of Psychiatric Medications in Palliative Care Setting

Aggressive symptom management is a hallmark of good palliative care. Off-label use of psychotropic medications has effectively treated symptoms of pain, nausea, and fatigue (Table 33.5). Health-care providers should discuss the benefits, risks, and burdens of prescribing these medications that have not received FDA or Health Canada approval for the

Table 33.5 Off-label psychotropic medication used in the palliative setting

Symptom	Palliative medications
Nausea and vomiting	Haloperidol, olanzapine, mirtazapine
Fatigue	Methylphenidate
Hiccups	Chlorpromazine, gabapentin
Neuropathic pain	Methadone, amitriptyline, nortriptyline, duloxetine, venlafaxine, mirtazapine, gabapentin
Refractory pain	Ketamine
Pruritus	Paroxetine, sertraline, fluvoxamine, mirtazapine

specific clinical indication, although commonly practiced in the palliative care setting.

While opioids have been the mainstay for most palliative pain management, numerous psychotropic medications are effective pain adjuncts and can often spare the amount of opioids prescribed. Neuropathic pain, often described as tingling, numbness, shooting, and/or burning pain, respond effectively to SNRIs, TCAs, and methadone. Methadone has stimulated a renewed interest because of its inhibition of norepinephrine and serotonin, as well as its antagonism to the NMDA receptor that modulates neuropathic pain. Ketamine at sub-anesthetic doses can be considered in refractory cases to opioids and other adjunctive analgesics [88].

Antipsychotics with their multiple receptor actions are used to treat multiple symptoms.

Haloperidol and olanzapine effectively treat nausea and vomiting. Recent studies have shown the safety of olanzapine for the prophylaxis of chemotherapy-induced nausea and vomiting [89]. Olanzapine can attenuate weight loss of advanced cancer patients when used as monotherapy [90]. Chlorpromazine and gabapentin are used for refractory hiccups.

Psychostimulants like methylphenidate demonstrate an improvement in cancer-related fatigue although the wakefulness promoter modafanil demonstrated no effect [91, 92]. Safety data on cardiovascular adverse outcomes of the use of psychostimulants in healthy populations are mixed. Because the palliative care population most often includes patients with advanced heart disease, psychostimulants are generally avoided in patients with cardiac disease. Finally, antidepressants in observational studies are used to treat pruritus [93].

33.1.9 Physician Aid in Dying

Physician-assisted death, also referred as physician aid in dying or (more controversially) physician-assisted suicide, exists at the interface among psychiatry, other specialties in medicine, and bioethics in the twenty-first century. The role of the psychiatrist is to deconstruct the terms in order to provide an ethical, legal, and practical framework where semantics play an essential role. Suicide often connotes self-completed death attributable to a psychiatric illness, although not always specific to psychiatric illness per se (e.g., many neurologic illnesses have a high rate of suicide). Conversely, physician-assisted death reflects an existential matter and not a psychiatric illness. This distinction requires a decoupling of the concepts of a self-destructive act and psychiatric illness. Suicide may be correlated with illness, not just from depression alone, although comorbid psychiatric illness must be ruled out and perhaps could be considered as part of the underlying systemic illness. Pathologizing suffering, as a dictum for medicalizing suffering at the end of life, has led to innovations in the field of palliative and hospice care. In the mid-1990s, an international expert task force convened at Hastings Center and was charged with gaining perspectives on advances in medical science and technology over the following 30 years with the goal of reconceptualizing and restating the core values of medicine for the twenty-first century as follows [94]:

- Prevention of disease and injury and promotion and maintenance of health
- Relief of pain and suffering caused by maladies
- Care and cure of those with a malady and the care of those who cannot be cured
- Avoidance of premature death and the pursuit of a peaceful death

These four concepts create a foundation for a synergistic approach between curative and palliative models of care, reflecting the limits of our ultimate mortality and medical technologies. Of particular relevance are the second and fourth concepts, the latter being somewhat elusive, with particular attention to the word "peaceful" [95]. The domains of palliative care and psychiatry overlap considerably when addressing suffering and supporting patients and families to achieve peace and dignity. The concept of demoralization categorizes existential distress in which meaninglessness and profound suffering may result in a desire to die [49]. Concern that demoralization is a form of depression led to the development of state-of-the-art innovations in palliative care, psychosocial, and spiritual interventions which were thought to mitigate a desire for hastened death. Interventions such as meaning-centered group therapy [65] focused on finding meaning in profound suffering, and dignity therapy addressed illness-related concerns and dignity-conserving repertoire while creating a social dignity inventory [60].

The request for hastened death can be categorized into four main areas: (1) responding emotionally to current circumstances, (2) communicating distress and suffering or desiring to explore ways to relieve distress, (3) seeking information about suicide or physician-assisted death, and (4) actively planning to seek to end one's life [96]. Common risk factors associated with a desire for hastened death include the patient feeling like a burden to others, loss of autonomy and ability to control one's death, depression and hopelessness, existential concerns, physical symptoms like pain, and fear of the future [96–98].

While patients emphasize dying with dignity, the role of the psychiatrist is to explore the nature of patient's suffering that would be so unbearable that death is preferable to the distress, fears, loss of control, and loss of self that patients may possibly face [99]. Sources of distress include uncontrolled physical symptoms, social factors including relationship problems, psychological disorders, and existential distress. Many patients fear uncontrolled physical symptoms, especially at the end of life [100]. Assessment and effective management of physical symptoms including pain, dyspnea, and nausea reassure patients that their care providers are available and committed. Life-threatening illness creates strains in relationships and further intensifies already frail relationships. Many ill patients are concerned about being a burden to their families as it relates to caregiving responsibilities, finances, and ultimately fear of abandonment. Grief,

depression, anxiety, cognitive impairment, personality disorder, and substance use disorder may also contribute to a patient's desire for hastened death [99, 101]. Finally, existential issues such as loss of dignity or meaning, anxiety about what happens after death, or belief in the existence of a higher power can contribute to requests for hastened death [102]. In an epidemiological review of suicide in later life, older adults who identified ill health as a precipitant for suicidal ideation were more likely to die by firearm, suggesting that viewing suicidal ideations as inherently pathological and psychiatrically aberrant limits our understanding from an existential approach that takes into account impaired quality of life in their actions if these individuals were given the option of physician-assisted death [103].

While therapeutic interventions seek to mitigate suffering, several points prevail. First, many patients in the advanced stages of terminal illness with intractable suffering are unable and/or unwilling to engage in any form of group psychotherapy. Second, some patients may reject the hypothesis that their suffering is a "failure to find meaning," further imputed to a human imaginal construct. For persons holding this point of view, pursuit of a peaceful death at a time and in a manner of one's own choosing is a reasonable choice and not an indication of suicidality or clearly defined psychiatric illness.

Teaching Point

Patient request for physician aid in dying or hastened death may stem from a number of reasons. Distinguishing the existential from a depressive desire for death can separate suffering from psychopathology.

Oregon and Washington were the first two US states to legalize physician-assisted death. Rather than use the term "physician-assisted suicide," the emphasis was placed on "death with dignity" to highlight how a terminally ill patient with intact decisional capacity can seek a lethal prescription to end his or her life in conditions of severe pain, suffering, debility, or poor quality of life. Terminally ill patients have a free choice predicated upon sound decision-making, ascertaining non-impulsive decisions, considering alternatives congruent with personal values, and evaluating the impact on others. The Canadian government recently passed federal legislation supporting "medical assistance in dying," the term adopted by the Canadian government rather than "physician-assisted death."

In North American states where physician-assisted death (or medical assistance in dying) has been approved, legislation specifies certain qualifiers for these patients (see Table 33.6). Patients must have a terminal illness (or a grievous and irremediable medical condition in Canada), have intact decisional capacity, and exempt from any contingent or proxy acts meaning that prescribed medications must be self-administered. A psychiatric evaluation is not mandatory although laws may specify that if a psychiatric disorder may be influencing decisional capacity, a psychiatrist or psychologist should be consulted for further evaluation.

Since the enactment of physician-assisted death in Oregon and Washington, numerous studies have been published examining the characteristics of patients who exercise this option. In Washington, out of 114 physician-assisted death inquiries, 44 (38%) did not pursue further evaluation, 30 (26%) initiated but did not complete the process, 40 (35%)

Table 33.6 North American states that have legalized physician aid in dying (medical assistance in dying)

State	Date passed	Legalization process	Residency requirement	Minimum age to request	Prognosis requirement	Number of requests to be made to health-care provider
Oregon	November 8, 1994	Voters approved by 51% majority	Yes	18	6 months or less	2
Washington	November 8, 2008	Voters approved by 58% majority	Yes	18	6 months or less	2
Montana	December 31, 2009	Montana Supreme Court hearing in *Baxter* vs. *Montana*	Yes	a	a	a
Vermont	May 20, 2013	State legislation approval	Yes	18	6 months or less	2
California	October 5, 2015	State legislation approval	Yes	18	6 months or less	2
Canada	June 17, 2016	Federal government legislation approval (Bill C-14)	Yes	18	No specific duration that the individual has to live	2

[a]Mandated by court decision

filled a prescription for secobarbital, and 24 (21%) died after secobarbital ingestion [104]. Patients were predominantly white, male, well educated, and diagnosed with cancer. The most frequently cited reasons for pursuing physician-assisted death included loss of autonomy (97%), diminished enjoyment of activities (89%), and loss of dignity (75%). There were no statistical findings to associate disease-specific symptoms or depression in patients seeking physician-assisted death. In Oregon where the Death with Dignity law is nearly identical to Washington's law, there have been 859 cases of physician-assisted death since the law was passed through the end of 2014 [105]. Terminally ill patients were most commonly diagnosed with cancer over 75%, followed by amyotrophic lateral sclerosis (8%); 90% were enrolled in hospice and 95% died at home. Decedents had a high educational level with a median age of 71 years. The requests for physician-assisted death were rarely based upon pain. The common reasons cited included the inability to maintain independence and control, minimizing dependence on others, and the desire to die at home. Three-quarters of Oregonians participating in physician-assisted death were assessed and ruled out to have a diagnosis of depression [106]. In Oregon and Washington, the rate of psychiatric evaluation requests has been historically low in comparison to overall physician-assisted death requests. While critics have called for mandatory psychiatric screening in all request cases of physician-assisted death, the expectations of such screenings remain a source of controversy with balancing autonomy of a vulnerable population versus casting psychiatric providers into the role of ethics consultants [94].

33.2 Case Studies

The following case-based studies reflect common scenarios patients with major NCD or life-limiting illness and their families face when functional status and quality of life decline. In each case, the role of palliative care is highlighted.

33.2.1 Case 1

Case 1 History

Mr. A. is an 80-year-old man with major NCD due to Alzheimer disease diagnosed 5 years ago. He was a former electrician who was previously an avid outdoorsman who vacationed at many national parks. He moved into an assisted living facility a year ago as his wife was having increased difficulty at home managing his wandering and agitation. During the past year, Mr. A. had three hospitalizations for recurrent aspiration pneumonia and a left hip fracture. Despite working with physical therapy, Mr. A. spent more than 50% of his time alternating between a chair and bed, resulting in a stage 2 pressure ulcer on the coccyx. He is admitted for the fourth time this year because of his refusal to eat and has lost 10 pounds in the past 2 months. On examination, Mr. A. is nonverbal and cachectic.

Mr. A.'s wife and daughter meet the palliative care team to discuss goals of care. His wife wishes for a permanent feeding tube to be placed hoping that it will reverse his weight loss, whereas his daughter is frustrated about the number of hospitalizations Mr. A. has had in the past year without any significant improvement. The consulting psychiatrist determined Mr. A. lacked decision-making capacity to consent for any invasive procedures, in part based on a MoCA score of 8. Prior to his major NCD diagnosis, Mr. A. wrote in his advance directive that he does not want to be kept alive artificially if his medical team determined there was no chance for meaningful recovery but made no specific mention about artificial nutrition. The advance directive designates his wife as the primary durable power of attorney for health-care decisions with his daughter as the alternate.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. Which should be the objectives identified in the meeting with palliative care team and the goals of care?

? Question 2. Based on this case with advanced major NCD, which changes in signs and symptoms help predict decline and aid in prognostication?

? Question 3. What is your response to Mrs. A.'s request for a feeding tube placement for her husband?

Case 1 Answers

Case 1 Answer 1 (Question 1—Which should be the objectives identified in the meeting with palliative care team and the goals of care?)

The palliative care team has multiple objectives in meeting with patients and families. The first is to ensure patient symptoms are appropriately managed. Uncontrolled symptoms such as pain or nausea can make the conversation about advance care planning difficult. Once patient symptoms are treated, the first step is to assess what patient and family know about their illness. Some patients and families may wish to have explicit and detailed information about prognosis including timeframe, while others prefer a general overview. The palliative care team provides important information about the trajectory of how a life-limiting illness can potentially lead to functional and cognitive decline. Through exploring patient values, it better understands how patient and family make medical decisions about the "what ifs," balancing hope while working on creating a care plan if complications or decline occurs in the future. It also explores if a patient is unable to make medical decisions for him or herself; the palliative care team will identify a legally recognized durable power of attorney for health care.

Case 1 Answer 2 (Question 2—Based on this case with advanced major NCD, which changes in signs and symptoms help predict decline and aid in prognostication?)

In the moderate to advanced stages of major NCD, the medical complications can often be as debilitating as the behavioral symptoms of the disease. Increasing frailty as indicated by progressive multisystems decline with the reduced ability to recover from acute stress is a hallmark of advanced major NCD. The more that patients spend time in bed, the more they become deconditioned. Patients with advanced major NCD are prone to dysphagia with subsequent risks for developing aspiration, pneumonias, and weight loss. In Mr. A.'s case, his bedbound status, falls, current aspirations, and weight loss all predicated a poor prognosis. Because major NCD is a terminal illness, the National Hospice and Palliative Care Organization recognizes infection, weight loss, and dependence on others for activities of daily living as primary factors for predicting a 6-month mortality in patients with major NCD.

Case 1 Answer 3 (Question 3—What is your response to Mrs. A.'s request for a feeding tube placement for her husband?)

The patient is in the advanced stage of major NCD. As discussed in ▶ Sect. 33.1.3, multiple medical complications can result from placing a feeding tube and create burdensome outcomes without significant improvement in terms of the quality of life of this patient. His bedbound status is unlikely to change, and artificial nutrition will not improve wound healing. A feeding tube also does not prevent aspiration or prolong life. Regardless of strong evidence against tube feeding, the role of the palliative care is not to persuade or dissuade wife from placing a feeding tube. Rather, the team helps the wife identify her goals of placing a feeding tube, explains how much a feeding tube may realistically meet or fail to meet her expectations, and explores how this intervention aligns or refutes with how the patient would define a quality of life. There are other means for helping the patient be comfortable such as careful hand-feeding if his wife forgoes feeding tube placement. Clinicians need to be mindful about placing a value judgment on how the patient and family define quality of life and, in this case, should focus on helping his medical decision-makers carry out Mr. A.'s values and preferences.

Case 1 Analysis Mr. A.'s behavioral and cognitive status contributed to his institutionalization in the earlier part of his disease. Medical complications related to the progression of his major NCD have led to increased frailty as evidenced by his repeated infections, falls, and frequent hospitalizations. Often families of patients living with major NCDs do not meet with palliative care team to discuss goals of care until functional decline becomes severe enough to require acute medical attention. In their meeting with Mr. A.'s wife and daughter, the palliative care team learned that Mr. A. valued his independence and outdoor activities. He was a man who disliked to sit even more than 5 minutes when he was healthy. His wife and daughter agreed that his quality of life in the past few years had declined substantially. With each hospitalization, the family noticed he had increasing limited mobility and became increasingly dependent on others for care. The family initially did not understand that Mr. A. had advanced major NCD, and the palliative care was able to discuss that his nonverbal status, repeated infections, weight loss, and bedbound status predicted a 6-month mortality. Therefore, the feeding tube, even if it were to be placed, would add little in prolonging his survival and likely lead to tube-related complications that could result in repeated hospitalizations. His wife and daughter agreed that further hospitalizations would add more burden and wished instead to focus on comfort-oriented measures. The palliative care team educated the family on how to hand-feed in lieu of tube feeds. The family agreed to hospice/end-of-life care for Mr. A. and avoided future hospitalizations.

33.2.2 Case 2

Case 2 History

Dr. S. is a 65-year-old widower, retired English literature professor without any past psychiatric history other than uncomplicated bereavement, with a past medical history significant for hypothyroidism and left frontal glioblastoma multiforme diagnosed 5 years previously. He initially presented with seizures to the emergency room and underwent a subtotal resection followed by radiation and chemotherapy. A few months after his diagnosis, his wife was also diagnosed with a glioblastoma multiforme and died just 6 months following her diagnosis. Following his wife's death, Dr. S. designated his 20-year-old daughter to be his durable power of attorney for health care. Dr. S. continued chemotherapy, remaining in remission for 5 years.

During the 5 years, he met with palliative care team intermittently to reiterate his goals of care that emphasized maintaining as much independence as possible functionally. At the time of recurrence, Dr. S. developed a profound nonfluent expressive aphasia that worsened under stress. In addition to his daughter, he had a supportive network of friends and family. With few treatment options other than symptom management, coupled with his worsening expressive aphasia, Dr. S. inquired into the option of physician-assisted death. Prior to his diagnosis of glioblastoma multiforme, Dr. S. was an excellent communicator and quite articulate, from which he derived a strong sense of purpose and meaning in his life. Further complicated by his rapidly deteriorating condition, he now faced the possibility of being rendered incapable of meaningfully participating in the physician-assisted death decisional capacity assessment.

Dr. S. discussed his wishes with his daughter, who was supportive of his goals. He was well known to both his treating primary and consulting physicians to whom he had expressed his wishes over time in relation to his goals of care and quality of life. Dr. S. pursued the required oral and written requests from his attending and consulting physicians, 15 days apart, as required by local state law. While both physicians were in general agreement with a 6-month terminal prognosis and believed the patient possessed the majority of the key elements for decisional capacity, he was referred for a

psychiatric evaluation to rule out worsening expressive aphasia due to psychological stress.

Dr. S.'s daughter accompanied him to his psychiatric evaluation. She expressed concern that her father's baseline aphasia worsened when he was under stress and asked to be present for the interview. As the evaluation attempted to rule out any element of coercion, the interview was conducted without the daughter present. Dr. S. was given the option to write his responses given his aphasia. The psychiatric evaluation was successfully completed with adequate time for the patient to express himself and allowed for modification of communications by various techniques such as hand and body gestures, cues, and various prompts. In meeting the benchmarks of decisional capacity, he was able to accurately recount from time of diagnosis various treatment regimens and disease progression without any current treatment options other than palliative care and hospice care. While pain was not a factor in his decision-making, his progressive inability to express himself and interact meaningfully, sense of loss of control and autonomy, and reliance upon others were significant factors in his decision-making. He shared the difficulties of witnessing his wife's decline and eventual demise with a similar disease process. He elaborated the inability to express himself far outweighed his prior history of headaches relative to his request, which alone would not have motivated him for such a request.

Dr. S. clearly did not meet criteria for major depressive disorder or exhibited any disordered thinking. Rather he was demoralized with his current state. His Patient Health Questionnaire-9 and Generalized Anxiety Disorder-7 scores were 5 and 3, respectively, indicating minimal depressive and anxiety symptoms over the previous 2 weeks. While his expressive aphasia precluded him from fully participating in the Mini Mental State Exam or Montreal Cognitive Assessment text, he successfully completed the salient aspects of the Frontal Assessment Battery, including the "Luria, Go/No-go" among other attentional tasks with his cognitive and neurological deficits correlating well with his left frontal lesion on brain MRI imaging, without evidence of leptomeningeal disease or other metastatic process. His medications consisted solely of levothyroxine. He denied any alcohol, substance, or tobacco use history. Laboratory studies were all within normal range. An electroencephalogram was normal without epileptiform activity.

After the decision to forgo any further treatment for the glioblastoma multiforme, Dr. S. opted to focus on comfort and aggressive symptom management with hospice support. With decisional capacity intact, Dr. S. was prescribed the lethal medication to end his life. He ingested the medication 3 months following his initial request surrounded by his family and close friends who were aware and supportive of his intentions and eventual outcome, with Dr. S. controlling the time and place of his death, and in accordance with his wishes and goals of care.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. What is the key difference between clinical depression and demoralization?

? Question 2. What statutes are shared between the Death with Dignity Act based in Oregon and Washington and California's End of Life Option Act?

? Question 3. In the case presented, what would definitively exempt this patient from receiving the lethal prescription under the Death with Dignity Act or End of Life Option Act?

? Question 4. What would likely be highest on the differential diagnosis if this patient had impaired attention?

Case 2 Answers

Case 2 Answer 1 (Question 1—What is the key difference between clinical depression and demoralization?)

In both clinical depression and demoralization in the medically ill, anhedonia, hopelessness, and a wish for hastened death can all coexist, with the latter based upon a life-threatening illness with no hope of improvement and which may worsen over time. Demoralization does not have a basis in disordered thinking influenced by depression or other psychiatric illnesses. Rather, it is based on existential despair that may be a plausible reason for patients to consider ending their lives. Demoralization is distinct from major depressive disorder with demoralization marked by distress and a sense of incompetence about the uncertainty in what direction to take. It can be viewed as a normal response to a stressor. Depressed patients experience anhedonia that inhibits action, even if they know which direction to take [49]. In the case, Dr. S. screened negative for depression and on clinical exam. His presentation is consistent with demoralization in light of his expressive aphasia, fear of loss of autonomy, and likelihood of dependence on others.

Case 2 Answer 2 (Question 2—What statutes are shared between the Death with Dignity Act based in Oregon and Washington and California's End of Life Option Act?)

For delineating the statutes shared between the Death with Dignity Act based in Oregon and Washington and California's End of Life Option Act, please refer to ◘ Table 33.6.

Case 2 Answer 3 (Question 3—In the case presented, what would definitively exempt this patient from receiving the lethal prescription under the Death with Dignity Act or End of Life Option Act?)

Despite a history of depression in Dr. S. the End of Life Option Act in California and the Death with Dignity Act in Oregon and Washington do not mandate psychiatric evaluations with every request. However, in cases where a

psychiatric illness is suspected to influence decisional capacity, the law specifies that a psychiatric assessment is required. The law also specifies medications prescribed to end one's life are to be self-administered. Therefore, the patient's inability to self-administer and ingest the medication would exempt Dr. S. from receiving the lethal prescription under these respective laws.

Case 2 Answer 4 (Question 4—What would likely be highest on the differential diagnosis if this patient had impaired attention?)

In the cases of an expressive aphasia, Alzheimer disease, or major depressive disorder, attention is generally not impaired. Expressive aphasia impairs language and the ability to communicate in either verbal or written form. Alzheimer disease is an irreversible, progressive brain disorder that slowly destroys memory and thinking skills and eventually the ability to carry out the simplest tasks without compromising attention. While severe major depression can result in impaired concentration, attention is generally intact, often associated with psychomotor retardation. However, delirium is a common presentation of impaired attention. Mr. S. is at high risk for delirium given the presence of a primary brain tumor. He also has a history of hypothyroidism which may also impair his attention if not treated appropriately.

Case 2 Analysis Dr. S. met four key criteria for decisional capacity for physician-assisted death per Appelbaum [107]: (1) understand relevant information, (2) appreciate a situation and its consequences, (3) rationally manipulate relevant information, and (4) communicate a clear and consistent choice. He demonstrated a clear understanding of his current condition, recollecting key landmarks in his diagnosis and treatment course, weighing the risks and benefits in a rational manner, all of which were experientially informed by a wife who predeceased him with a similar medical condition. Fortunately, he had uninterrupted follow-up over several years with the same primary and consulting physicians with well-documented clear and consistent choices over time for treatment options and a lack thereof, with a primary focus on quality of life. He was consistent in the pursuit of an end-of-life option predating legal approval if there were no other treatment options available. (See ▶ Chap. 9). The primary challenge in assessing this patient for decisional capacity lies in his cognitive and neurological impairment (i.e., nonfluent expressive aphasia). The nature of this assessment demonstrates different roles for speech/language pathologists [108], neuropsychologists, and psychiatrists in the assessment. Clearly, this patient was not clinically depressed but rather demoralized. His demoralization stemmed from his expressive aphasia, coupled with an impending terminal condition with a high likelihood of further impairments including significant loss of autonomy and control over his life. Dr. S. was transparent with family and friends and consistent with his goals of care without concerns for coercion.

33.3 Key Points: Palliative Care for Geriatric Psychiatric Patients with Life-Limiting Illness

- Palliative care is a patient-centered care, supporting patients with life-limiting illnesses from the time of diagnosis to the end of life.
- Major NCD is often overlooked as a terminal diagnosis as cognitive and behavioral symptoms dominate the early part of the disease trajectory. As the disease advances, a number of physical complications may warrant hospitalization or invasive treatments, depending on the goals of care. Palliative care prepares patients and families for potential complications while using goals of care to guide treatment.
- Goals of care and prognosis will determine the workup and management of delirium, depression, and anxiety. Immediate symptom relief may preclude an extensive workup.
- Collaboration with medical specialists, palliative care clinicians, social workers, and chaplains ensures that physical, emotional, and existential distress is optimally managed with medications that often are high risk (e.g., opioids, benzodiazepines, psychostimulants).

33.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ1. At what point would a palliative care consult be most helpful to patient and family in the normal disease trajectory of major NCD due to Alzheimer disease?

A. At the time of diagnosis.
B. Family is unable to care for patient because of behavioral problems.
C. Patient has been hospitalized four times in a 12-month period due to repeated infections.
D. Patient is bedbound and nonverbal.

Answer: A

While a palliative care consult would be appropriate for any of the scenarios above, palliative care can be most effective in the early part of the disease, especially at the time of diagnosis. Early palliative care involvement provides the opportunity for patients and families to identify patient values and preferences for care that will guide medical goals of care. The need for identifying patient goals is especially critical if diagnosed with a progressive disease that will likely impair patient decision-making capacity and communication abilities in the future. Goals are likely to change over time depending on patient cognitive and functional status. While such conversations are difficult, patients and families can be reassured that they are honoring patient wishes and families do not have to second guess themselves when

asked to make decisions once patients have been determined to lack decision-making. The patient in response D may be appropriate for hospice care. Palliative care is distinct from hospice, although many palliative care providers have expertise in caring for patients at the end of life. Therefore, the correct answer is A.

MCQ2. A 70-year-old man with a history of depression presents with chemotherapy-induced neuropathy involving his lower legs and feet. His depression is moderately controlled with sertraline although he had one relapse of depression in the past 2 years. He has no prior cardiac history. Which additional adjunctive medication would be most specifically indicated to help with neuropathic pain?

A. Bupropion
B. Methylphenidate
C. Nortriptyline
D. Mirtazapine

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Answer: C

TCAs such as nortriptyline are frequently used in the palliative care setting to treat neuropathic pain. Nortriptyline is preferred over amitriptyline in the geriatric setting since the former medication has fewer anticholinergic side effects than amitriptyline. While the other medications are appropriate adjuncts for treating major depression, they are not used to treat neuropathy. Therefore, the correct answer is C.

MCQ3. A 72-year-old woman is diagnosed with ovarian cancer. Her pain has been refractory to treatment despite usual medications. She presents to the psychiatrist for increasing anxiety around pain control and shares she has been increasing the use of hydromorphone more than what has been prescribed. She has a history of alcohol abuse in her 30s following the death of her child. Which of the following approaches is *not* acceptable for the psychiatrist to take as the next step?

A. Review the case with the patient's oncologist.
B. Check the state Prescription Monitoring Program.
C. Discontinue hydromorphone and start short-acting morphine.
D. Obtain a urine drug screen.

Answer: C

While an opiate rotation may be indicated for refractory pain, additional information needs to be obtained about the patient's current disease status, past and current substance use, and other possible drug diversion activity. The Prescription Monitoring Program may provide information about whether the patient has sought additional providers for opiates. The patient may benefit from starting a long-acting opiate to minimize the use of short-acting opiates. Therefore, the correct answer is C.

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Caregiver Burnout

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34.1 Background

34.1.1 Definition

Caregiver burnout is traditionally defined as the degree to which a caregiver's emotional or physical health, social life, or financial status has suffered as a result of caring for a relative with major or mild neurocognitive disorder (NCD), other neuropsychiatric conditions, or functional impairment. Caregiver burden has been extensively studied in patients with major NCDs, although it may affect any caregivers of patients with other neuropsychiatric disorders, including other illnesses manifesting with cognitive impairments, functional impairments, or isolated behavioral symptoms. This chapter will focus on the caregivers of patients with major NCDs, since the dynamics, recognition, and management of burnout among caregivers of patients with NCDs are fundamentally similar to those encountered among caregivers of patients with other chronic functional decline and neurologic and neuropsychiatric conditions.

Caregivers are often older adults themselves and particularly vulnerable to the physical effects of caregiving. Individuals are often exposed to chronic stress activation, increasing the risk of neuropsychiatric comorbidities such as depression or anxiety spectrum disorders, health problems including decreased immune system functioning, cardiovascular problems, and increased physical symptoms [1]. Chronic stress activation associated with caregiving is correlated with both the onset of new illnesses and also with accelerated disease progression among those who are already ill. Chronic mental and physical burden on caregivers may result in reduced quality of care of patients, which may worsen patients' health status and cause behavioral and psychological disturbances associated with NCD. Caregivers are at significantly increased risk of ending caregiving when their physical or emotional health declines to the point that they no longer are able to carry out the tasks required. Understanding the factors associated with caregiver burnout in each stage of cognitive decline, and related increasing care demands, should be informative not only for caregivers in order to alleviate caregiver burnout but also for healthcare professionals for effective NCD treatment in daily practice.

Caregiver burnout is a primary predictor for long-term care placement of patients. It is important to identify factors of burden on caregivers of patients with major NCDs living in the community to prevent early nursing home placement and deterioration of caregiver's health and reduce adverse health outcomes for patients [1]. Training opportunities provided for family caregivers have been shown to reduce the impact of caregiving on the delivery of effective care [2]. It should be noted that care demands placed on a caregiver continue to increase over time as a patient's illness, cognitive status, functional status, and behavioral symptoms progress over time.

Beyond the adverse effects on an individual caregiver's physical and emotional health, there are also adverse systemic effects that may extend to his or her employment and work productivity. Many caregivers report having to take less demanding jobs, to take early retirement, to turn down promotions, to lose job benefits, or to give up work entirely. Others are forced to take on debt to compensate for lower income or to pay for in-home supportive services [3]. Interventions to help the caregiver can lead to long-term improvements in caregiver depressive symptoms, social support, and stress appraisals and may delay nursing home placement for the patient while improving quality of life for both patient and caregiver [1].

34.1.2 Epidemiology

By some estimates, more than 15 million adults in the United States currently provide care to relatives, saving the healthcare system billions of dollars annually [4]. The National Alliance for Caregiving/American Association of Retired Persons (NAC/AARP, 1997) estimated that nearly one in four US households with a telephone contained at least one caregiver. According to the World Alzheimer Report (2012), there were approximately 36 million people suffering from major NCDs worldwide and that number is expected to increase to 66 million by 2030 and 115 million by 2050 [2]. (See ▶ Chap. 18). With NCD patients, as the disease progresses over time, so too does the level of caregiving required. The median survival time in Alzheimer disease patients is approximately 11.8 years, and the mean hours of care required increase from 13.1 per week for patients with mild NCD to 46.1 for those with more advanced disease; additionally, up to 90% of patients with major NCDs will be institutionalized before death [5].

Caregivers are most likely to be spouses (61%) than children (29%) or other relatives (11%) [6]. NCD caregivers are more likely than non-NCD caregivers to be spouses versus adult children (7.2% vs 3.1% spouses, 48.9% vs 52.8% adult children). Women constitute the majority of caregivers whether providing care for someone with NCD (72.5% female) or someone with another condition (68.1% female) [3].

According to some studies, racial differences exist between the prevalence of caregiver burnout across caregivers of different cultural and ethnic backgrounds. The REACH (Resources for Enhancing Alzheimer's Caregiver Health) study compared African American, Caucasian, and Hispanic caregivers and found differences for depressive affect and well-being, where African American and Hispanic caregivers reported less depressive affect and better well-being than Caucasians [5]. Reviews on race, ethnicity, and culture suggest that minority caregivers are generally less distressed than Caucasian caregivers, especially when the index of distress is depression. The results often reflect more resilience among minority caregivers but may also reflect different cultural meanings and expectations attached to caregiving or family structures.

Evidence has also suggested that a combination of loss, prolonged distress, the physical demands of caregiving, and biological vulnerabilities of older caregivers may compromise their physiological functioning and increase their risk for

physical health problems, leading to increased mortality [4]. Older spousal caregivers are more likely than non-caregivers not to engage in preventive health behaviors like exercise and are more likely to forget to take their medication. They also report not getting enough rest or time to recuperate from an illness [7]. In a 4-year prospective study, after adjusting for sociodemographic factors, prevalent disease, and subclinical cardiovascular disease, participants who were providing care and experiencing caregiver strain had mortality risks that were 63% higher than non-caregiving controls. The study concluded that being a caregiver who is experiencing physical or emotional strain is an independent risk factor for mortality among older spousal caregivers [4].

Risk Factors

There are a number of risk factors that contribute to an increased likelihood of caregiver burnout, including the amount and type of care required, characteristics of the patient and caregiver, and psychological aspects of the caregiver. Not surprisingly, patients who require higher levels of supervision and assistance with activities of daily living (ADLs) and instrumental activities of daily living (IADLs) are associated with greater risk of caregiver burnout [3]. Assistance with ADLs may include physical contact with a patient when helping him or her with transferring—getting out of a chair/bed, getting dressed, feeding, getting to and from the toilet, changing diapers, and bathing and showering. Assistance with IADLs may require a lesser degree of physical contact with the patient but may be time consuming or require increased help with supervision when managing finances, grocery shopping, housework/chores, preparing meals, organizing and administering medications, or arranging transportation. Morning care is often a period where more interaction between caregivers and patients occur and agitation or resistant behaviors are more frequent [8]. Overall, evidence consistently suggests that behavioral problems or psychological symptoms are the primary risk factors associated with caregiver burden and burnout [2]. Characteristics of a patient or caregiver also may contribute to higher risks of caregiver burnout. Patient characteristics that increase risk of caregiver burnout include [2, 9]:

- Lower education (the lower the education, the greater the burden)
- Lower cognitive functioning and functional status (the lower the cognitive and functional ability, the greater the burden)
- Behavioral disturbances (e.g., waking up at night for no apparent reason, pacing up and down, wandering behaviors, psychomotor agitation, aggressivity)
- Verbal aggressiveness (e.g., unwarranted accusations, verbally abusive, swearing, crying, inappropriate laughter)
- Memory impairment (e.g., asks the same questions repeatedly; loses, misplaces, or hides things; hoards things for no apparent reason)
- Motor aggressiveness (e.g., destroys property or clothing, makes physical attacks, throws food)
- Incontinence (urinary or fecal, diaper changes, clothing changes, bedsheet changes)
- Apathy (e.g., lack of interest, sleeps excessively during the day, resists IADLs/ADLs)
- Geriatric syndromes (e.g., sleep disturbances, problems with eating, vision and hearing impairments, gait and balance problems, fall risk, delirium/confusion, incontinence, skin breakdown)

Caregiver characteristics that increase risk of caregiver burnout include [1, 2, 10, 11]:

- Sociodemographic factors (e.g., Caucasian ethnicity associated with greater burden from caregiving than African American, Hispanic, and Asian populations)
- Comorbid medical conditions
- Premorbid relationship with patient, with better relationships negatively associated with perceived burden
- Comorbid depressive symptoms
- Anxiety symptoms
- Aggressiveness and authoritarianism toward patient
- Poor coping skills
- Poor social support
- Lower monthly income
- Sex (female)
- Lower educational level
- Cohabitation with patient

Psychological factors that increase subjective reports of caregiver burden include negative conceptualizations or cognitions related to the caregiving experience. For instance, when a caregiver perceives the act of providing care for a family member negatively, such as "bearing a load" or "something that is oppressive or worrisome," research indicates caregivers who report a larger amount of subjective burden are at higher risk for negative health sequelae such as depression; therefore, subjective burden is important in predicting caregiver burnout outcomes [12]. Negative psychological conceptualizations may include caregivers describing their experience as [12]:

Hassle Minor events appraised as threatening to a person's well-being or as annoying or troublesome individually that can have minimal influence, but minor stressors may have cumulative effects, producing chronic stress. Assistance with ADLs may be conceptualized as a hassle by a caregiver and increases with behavioral disturbances.

Strain When a caregiver feels exertion is excessive, difficult, or exhausting, often in the context of multiple simultaneous demands such as cooking, assisting with toileting, and behavioral disturbances.

Stress Anything causing body or mental tension that alters one's sense of equilibrium. Perceived stress affects subjective burden.

Overall, each of the risk factors described previously has a cumulative and chronic adverse effect on a caregiver and contributes to a chronic stress response and worsening

negative conceptualizations, which ultimately increase risk of caregiver burnout.

Protective Factors

A number of protective factors have been identified to reduce subjective reports of caregiver burden and risk of burnout. Larger social support networks and better caregiver support resources are associated with significantly less burden, depression, greater life satisfaction, and fewer health problems than caregivers with fewer social contacts. Additionally, participation in caregiver support groups is associated with delaying long-term care placement [10, 13]. Psychological factors and positive conceptualizations of the caregiver experience have shown to mediate subjective reports of caregiver burden and outcomes. The following are examples of positive psychological factors shown to protect against caregiver burnout [12]:

Caregiver esteem Studies indicate caregiver confidence and satisfaction with oneself are inversely related to reported levels of depression.

Uplifts of care The act of caregiving makes one feel good, joyful, or satisfied. Research suggests feelings of uplift buffer the effects of hassles; when caregiver reports of uplifts outweigh hassles, caregivers report less distress and, consequently, burnout.

Caregiver satisfaction The effects of caregiving that give life a positive benefit have shown to relate to caregiver burden and contribute to positive or negative caregiver outcomes.

Finding or making meaning through caregiving The Finding Meaning Through Caregiving Scale was developed for use in assessing positive aspects of and ways of finding meaning through caregiving. Caregivers who are able to find higher levels of meaning had lower depression scores. The process involved expectations, explanations, and strategies.

Gain in caregiving experience This relates to the extent a caregiver conceptualizes the act of caregiving as enhancing or enriching his or her life, which is suggested to be related to caregiver's coping mechanisms and social support. Gains were found to moderate the effect of stress and negative effects.

Appraisal Appraisals of the caregiver regarding his or her abilities and of the caregiving situation in general have been proposed as mediators of burden and outcomes.

Overall, various protective factors have shown to have a positive effect on reducing risk of caregiver burnout. These factors underscore the importance of educating caregivers on the importance of developing broad social support networks, engaging with community support resources, participating in caregiver support groups, and practicing positive conceptualization frameworks.

34.1.3 Etiology

The etiology of caregiver burnout is largely multifactorial. It is influenced by a multitude of risk factors and protective factors that ultimately affect a caregiver's ability to sustain his or her caretaking responsibilities despite negative physical health, psychological health, and interpersonal and financial stressors. Some researchers have proposed the caregiving stress process model and likened caregiving to being exposed to a severe, long-term chronic stressor [14]. The caregiving stress process model suggests that adverse events lead to negative changes in a caregiver's life, leading to physiological changes associated with chronic stress via the hypothalamus-pituitary-adrenal axis. Chronic caregiver stress is associated with changes in endocrine and immune function, affecting physical and psychological health problems in caregivers [14]. Figure 34.1 shows the effects of caregiver stress on a caregiver [14]. Primary stressors placed on caregivers include the level of the patient's cognitive impairment, the frequency of patient problem behaviors (e.g., agitation, restlessness, wandering, aggression), the number of hours per week spent providing physical assistance with IADLs or ADLs (e.g., shopping, cooking, housework, finances, bathing, dressing, toileting), and the demands of helping a patient navigate the healthcare system (e.g., getting to appointments, medication adherence, insurance/administrative issues). Coping and social supports can mediate outcomes of burnout.

34.1.4 Clinical Presentation

Caregiver burden may present in different ways, typically affecting multiple domains related to physical health (e.g., fatigue, self-neglect, declining overall health), increased symptoms of depression or anxiety spectrum disorders, interpersonal changes between caregiver and patient (e.g., decreased intimacy, increased personal criticism, hostility, abuse), employment-related issues (e.g., missing work, taking extended leaves of absence, turning down promotions, giving up work shifts, early retirement), decrease in social activities (e.g., hobbies, vacations, leisure time, exercise), conflicts within the family (e.g., arguments about caregiving responsibilities, healthcare decisions, not contributing enough support), and financial strain (e.g., overspending on care costs, dipping into savings accounts, taking on debt to cover expenses) [3].

According to the Alzheimer's Association in the United States, there are ten symptoms of caregiver stress that may lead to caregiver burnout [15]:

1. Denial about the NCD disease and its effect on the person who has been diagnosed
2. Anger at the patient with Alzheimer disease or frustration that he or she cannot do the things he/she used to be able to do
3. Social withdrawal from friends and activities that used to make the caregiver feel good

4. Anxiety about the future and facing another day
5. Depression that breaks a caregiver's spirit and affects his or her ability to cope
6. Exhaustion that makes it nearly impossible to complete necessary daily tasks
7. Sleeplessness caused by a never-ending list of concerns
8. Irritability that leads to moodiness and triggers negative responses and actions
9. Lack of concentration that makes it difficult to perform familiar tasks
10. Health problems that begin to take a psychological and physical toll

Using a standardized consensus-recommended methodology, mistreatment and neglect by family caregivers have been detected in nearly half of patients with major NCDs living at home. Physical abuse was more likely to occur when the caregiver perceived higher burden, reported depressive or anxiety symptoms, or felt that his or her role was being limited due to caregiver's emotional problems. Physical or verbal aggression from the patient was also significantly associated with physical abuse. Neglectful caregivers were more likely to have a higher perceived burden and fewer social contacts, and low income and education further contributed to the likelihood of patient mistreatment [16]. These findings underscore the importance of assessing the caregiver's emotional state and perceived burden and, when found to be poor and high, respectively, warrant screening for physical and psychological abuse as well as neglect (see ► section Screening for Elder Mistreatment and Neglect).

Overall, there are no consistent specific physical findings associated with caregiver burnout that definitively help diagnose the condition. However, oftentimes, symptoms of declining caregiver health, depressive symptoms, and assessment of stressors may help clinically conceptualize caregiver burnout and guide management strategies to optimize caregiver functionality and patient outcomes.

34.1.5 Diagnostic Evaluation

Given the multifactorial nature of caregiver burnout and nonspecific physical exam findings related to the condition, taking a thorough clinical history is the first step in assessing for caregiver burnout. Research indicates caregivers who report a larger amount of subjective burden are at higher risk for negative health sequelae such as depression and that subjective burden is important in predicting outcomes [12]. An indication to assess caregiver burnout is not always apparent, since caregivers do not typically volunteer that they are feeling overwhelmed by caregiving responsibilities.

Clinical History

Obtaining a thorough history is critical. Caregiver burnout may present directly or indirectly depending on whether the patient presenting is the caregiver or the patient. In a general psychiatric evaluation, oftentimes, caregivers may present with a chief complaint of worsening depressive or anxiety symptoms. As part of a complete psychiatric examination, assessing for predisposing, precipitating, and perpetuating stressors may reveal caregiver responsibilities if a patient presenting does not volunteer this information. In the care of a dependent, older adult, geriatric medicine emphasizes the centrality of the physician-patient-caregiver triad and

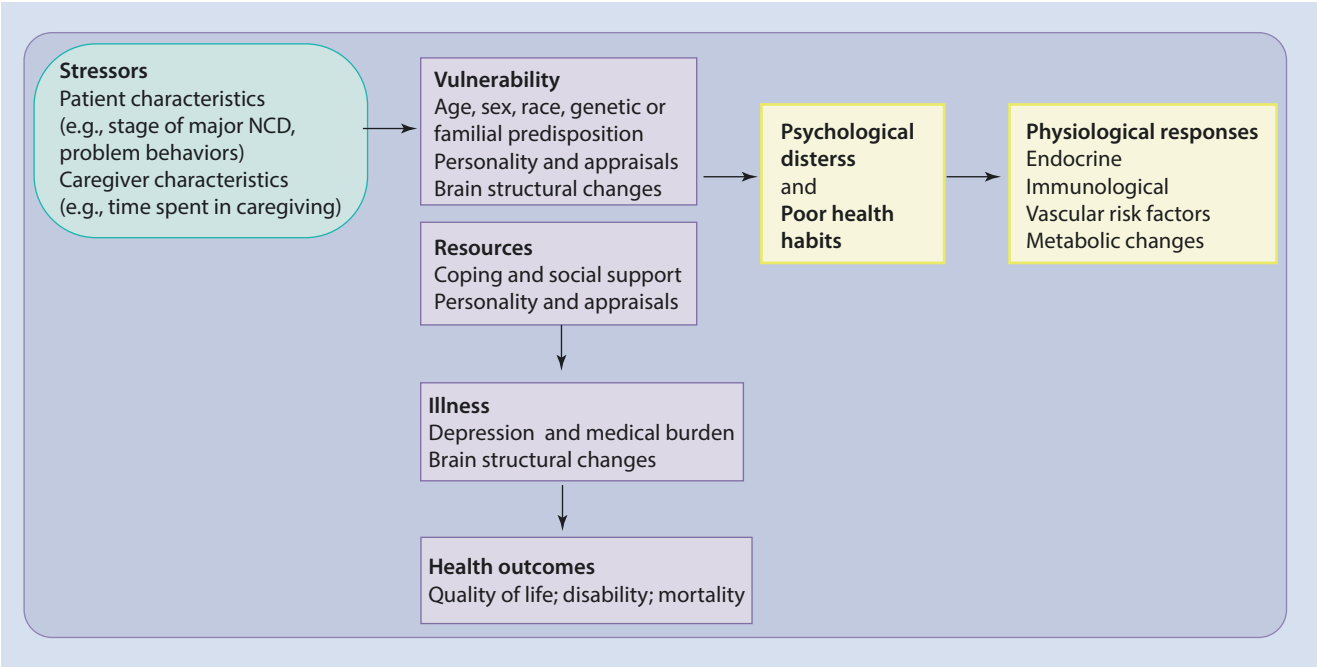


Fig. 34.1 The effects of caregiver stress on a caregiver [11] (Republished with permission of Future Medicine Ltd, from Lavretsky [14])

the importance of promoting caregiver well-being, even when the caregiver is not also a patient. If a patient presents for psychiatric evaluation and is accompanied by his or her caregiver, it is recommended to interview the patient and caregiver separately so as to obtain sensitive information that may not be appropriate to discuss with both persons present. To allay the patient's suspicion that the caregiver may be talking about them behind their back, the physician can create an excuse to remove the caregiver from the room (e.g., by ordering complete orthostatic vital signs by the nursing assistant). Sometimes it is useful to incorporate orthostatic vital signs into the routine nursing intake, providing approximately 10 minutes to interview the caregiver. When examining a caregiver, it is important to keep in mind that caregivers who report a higher subjective burden are at higher risk for negative health complications such as depressive disorders. When screening a caregiver for signs of burnout, topics to explore include employment-related issues (e.g., time off, leave of absence, reduced work hours), physical symptoms (e.g., worsening health status), emotion (e.g., worsening mood symptoms, irritability, attitude toward patient), role stress (e.g., lifestyle changes, given up vacations, hobbies, free time, exercise), financial strain, and family dynamics (e.g., increases in family conflicts over caregiving).

An example of a screening instrument for caregiver burnout is the Caregiver Strain Index [17]. It is a screening tool for caregiver burnout that may be used to quickly identify families with potential caregiving concerns. It is a 13-question instrument that measures strain related to care provision. There is at least one item for each of the following major domains: (i) employment, (ii) financial, (iii) physical, (iv) social, and (v) time. Positive responses to seven or more items on the index indicate a greater level of strain. It was developed with a sample of 132 caregivers providing assistance to recently hospitalized older adults and is appropriate for caregivers of any age [17]. ◘ Figure 34.2 lists the Caregiver Strain Index screening instrument [17].

Screening for Elder Mistreatment and Neglect

Mistreatment (intentional or otherwise) of the patients by caregivers can be a cause of psychiatric as well as physical morbidity. Elder mistreatment or abuse can take the form of physical mistreatment, psychological mistreatment, financial exploitation, neglect, or combinations thereof. Self-neglect is considered by many as a form of elder mistreatment because of the inability to provide for one's basic needs because of physical and/or mental disability.

Elder abuse is a serious reportable condition that may occur with patients with major NCDs due to their increased vulnerability and inability to recognize or report it. Caregivers who experience negative conceptualizations of their caregiving experiences are at increased risk for perpetrating elder mistreatment or abuse. It is worth noting, however, that not all elder abuse is associated with caregiver burnout; some caregivers are manipulative in mistreating older adults and are not necessarily "burned out" per se. It is also important to bear in mind that mistreatment of older adults by non-caregiving family members, persons in contact with the patient, manipulative business people, and other exploitative situations is always a possibility a clinician should be aware of when screening for mistreatment or when educating family members. Abuse may present in various forms including:

- Physical: causing physical pain or injury
- Emotional: verbal assaults, threats of abuse, harassment, and intimidation
- Neglect: failure to provide necessities, including food, clothing, shelter, medical care, or a safe environment
- Confinement: restraining or isolating a patient
- Financial: misuse or withholding of the patient's financial resources
- Sexual: touching, fondling, or any sexual activity when a patient is unable to understand, unable/unwilling to consent, threatened, or physically forced

Signs of abuse include [15]:

- Bruises, pressure marks, broken bones, abrasions, and burns
- Unexplained withdrawal from normal activities, a sudden change in alertness or unexpected depression
- Bruises around the breasts or genital area
- Sudden changes in financial situation
- Unattended medical needs, poor hygiene, and unusual weight loss
- Belittling, threats, or other uses of power
- Strained or tense relationships and frequent arguments between a caregiver and patient

For the clinician, identifying elder mistreatment or abuse can be challenging and often requires collaboration with the patient's primary care physician to screen for physical signs of potential abuse and neglect, such as poor hygiene, unexpected weight loss, bickering between the patient and caregiver while in the office, flinching or withdrawal by the patient when approached by the caregiver, and failure of the caregiver to join the patient in the examination room to provide collateral history. Important historical clues include deterioration of the patient's medical condition, such as worsening blood pressure or glucose levels, or more frequent exacerbations of previously controlled conditions like heart failure and chronic obstructive pulmonary disease. Failure to fill or renew prescriptions or obtain prescribed durable medical equipment can indicate neglect or, when copayment is required for these items, of financial abuse. Abuse of dependent older adults represents a significant risk factor for admission to the emergency department and hospital [18, 19]. Therefore, frequent emergency department visits and hospital readmissions should also raise suspicion about neglect. In the presence of concern about caregiver burnout, unexplained withdrawal of the patient from normal activities, a sudden change in alertness, or unexpected depression should raise suspicion of abuse. Other physical clues of abuse include:

- Unexplained rib fractures on a chest X-ray or other unexplained trauma.
- Unexplained burn marks.

THE CAREGIVER STRAIN INDEX

I am going to read a list of things that other people have found to be difficult. Would you tell me if any of these apply to you? (Give examples)

	Yes = 1	No = 0
Sleep is disturbed (e.g., because _____ is in and out of bed or wanders around at night).		
It is inconvenient (e.g., because helping takes so much time or it's a long drive over to help).		
It is a physical strain (e.g., because of lifting in and out of a chair; effort or concentration is required).		
It is confining (e.g., helping restricts free time or cannot go visiting).		
There have been family adjustments (e.g., because helping has disrupted routine; there has been no privacy).		
There have been changes in presonal plans (e.g., had to turn down a job; could not go on vacation).		
There have been other demands on my time (e.g., from other family memebers).		
There have been emotional adjustments (e.g., because of severe arguments).		
Some behavior is upsetting (e.g., because of incontinence; _____ has trouble remembering things: _____ accuses people of taking things).		
It is upsetting to find _____ has changed so much from his or her former self (e.g., he or she is a different person than he or she used to be).		
There have been work adjustments (e.g., becasue of having to take time off).		
It is a financial strain.		
Feeling completely overwhelmed (e.g., because of worry about _____; concerns about how you wil manage).		
Total score (Count yes responses. Any positive answer may indicate a need for intervention in that area. A score of 7 or higher indicates a high level of stress.)		

Robinson, B, (1983). Validation of a Caregiver Strain Index. Journal of Gerontology, 38, 344-348. Copyright @ The Gerontological Society of America. Reproduced by permission of the publisher.

Fig. 34.2 Caregiver Strain Index Screening Instrument [17] (Republished with permission of Oxford University Press, Journals of Gerontology; Analysis of the Reliability of the Modified Caregiver Strain Index, by Thornton M, Travis SS. 58(2), 2003)

- Unexplained bruises in places unlikely to be sustained in a fall (e.g., abdomen or chest wall). Although the sides of the arms and backs of the hands in older persons often sustain ecchymoses from benign, minor trauma, certain patterns of bruises and their location can raise suspicion. A circumferential bruise around the wrist or arm suggests forceful grabbing of the patient, and this suspicion should be increased when similar bruises are seen in different stages of evolution (e.g., a new violet ecchymosis plus an older, yellow bruise). Bruises on the insides of the legs or arms should not occur in normal activities.
- Bruises around the breasts or genital area may be a sign of sexual abuse.
- Presence of fecal or urinary incontinence, or an excessively soiled diaper, especially in the presence of skin breakdown or perineal rash.

The caregiver interview for possible abuse must be approached delicately in order not to alienate the caregiver and potentially remove the patient from important clinical monitoring, which can help to mitigate the abuse. Questions should be nonthreatening, neutral or sympathetic in tone, and be leading in nature. Examples include:

- "It must difficult changing your loved one's diaper so often."
- "Do you sometimes find yourself losing your patience?"
- "Do you ever feel that you can't take it any more?"

When aggressive behavior in the patient is reported, more directed questions can be asked:

- "What do you do when your loved one gets angry and throws things at you?"
- "Do you ever find yourself losing your temper at your loved one?"

The responses to these questions can give clues to behavioral interventions (see ▶ Sect. 34.1.6). Overall, safety and well-being are important priorities to keep in mind when assessing for caregiver burnout. Being vigilant for signs of mistreatment or abuse potentially may protect vulnerable patients from further harm and preserve their quality of life.

34.1.6 Interventions

Psychosocial interventions for caregivers could have a positive effect on measures of physical health such as acute hospitalization, stress-induced blood pressure reactivity, sleep quality, and immune function, which in turn may lead to improvements in caregiver depressive symptoms, social support, stress appraisals, and delay of nursing home placement [1]. Referring caregivers to engage with family psychotherapy, stress management classes, or caregiver skill training session is a way to engage caregivers proactively, since oftentimes caregivers do not typically seek out counseling, psychotherapy, or other professional assistance [20]. Unfortunately, the most stressed caregivers are commonly those whose caregiving responsibilities preclude taking advantage of the aforementioned support services. In these cases, the patient's visit to the physician may be the most expedient way to provide counseling and support to the caregiver in the context of the patient's visit. For clinicians concerned about nonreimbursable activities like telephone calls, these "extra" office visits provide valuable counseling time and are ethically justified by the previously described triadic nature of geriatric healthcare.

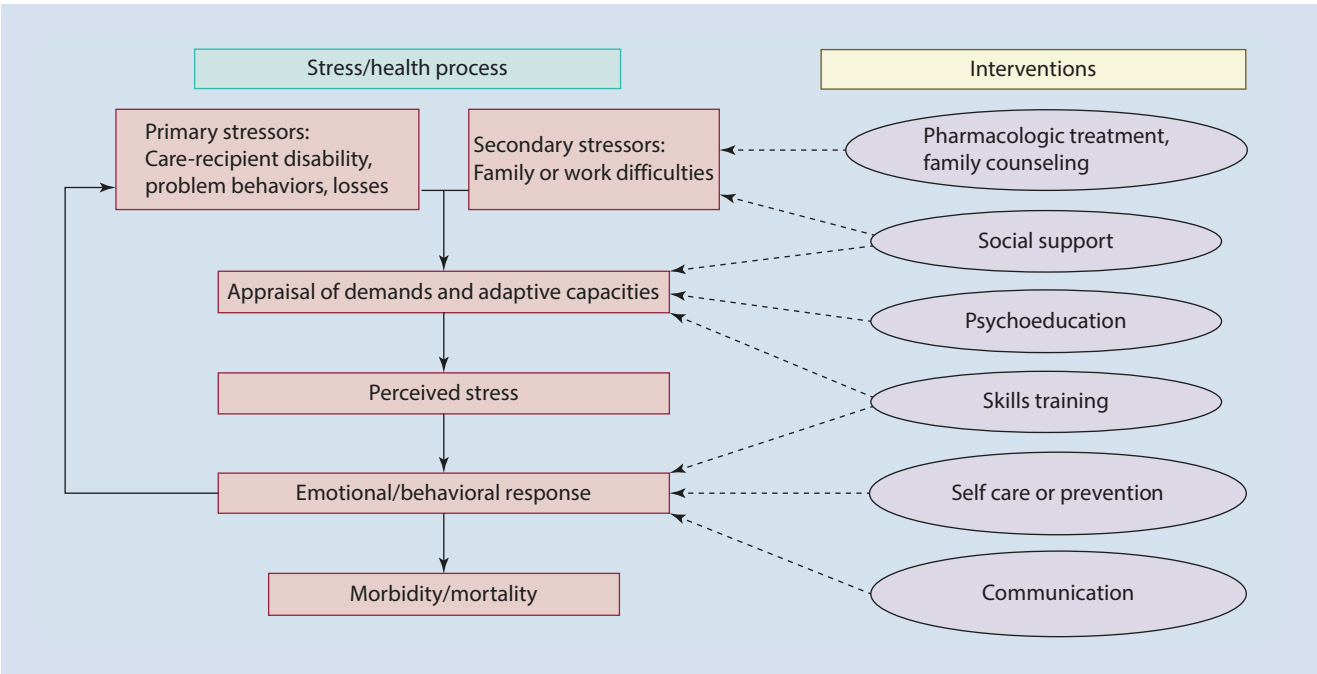
Current evidence suggests enhanced counseling and support consisting of individual and family counseling, support group participation, and continuous availability of ad hoc telephone counseling are associated with increased good self-rated health of caregivers and decreased ratings of burden; the effects of providing these interventions were significant after 4 months and continued for up to 2 years [1].

Recommendations from the Alzheimer's Association to optimize caregiver health include:

- Routine visits to a primary care physician to screen for changes in physical and mental health
- Exercising regularly to help relieve stress, prevent disease, and optimize mental health
- Eating healthy, such as the Mediterranean diet, to optimize physical health and to protect the brain
- Relaxation techniques and breaks from caregiver duties to reduce stress levels and allow for physical and emotional rest

Counseling and educating caregivers about major NCDs may help optimize psychological protective factors reducing risks of caregiver burnout. Counseling efforts shown to be effective focus on improving caregiver esteem, uplifts of caregiving, caregiver satisfaction, finding or making meaning through caregiving, finding gains in the caregiving experience, and caregiver appraisal of his or her abilities [12]. Overall, evidence suggests psychoeducational interventions may reduce direct caregiver burnout [8]. ◘ Figure 34.3 shows some important caregiver intervention strategies [14].

Referring caregivers to national or local caregiver websites and resources may help reduce burden and demands of



◘ **Fig. 34.3** Caregiver intervention strategies [11] (Republished with permission of Future Medicine Ltd, from Lavretsky [14])

providing care for patients with major NCDs. Services commonly used and shown to benefit caregivers include:

- Financial information service
- Support groups
- Temporary care service
- Adult day care/senior care
- Personal or nursing care
- Housework
- Meal services
- Transportation services
- Home modification
- Assistive devices

A list of resources for caregivers as well as any individuals concerned with elder mistreatment in the United States and Canada includes:

- Eldercare Locator: the U.S. directory of community resources. 800–677–1116. ► www.eldercare.gov
- Family Caregiver Alliance. 415–434–3388. ► www.caregiver.org
- Medicare Hotline. 800–633–4227. ► www.medicare.gov
- National Alliance for Caregiving. 301–718–8444. ► www.caregiving.org
- National Family Caregivers Association. 800–896–3650. ► www.nfcacares.org
- National Alliance for Mental Illness. ► www.nami.org
- Canadian Mental Health Association. ► www.cmha.ca
- Alzheimer's Association. ► www.alz.org
- Alzheimer Society of Canada. ► www.alzheimer.ca
- National Clearinghouse on Abuse in Later Life. ► http://ncall.us
- Provincial and territorial resources on elder abuse in Canada. ► www.seniors.gc.ca

Interventions for patients suggested to reduce caregiver burden include pharmacological interventions, cognitive and functional assessments, and attending adult day centers. Pharmacological interventions may help reduce behavioral disturbances associated with major NCDs such as insomnia, agitation, psychosis, or mood symptoms [2] but should be reserved in cases where behavioral therapies are unsuccessful. (See ► Chap. 22.) Obtaining cognitive and functional assessments may help identify deficits and guide assistance needs. ◘ Table 34.1 presents the list of ADLs and IADLs. Neuropsychological testing may be helpful to identify impaired cognitive domains to help a caregiver and clinician better understand care needs. Identifying troublesome or frequent patient behaviors using a standardized instrument like the Neuropsychiatric Inventory creates a basis both for assessing burden and developing therapeutic interventions [21]. Occupational therapy assessments may be helpful to guide assistance needs with IADLs and ADLs and help caregivers better conceptualize deficits and address potential safety risks. Adult day health centers can provide daytime respite for caregivers and provide patients with increased stimulation, physical activity, and social engagement.

◘ **Table 34.1** Activities of daily living and instrumental activities of daily living

Activities of daily living (ADLs)	Instrumental activities of daily living (IADLs)
Feeding	Using the telephone
Continence	Shopping
Transferring	Preparing food
Toileting	Housekeeping
Dressing	Doing laundry
Bathing	Using transportation
	Handling medications
	Handling finances

In summary, the care of the dependent older adult involves a triad of clinician, caregiver, and patient. Given the indispensable role of the caregiver in caring for the dependent older adult, the physical and psychological health of the caregiver must be balanced against "optimal" care of the patient. This sometimes entails ethical and clinical dilemmas, e.g., deciding to proceed directly to chronic use of a sedating antipsychotic for agitation and exposing the patient to an increased risk of mortality because starting a selective serotonin reuptake inhibitor antidepressant and gradually up-titrating it for optimum effectiveness would take too long. Preventing caregiver burnout entails the delicate balancing act of promoting the caregiver's well-being and the best medical care for the patient, even when the caregiver is not officially a patient.

34.2 Case Studies

The following case-based studies are reflective of the symptomatology and common presentations representing caregiver burnout and management strategies to mitigate the effects of burnout and optimize the health, safety, and quality of life of both the patient and the caregiver.

34.2.1 Case 1

Case 1 History

Ms. A. is a 50-year-old divorced Caucasian woman with no previous psychiatric history referred to psychiatry by her primary care physician for treatment of possible depressive disorder. Ms. A. initially presented to her primary care physician with chief complaint of lower left-sided back pain for the past 2 weeks with increasing intensity. She is the primary caregiver for her 80-year-old father with major NCD due to Alzheimer disease. She attributes her back pain to assisting her father getting out of bed in the morning and ambulation. Her primary care physician found a mild erythematous rash in the affected area. She was diagnosed with shingles and was managed appropriately. During her primary care evaluation, she was also found to be tearful and reporting feeling sad

and being under a lot of stress. She was, therefore, referred to the psychiatry service for management of her depressive symptoms.

During her initial psychiatric evaluation, Ms. A. reports she has been feeling sad for the past 2 months. She moved in with her father a year ago from another city with her 12-year-old son to take care of her father. She reports feeling very stressed, hopeless, and helpless most of the time. She feels guilty for feeling unable to give her son and her father the attention they "deserve." She previously enjoyed yoga every morning prior to her move but now is unable to practice daily yoga because she is afraid to leave her father home alone. She also reports diminished interests in previously pleasurable activities and also reports feelings of guilt when she spends time away from her father or son. She denies any changes in her appetite but reports difficulties falling asleep at night due to excessive worrying about her father since he fell 1 month prior in the middle of the night attempting to get out of bed without her assistance. She feels relieved her father did not have any medical complications from the fall but, nevertheless, constantly worries it will happen again.

Ms. A. reports that her father previously lived with Ms. A.'s mother until she passed away 1 year ago; since her passing, he has become increasingly more dependent on Ms. A. for ADLs and all IADLs. She finds it most difficult in the morning time when she has to help her son prepare for school and also assist her father out of bed and with getting dressed. She feels frustrated with herself due to losing patience with her father as he repeats questions often.

She works for an information technology company and feels thankful her company allowed her to maintain her previous job after moving by working remotely from home. However, she reports that she turned down a promotion to become the department manager, as she had to move. She enjoys her job flexibility as it allows her to stay home but acknowledges missing her old circle of friends. She has not been able to socialize since her move as she spends most of her days taking care of her father, working from home, and caring for her son after school.

Her initial psychiatric assessment is negative for any other psychiatric symptoms, any past psychiatric history, family history, or substance abuse. Her past medical history is unremarkable except her recent diagnosis of shingles. She does not take any other medications except for an opioid prescribed by her primary care physician for pain management. A Patient Health Questionnaire-9 (PHQ-9) score was 8 (subthreshold for major depressive episode).

At the end of her visit, you discuss her depressive symptoms and the possibility of caregiver burnout. She does not wish to start a new medication for management of her mood and sleep symptoms but is interested in a social work consultation and learning more about resources available in the community for coping with her father's condition.

Case 1 Questions and Answers

Case 1 Questions

? Question 1. What are the major risk factors for caregiver burnout in this case?

? Question 2. What are the pertinent aspects of this case that point to caregiver burnout?

? Question 3. What are the possible community resources available for Ms. A.?

Case 1 Answers

Case 1 Answer 1 (Question 1—What are the major risk factors for caregiver burnout in this case?)

The following are the main risk factors for caregiver burnout in Ms. A.'s case:

- Caucasian ethnicity
- Female sex
- Poor social support
- Anxiety and depressive symptoms
- Comorbid health conditions (infection and pain symptoms)
- Negative conceptualization of her caregiving abilities
- Decreased activities not related to caregiving
- Employment sacrifices due to caregiving responsibilities
- Cohabitation with patient
- Increasing demands on the amount and type of care required (some ADLs and all IADLs)
- Multiple responsibilities of caring for her young child while being the primary caregiver
- Father's worsening cognitive impairment
- Behavioral disturbances of the patient

Teaching Point

It is important to be familiar with the risk factors for caregiver burnout to help identify and delineate it from patients who may present solely with a chief complaint of depression or anxiety.

Case 1 Answer 2 (Question 2—What are the pertinent aspects of this case that point to caregiver burnout?)

Other than common symptoms of depression and anxiety, there are key aspects of this case that increase the likelihood of caregiver burnout. Ms. A. repeatedly describes feeling excessively stressed and frustrated due to her situation providing care for her father. She also reports feeling guilty and she does not enjoy yoga as she did before. Changes in her social activities and distance from her friends as a result of moving to a new city in addition to having to turn down a job promotion are key aspects of the history a clinician should consider when evaluating a patient for caregiver burnout.

Other than missing an important occupational opportunity, changes in work environment and having to work from home, interacting with others less frequently, and worsening health conditions all point toward caregiver burnout.

Teaching Point

In addition to recognizing caregiver burnout risk factors, it is also important to recognize signs and symptoms pointing toward underlying burnout to guide incorporating more focused screening tools such as the Caregiver Strain Index questionnaire. Diagnostically, this case could represent adjustment disorder given the context and temporal sequence of stressor and symptoms, with the symptoms being subthreshold for a more substantive neuropsychiatric illness (e.g., major depressive disorder). Unlike in a major depressive episode, management strategies to mitigate the risks of caregiver burnout may focus more on supportive and educational resources. The physician should also address possible problematic use of opioids, even if initially prescribed for a pain condition, in a patient with any emotional distress, and screen for surreptitious substance use disorder in this context (see ► Chap. 16 on substance use).

Case 1 Answer 3 (Question 3—What are the possible community resources available for Ms. A.?)

The following options may be considered in this case [15]:

A3.1. *Adult day care centers:* Adult day care centers provide a safe environment for patients with major NCDs who require care during the work days, providing a primary caregiver with brief respite to rest or manage other activities. Adult day care centers are appropriate for caregivers who work during the day, have other responsibilities, or also provide care to other family members.

A3.2. *In-home healthcare:* In-home healthcare may include a wide range of services including companion services, assistance with ADLs, housekeeping services, wound care, and skilled nursing care, while the patient in need of care remains home. In-home healthcare is appropriate for patients who are unable to leave home or to attend day care facilities on daily basis due to transportation difficulties.

A3.3. *Transportation services:* There are supportive transportation services that may provide transportation to patients with major NCDs to help relieve excess demands placed on caregivers. These services may help improve patient participation in adult day programs or medical appointments that otherwise may not be feasible, placing further responsibilities on a caregiver.

A3.4. *Respite care:* Respite care can provide caregivers with an option to temporarily rest and to manage other tasks, while patient continues to receive care in a safe environment. Respite care can be provided at home or at a designated facility by friends or other family members or by paid professional services. Respite care is appropriate for caregivers who may require more free time than provided by adult day centers. Respite care is available both in prescheduled settings and emergency situations.

A3.5. *Residential care:* If the patient in need of care requires more care than what may be provided at home, residential care may be a more reasonable plan. Residential care is appropriate for caregivers who are no longer able to remain the primary caregiver.

A3.6. *Hospice care:* Hospice care focuses medical attention on comfort and dignity at the end stage of life. Hospice care may be more appropriate for patients with advanced major NCDs or other terminal medical conditions.

Teaching Point

Being familiar with and referring caregivers to community resources is important in optimizing caregiver support and reducing progressively increasing demands placed on caregivers, ultimately reducing risk of caregiver burnout.

Case 1 (Continued)

During your initial evaluation, you make recommendations to Ms. A. to ask for help from other individuals in the family and friends for respite care if possible. You also advise her to maintain daily to weekly communication with old friends for emotional support, to exercise daily, and to devote some time every day to activities she enjoyed in the past and to spend some time outside of the home. You also refer Ms. A. to social work services. You advise her to discontinue the use of opioid pain medication and offer her a nonsteroidal anti-inflammatory drug instead.

At a 1-month follow-up visit, Ms. A. reports she met with a social worker to discuss financial resources and supportive services available in the community, local caregiver support groups, in addition to obtaining further education about major NCD and caregiver burnout. She reports her father now receives in-home healthcare services 3 days a week, during which her father receives care from a trained professional in addition to physical therapy. For the remainder of the week, a retired neighbor and an old friend of her father visit 2 hours a day. Ms. A. reports she has been able to utilize this time for a 30-minute walk every day and also to return to her yoga practice every morning. She reports feeling less guilty and is happy she is able to spend more time with her son. She also finds more pleasure in taking care of her father and feels she is a more effective caregiver. The in-home health services also assessed their home for fall hazards, and Ms. A. has made changes at home to reduce risk of her father falling, which gives her added peace of mind and stress reduction.

Ms. A. reports a significant change in her depressive and anxiety symptoms. She is able to sleep better at night and worries less often about her father having another accidental fall. She overall finds caring for her father a meaningful experience and is glad her son has an opportunity to spend more time with his grandfather. She feels less guilty about enjoying her time and finds herself more efficient caring for her family and fulfilling her job responsibilities.

Teaching Point

Recognizing negative conceptualizations in a caregiver's perception of caregiving and providing cognitive restructuring tools toward more positive perspectives may mediate risks of caregiver burnout. Education and support groups may help caregivers focus on uplifts of care, elements of caregiving that provide satisfaction, finding meaning through caregiving, identifying gains from the caregiver experience, and positive appraisals of caregiving.

Case 1 Analysis In Case 1, Ms. A. had a mixed clinical presentation of depressive and anxiety symptoms in the setting of multiple social stressors including providing care to her father with major NCD, single parenthood, and changes in her living environment. In addition to conventional symptoms of depression and anxiety, she also demonstrated some issues including feeling stressed and frustrated caring for her father, occupational changes and missing an important job opportunity due to her father's medical condition, and feeling guilty about enjoying her time and not being a proper caregiver for her father and son. During her evaluation, psychopharmacological approach was deferred, and instead she was referred to social work services for further caregiver education, support, and resources available in the community. She was advised to make changes in her daily routine to improve her stress management strategies. In a 1-month follow-up, she showed significant improvement in her symptoms due to decreased stress and better utilization of resources. This case demonstrates the importance of and impact of facilitating access to supportive care services in preventing and treating caregiver burnout prior to or in addition to medication management of depressive or anxiety symptoms of the condition.

34.2.2 Case 2

Case 2 History

Mr. B. is a 93-year-old man, with advanced major NCD due to Alzheimer disease and posttraumatic stress disorder (PTSD), currently being treated with donepezil 10 mg daily and sertraline 100 mg daily, who was brought in by his daughter for an initial geropsychiatry clinic examination due to agitation behaviors for the past 3 months. His daughter is 65 years old and is Mr. B.'s primary caregiver. She reports he is unable to sleep and is up yelling throughout the night. During the day, he is irritable and physically aggressive. When examining Mr. B. with his daughter present in the room, you observe she often will speak over him or answer questions for him. Noting this behavior, you decide to interview Mr. B. and his daughter separately and politely request Mr. B.'s daughter to step out of the examination room to minimize distractions, while you examine her father and that you will allow time to speak with her individually afterward as well.

Mr. B. appears calm and cooperative, is in reasonably good physical health for a 93-year-old, and describes his mood as "fine." He uses a wheelchair for clinic visits but is able to ambulate short distances and transfer with assistance. He is able to state his name correctly but is unable to correctly state the date or location. He denies having any memory problems despite documentation in his chart of major NCD. One year earlier, his Montreal Cognitive Assessment (MoCA) was 10 out of 30, losing points on visuospatial/executive functioning, attention, delayed recall, and orientation. You decide to recheck his cognitive functioning and now he scores 8 out of 30.

He is unable to provide meaningful responses to most questions and states "you'll have to ask my daughter, she takes care of me." He otherwise denies problems with sleep, interests, feelings of guilt or worthlessness, energy level, concentration, appetite, and psychomotor changes and denies suicidal or homicidal ideation. He denies auditory or visual hallucinations, and there is no delusional thought content. On brief physical exam, you notice he has a suspicious bruise on his upper arm, but Mr. B. is unable to state how or when it happened. You then do a thorough examination of the rest of his body and find no other abnormalities. You suspect there may be abuse potential and ask him if he feels safe at home or if anyone has hurt him. He responds that he feels "fine" and everything is "okay" at home, and so you move on to speaking with his daughter.

Mr. B.'s daughter enters the examination room, and Mr. B. is accompanied to the waiting room with supervision from staff member while he waits. His daughter immediately breaks down into tears, stating she "doesn't know what to do anymore." She expresses she recently had her father move in with her 3 months ago because she could no longer afford to pay for his assisted living facility; he had previously lived in the same facility for 2 years without problematic behavioral incidents. Mr. B.'s daughter reported that since his moving in with her, she has taken a leave of absence from work to care for him. She reports she has gone into debt from not working and trying to cover his living expenses. She reports her own health conditions have worsened and she cannot sleep anymore due to her father's nighttime agitation and yelling. You inquire what he says when he is yelling, and she reports that it sounds like, "he is on a boat under attack," which she believes is probably related to his military experiences as a young man, reminding you that he has a past diagnosis of PTSD. You screen for his functional status and discover that Mr. B. is impaired with all IADLs and requires assistance with most ADLs. When she is describing what he needs assistance with, the tone of her speech becomes irritable and

annoyed. You ask her if she has ever felt angry or frustrated with him, and she becomes tearful again. She states she feels that everything feels like a hassle, and his aggressive behaviors and nighttime symptoms are the biggest problems, "if only I could get some sleep, I wouldn't feel so overwhelmed." She expresses her concern about the future and feels anxious about not knowing what the future holds. You complete a full initial psychiatric assessment with the information the daughter provides and do not find any further pertinent information related to past psychiatric history, family history, medical history, social history, substance abuse history, or legal history.

At the end of the visit, you bring her father back into the examination room and counsel them both that you would like to start her father on a treatment with a cognitive enhancer, memantine, given his advanced stage of major NCD due to Alzheimer disease, and also treatment with prazosin at night for his nightmares. You also will refer her for a social work consultation to optimize supportive services and plan for the future.

Case 2 Questions and Answers

Case 2 Questions

? Question 1. What are common triggers for behavioral disturbances associated with major NCD you may screen for and counsel the patient about?

? Question 2. What are the signs of physical abuse to screen for with patients with major NCDs and what do you do if you suspect abuse?

? Question 3. What are future considerations to address with the caregiver to plan ahead?

Case 2 Answers

Case 2 Answer 1 (Question 1—What are common triggers for behavioral disturbances associated with major NCD you may screen for and counsel the patient about?)

Behavioral disturbances are commonly associated with major NCD, and as the disease progresses, so too does the risk for agitation. In this case, Mr. B. demonstrates he lacks insight into his cognitive deficits, which is referred to as "anosognosia." Oftentimes with patients with major NCDs, lacking insight to his or her condition leads to increased agitation behaviors. Behavioral disturbances may be physical or verbal and may be related to identifiable stressors or for no apparent reason. (See ▶ Chap. 22.) Common triggers may relate to patients experiencing physical discomfort, poor communication between a patient and caregiver, and environmental factors.

Regarding physical discomfort, it is important to assess whether a patient is experiencing any pain or other discomfort. Oftentimes, geriatric patients with major NCDs may have urinary tract infections, constipation, or pain symptoms. Due to their level of cognitive impairment, they may not be able to articulate their symptoms or complaints easily and may express it through physical aggression. It is helpful to counsel caregivers to be mindful of how frequently a patient is urinating or defecating to help inform whether there may be any changes from the patient's baseline that may suggest any physical discomfort. Also, regarding pain symptoms, it is important to note any grimacing or wincing expressions in a patient that may point toward physical annoyances that may be addressed to optimize comfort for the patient. Sometimes, there may be subtle signs that may point toward physical discomfort in a patient, such as an itch or tight clothing, and a caregiver should routinely note any restlessness in a patient's behavior or note any redness or skin irritations. Overall, behavioral symptoms, particularly if they are of sudden onset, should be documented, and patients should be followed up regularly with a thorough medical checkup to rule out any underlying medical conditions.

Poor communication is another factor that may contribute to behavioral disturbances in patients with major NCDs. Oftentimes patients with major NCDs do not comprehend complex instructions or when too much information is provided at once. Patients with major NCDs may pick up on other behavioral cues from the caregiver such as irritability or anger, which may lead to agitation behaviors. It is important to remain calm and positive when working with patients with major NCDs. When communicating, it is important to use simple and easy-to-understand language. Use shorter sentences. Ask one question at a time, and try to avoid asking compound questions such as "Do you feel tired or hungry? Do you have to use the bathroom?" Appreciating the level of cognitive impairment is important so as to meet the patient at the level of understanding he or she is capable of, so as to avoid overwhelming or confusing the patient further.

Environmental factors may also contribute to behavioral disturbances in patients with major NCDs. A chaotic environment may overstimulate a patient and lead to agitation or aggression. Loud noises, being around new people, rambunctious pets, televisions, and radios, all may contribute to disorienting stimuli for a patient with major NCD. Recent changes in living environment may make a cognitively impaired patient feel disoriented or lost, which may increase risk of anxiety or agitation. It should also be noted that many patients tend to function better during a certain time of the day; typically mornings are better than evenings. It is best to educate caregivers about planning activities such as bathing, eating, and grooming, around the patient's optimal alertness patterns. This may help reduce "forcing" a patient to do things when he or she is typically less alert or more resistant.

Sleep problems, such as a sundowning, are common behavioral problems in patients with major NCDs. "Sundowning" refers to behavioral disturbances that begin at dusk and last into the night, oftentimes affecting a patient's sleep patterns. According to the Alzheimer's Association, up to 20% of patients with major NCDs will experience increased confusion, anxiety, and agitation beginning late in the day. Others may experience changes in his or her sleep schedule and restlessness during the night. A disruption in a patient's sleep-wake cycle may lead to further behavioral disturbances [15].

Contributing factors may include end-of-the-day exhaustion, circadian abnormalities, reduced lighting, and increased shadows causing worsening confusion and fear in a cognitively impaired patient, or patients with major NCDs may display behavioral reactions to nonverbal cues from frustrated caregivers who are irritable after a long day. It is important to speak to a clinician to help rule out any other underlying causes for sleep disturbances and to consider prescription of a sleep aid to help normalize circadian rhythms and/or address nighttime sleep problems such as obstructive sleep apnea or (as in this patient's case) PTSD-associated nightmares. Other strategies to consider regarding sleep problems including sundowning involve keeping the home well-lit in the evenings, which may reduce dark areas or shadows that may increase fear and/or confusion with cognitively impaired patients. Maintain a schedule, and optimize consistent routines as much as possible to reduce confusion. Plan more activities during the day to keep a patient with major NCD active and alert. Patients who rest or nap during the day are more likely to be awake at night; engaging patients with adult day centers a few days a week is an appropriate way to stimulate patients during the day while providing respite for a caregiver to tend to other obligations and self-care. Avoiding stimulants or substances such as nicotine, alcohol, and caffeine will help reduce overactivation before bedtime, while avoiding big meals earlier in the day may reduce daytime somnolence [15].

Teaching Point

It is important to screen for and educate caregivers on common triggers for behavioral symptoms associated with major NCDs, which include patients who experience physical discomfort or pain, poor caregiver communication, aggravating environmental factors, sleep issues, and sundowning.

Case 2 Answer 2 (Question 2—What are the signs of physical abuse to screen for with patients with major NCDs and what do you do if you suspect abuse?)

Patients with cognitive impairment are particularly vulnerable to different types of abuse because they are often unable to recognize or report it. According to major NCD and mental health organizations, typical signs of abuse to look for during an examination of a patient or in observing how a caregiver interacts with a patient include [15, 22]:

- Bruises, abrasions, burns, pressure marks, and broken bones may suggest physical abuse or mistreatment.
- Belittling, threats, or other displays of power dynamics from caregivers may suggest increased risk of abuse when a caregiver is alone with a patient.
- Strained interactions, tense relationships, or arguments can be a sign of abuse and may warrant a thorough physical examination to rule out any abnormal physical findings suggestive of abuse.
- Bedsores or unattended medical symptoms, poor hygiene, or weight loss may indicate intentional or unintentional neglect from a caregiver and should be reported.

Overall, if there is any reasonable suspicion of abuse, whether physical, emotional, financial, or neglect, it should be reported to the local adult protective services division or to a long-term care ombudsman to ensure the well-being of a vulnerable patient. You do not need to prove that abuse is occurring, only that you have reasonable concern about a patient—it is up to the investigators to follow up and investigate any suspicions. If you suspect a patient is at imminent risk, it may warrant separation from a caregiver until further information may be obtained or alternative placement is arranged.

Teaching Point

When examining a patient with major NCD and his or her caregiver, being familiar with and confident in recognizing typical signs of abuse will help determine when to report reasonable suspicions of abuse while optimizing patient safety, well-being, and quality of life.

Case 2 Answer 3 (Question 3—What are future considerations to address with the caregiver to plan ahead?)

The role of being a primary caregiver for a patient with major NCD can be a very stressful and oftentimes unfamiliar responsibility. It is important to bear in mind that as a NCD progresses, so too do the demands placed on a caregiver. It is of utmost importance, then, to proactively plan for foreseeable stressors and complications in caring for patients with major NCDs. Avoiding planning for future problems often leads to unexpected crises when a caregiver is unprepared, increasing the likelihood of caregiver burnout. Planning ahead involves addressing legal issues, cost/financial planning issues, and creating a plan for when emergencies arise.

Making legal plans in advance, early in the course of disease, is important to allow a patient with cognitive impairment to participate in the process and to express his or her wishes for future care and decisions. This helps to eliminate family disagreements that may arise during a stressful time when a patient's health deteriorates. Advance directives enable a patient to designate who may make decisions on his or her behalf. Early planning allows time to work through complex legal and financial planning demands that may arise with estate planning or long-term care. Examples of legal planning may include living wills, trusts, powers of attorney, and code status. Engaging a patient when he or she is healthy and at an early stage of major NCD is a way to help preserve autonomy and dignity in a patient, rather than raising these issues during a time of stress and anxiety such as a hospitalization or acute decline in functionality.

The costs of caregiving can be overwhelming for caregivers who are unprepared and uninformed. Making financial plans early in the course of a diagnosis of major NCD may help to maintain a secure and healthy financial future for a patient's and caregiver's family. Meeting with a social worker may help educate a caregiver on common care costs to plan for. Costs commonly associated with caregiving in patients with major NCDs may include costs of follow-up medical care, medications, durable medical equipment, safety-related expenses such as home safety modifications, wander guards, personal care supplies, adult day care services, transportation services, in-home supportive services, or full-time residential care services. Anticipating the complexities of managing correspondence with financial institutions, insurance companies, estate/trust entities, billing agencies, investment/mortgage accounts, or other benefits a patient is identified with may help to reduce the adverse effects of dealing with these important complex financial responsibilities simultaneously during the end-of-life phase of a deteriorating family member.

Preparing for emergencies is helpful in reducing caregiver anxiety and empowering him or her to know what to do in case of a crisis. Inevitably crises will arise in the course of caring for a patient with major NCD. To help avoid a caregiver feeling powerless, unprepared, or overwhelmed during an emergency, having the following information consolidated, organized, and easily accessible will help avoid feeling powerless [15]:

- Phone numbers of the patient's healthcare providers (primary care physician, psychiatrist, psychotherapist)
- Family members and friends who can be supportive during an emergency
- Local crisis line phone numbers, which can be found on the Internet by searching "mental health crisis services" and the name of your county
- Addresses of walk-in crisis centers or emergency departments
- The contact for local suicide prevention services (the US National Suicide Prevention Lifeline: 1–800–273-TALK (8255); The Canadian Association for Suicide Prevention: ► http://suicideprevention.ca/need-help; The International Association of Suicide Prevention: ► http://www.iasp.info/resources/Helping_Someone)
- The patient/caregiver's address and phone number
- The patient's diagnosis, allergies, and medication list
- Previous suicide attempts, psychotic symptoms, and medical problem list
- History of substance use, including over-the-counter drugs
- List of triggers for agitation and behavioral strategies that help calm or distract the patient

It is helpful to keep multiple copies of this information, so it is readily available in any potential situation such as at home, in the car, or out in public. Properly preparing for the challenges associated with caregiving for patients with major NCDs not only may help to empower caregivers, but it also may reduce anxiety and resolve uncertainties associated with the progression of major NCDs.

Teaching Point

When managing a patient with major NCD, it is important early in the course of the disease to educate and counsel caregivers on the importance of planning ahead with issues such as advance directives, cost planning, and preparing for emergencies.

Case 2 (Continued)

At a 1-month follow-up visit, Mr. B. returned with his daughter. She notes that his agitation behaviors improved after starting treatment with memantine. Combined treatment with memantine and cholinesterase inhibitors has shown to be effective in patients with Alzheimer disease, particularly in slowing cognitive impairment and preventing the onset of agitation and aggression in Alzheimer disease patients [23]. She wonders if part of the problem was related to his not being able to sleep well before. Studies with prazosin have shown to reduce nightmare severity in patients with PTSD [24]. Fortunately, the patient's daughter reports since starting the prazosin treatment for his PTSD-associated nightmares he is able to sleep through the night and no longer stays up all night vocalizing. Mr. B.'s daughter also reports she was able to meet with a social worker since the last visit and was able to learn about future planning strategies and ask more detailed questions related to her stressful situation regarding financial and advance directives. Overall, Mr. B.'s daughter reports feeling less overwhelmed at the follow-up visit. She reports she is able to get a better sleep, her father appears more even-tempered during the day, and she feels more rested and less stressed as a result. She appreciates the changes and the referral to see a social worker. No further medication changes are made at the follow-up visit, but you refer Mr. B.'s daughter to national caregiver resource websites to continue to seek out further education and support regarding the challenges associated with being a primary caregiver.

Case 2 Analysis In this case, the patient, Mr. B., presents with his daughter who happens to be his primary caregiver. Oftentimes, a patient with moderate to severe major NCD may be accompanied by a family member who may or may not be the patient's primary caregiver. When managing any patient with a major NCD, particularly with functional disabilities and behavioral disturbances, it is important to be vigilant of who is the primary caregiver. Knowing who spends the most time with a patient, in turn, will help focus attention on assessing for caregiver burnout. Identifying warning signs is important to help guide management and optimize access to caregiver support, education, and resources; the duties of caregiving become increasingly more demanding and stressful with NCD disease progression. In this case, Mr. B.'s daughter displays financial strain, reporting she is going into debt. She experiences employment struggles reporting she has taken a leave of absence from work to care for her father, in addition to reporting that her own health conditions have worsened as a result of taking care of her

father. Lastly and most importantly, there are clear behavioral disturbances present in this case, which are the leading causes for caregiver burnout and institutionalization of patients with major NCDs [2]. Being familiar with common triggers for behavioral symptoms may make it easier to recognize and educate caregivers to reduce agitation behaviors. Recognizing and discussing common triggers and risk factors for agitation are important when communicating with caregivers early in the course of illness to reduce excessive burden of behavioral disturbances; treating preventable risk factors is key in optimizing caregiver well-being and reducing risk of burnout.

Also, being aware of who a patient's primary caregiver is may provide insight into who carries the highest risk for abusing a geriatric patient. In this particular case, there were subtle behavioral cues between the patient and caregiver interactions that raised suspicion of possible elder mistreatment or abuse before the physical exam finding was revealed. When Mr. B.'s daughter would speak over him, it represents a display of power dynamics, which may increase risk of abuse when she is alone with her father. Being familiar with and confident in recognizing typical signs of abuse will help optimize patient safety, well-being, and quality of life. As discussed previously in *Case 2 Answer 2*, red flags should be raised if you observe any suspicious physical findings (e.g., bruises, abrasions, burns, pressure marks), displays of power dynamics (e.g., interrupting, speaking over someone, belittling, threats), strained interactions (e.g., tense relationships, arguments), or signs of neglect (e.g., bedsores, poor hygiene, weight loss, unmanaged medical symptoms). Being familiar with signs of elder abuse and neglect will help determine when there is a reasonable suspicion for neglect and when to report concerns for abuse.

Lastly, this case discusses overall strategies to help caregivers plan ahead and avoid a crisis situation resulting from multiple simultaneous demands. It is important to consider that as major NCD progresses, oftentimes caregivers are consumed by daily responsibilities of attending to functional and behavioral demands of a patient and put off legal or financial planning. Oftentimes this is not done until the end stage of life when important legal and financial responsibilities become more pressing. This case highlights the importance of planning ahead with issues such as advance directives, cost planning, and preparing for emergencies. Preventing simultaneous stressors from piling up will reduce the risk of being unprepared during crises. Juggling the emotional stress of losing a family member, increasing care needs of advanced major NCD, and financial and legal demands with end-stage major NCD dramatically increase the risk of caregiver burnout and deprive a caregiver of a rich life-defining process of losing a loved one. Taking each of these points in this case into consideration not only will help reduce risk of caregiver burnout, but it may also help preserve a rich and meaningful experience created through the caregiving relationship.

34.3 Key Points: Caregiver Burnout

- Caregiver burnout is a primary predictor for long-term care placement of patients. It is important to identify factors of burden on caregivers of patients with major NCD living in the community to prevent early nursing home placement and deterioration of caregiver's health and reduce adverse health outcomes for patients.
- Care demands placed on a caregiver continue to increase over time as a patient's illness, cognitive status, functional status, and behavioral symptoms progress over time.
- A combination of loss, prolonged distress, the physical demands of caregiving, and biological vulnerabilities of older caregivers may compromise physiological functioning and increase risk for physical health problems, leading to increased mortality.
- It is important to recognize caregiver burnout risk factors in major NCD patients and in caregivers, which have cumulative and chronic effects on a caregiver and contribute to a chronic stress response and worsening negative conceptualizations, which ultimately increase risk of caregiver burnout.
- Educating caregivers on the importance of developing broad social support networks, engaging with community support resources, participating in caregiver support groups, and practicing positive conceptualization frameworks have shown to reduce risk of caregiver burnout.
- Caregiver burden may present in different ways, typically affecting multiple domains related to physical health, symptoms of depressive or anxiety disorders, interpersonal changes between caregiver and patient, employment-related issues, decrease in social activities, conflicts within the family, and financial strain.
- Diagnosis of caregiver burnout is achieved primarily through taking a thorough history. Caregiver burnout may present directly or indirectly depending on whether the patient presenting is the caregiver or the patient. In a general psychiatric evaluation, oftentimes caregivers may present with a chief complaint of worsening depressive or anxiety symptoms.
- Elder mistreatment or abuse is a serious reportable condition that may occur with patients with major NCDs due to their increased vulnerability and inability to recognize or report it. Being vigilant for signs of abuse potential may protect vulnerable patients from further harm and preserve their quality of life.
- Interventions for patients suggested to reduce caregiver burden include pharmacological approaches, cognitive and functional assessments, and social work referrals to utilize community resources. Referring caregivers to engage with family therapy, stress management classes, or caregiver skill training session is a modality to engage caregivers proactively, as many caregivers do not typically seek out counseling or psychotherapy or professional assistance.

34.4 Comprehension Multiple Choice Question (MCQ) Test and Answers

MCQ 1. Which of the following risk factors is the strongest predictor of caregiver burnout?

A. Increased functional assistance needs with IADLs and ADLs
B. Patient urinary and fecal incontinence
C. Worsening caregiver health conditions
D. Increased behavioral disturbances in the patient
E. Worsening patient cognitive decline

Answer: D

Although all of the above answer choices are risk factors for caregiver burnout, evidence has shown that increased behavioral disturbance in the patient is the leading predictor of caregiver burnout and early institutionalization of patients with major NCDs.

MCQ 2. Which of the following caregiver management strategies is associated with delaying long-term care placement of a patient?

A. Participation in caregiver support groups
B. Decreasing the number of hours of employment to spend more time caring for a patient
C. Moving in with a patient to improve convenience of caregiving
D. Allowing caregivers to vent about their frustrations of caregiving

Answer: A

Participation in caregiver support groups has shown to be associated with delaying long-term care placement of patients with major NCDs. Answer choices B, C, and D are not associated with lowering risk of caregiver burnout.

MCQ 3. Which of the following interventions is mandatory when managing a caregiver burnout case?

A. Referral to a social worker for supportive services
B. Providing respite care for a caregiver
C. Notify adult protective services for suspicious clinical findings of abuse
D. Prescribe antidepressant medication for a caregiver who complains of feeling stressed

Answer: C

As a mandated reporter, clinicians must notify adult protective services for clinical findings suspicious of abuse. Answer choices A, B, and D may all be recommended when working with caregiver burnout cases, but they are not mandatory interventions.

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Geriatric Telepsychiatry: Opportunities, Models, and Outcomes

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35.1 Background

35.1.1 Definition and Healthcare Context

Healthcare is being confronted with questions on how to deliver quality, affordable, and timely care to patients in a variety of settings [1]. Telemedicine increases clinical operating efficiency by getting the clinician's expertise to the point of service and coordinates teamwork for clinical, administrative, and informal care. Telemedicine (including telepsychiatry (TP)) adds versatility to service delivery by improving access to care, leveraging expertise of key disciplines to the point of service, and disseminating education [2]. Overall, telemedicine, cross-training, stepped care roles, and use of clinically "versatile" clinicians all help to fill "holes" in services for patients. Evidence-based treatment becomes more accessible, better disseminated, and in "real-time" with use of health technologies [3].

35.1.2 Epidemiology

The population of older adults in the USA continues to grow, with a projected increase from 40.3 million individuals over age 65 in the year 2010 to 72.1 million by 2030 and over 80 million by year 2050; the number of older adults with mental illness is also projected to rise commensurately [4, 5]. The proportion of older adults is growing faster than any other age group as a result of longer life expectancy. Older adults are particularly at risk for other health problems, have reduced access to appropriate care, and poorer self-assessment of their health; rural older adults are further disadvantaged relative to their urban counterparts [6]. Furthermore, families/caregivers are profoundly affected because over 75% of older adults are cared for at home [7].

35.1.3 Telemedicine and Telepsychiatry Evolution

Adult American Telemedicine Association (ATA) videoconferencing guidelines are helpful [8, 9], and steps are being taken toward a child and adolescent telemental health (TMH) guideline [10] based on input from the American Academy of Child and Adolescent Psychiatry. In TMH research and evaluation, there are areas that show steady progress (e.g., adult TP comparison to in-person care, models of care including asynchronous telepsychiatry (ATP), posttraumatic stress disorder, cultural and language applications), some that are rapidly growing (e.g., child and adolescent) and many that require much more emphasis (e.g., geriatric, emergency department (ED) TMH, forensic populations, inpatient) [3]. Areas needing more emphasis may be limited by many factors (e.g., size of the field, number of practitioners or researchers in that area, and system issues).

Geriatric data are emerging, but more studies are needed related to access to service, functional challenges, and primary care provider (PCP) attitudes [11]. There are many descriptive, non-randomized nursing home TP studies with positive outcomes, usually for depression or major neurocognitive disorder, and these show that consultant time is efficiently used [12]. Other assessment, cognitive intervention, and outcome studies—many done in medical settings—have direct in-person comparison groups with outcomes being equal (Table 35.1). In order for a TP program to be embraced, outreach to local PCPs, nurses, and other community healthcare workers is needed; a long-standing relationship between PCPs and a local geriatric MH outreach team is helpful [13]. A Canadian national survey of TP programs found that the number of geriatric consultations was low relative to adult and child/adolescent consultations [14].

Since older adults may reside in rural or nursing home settings, they often have physical limitations and/or have financial concerns. One of the best options for increasing access and leveraging specialist time for people in these situations may be telemedicine. Synchronous telepsychiatry (TP) has increased access to care in urban, suburban, and rural settings with high satisfaction even among people of different cultures [2, 3, 15] and by collaborative care [16]. Data on care for older adults are emerging, but more studies are needed in telemedicine and TMH, particularly in medical settings like nursing homes, which also lack adequate access to psychiatrists. Telehealth also facilitates education to healthcare professionals about specialty care.

35.1.4 Objectives

This chapter will help the reader to:

1. Learn and compare the TP evidence base versus in-person care for geriatric patients and settings.
2. Evaluate the pros and cons of TP models.
3. Improve clinical outcomes by coordinated care with primary care, interdisciplinary staff, and others through technologies.

35.2 Case

35.2.1 Presentation

History of the Present Illness A 72-year-old Mexican American man was referred by his PCP for "resistant depression," as he reported low mood, tearfulness, and a host of somatic complaints. Escitalopram was started at 10 mg/day, and after 4 months of treatment, his depression had persisted. The patient had missed some appointments without a clear explanation. He also had diabetes mellitus, hypertension, and a few miscellaneous physical complaints. The PCP was a Caucasian male in his 30s, a Spanish speaker, who saw all ages of patients in the rural clinic.

Teleconsultation The 60-minute evaluation was done by a 35-year-old "pinch hitter," a Spanish-speaking Mexican American female psychiatrist instead of the usual male

Table 35.1 Summary of telepsychiatric clinical/outcome studies for older adult patients (references for those mentioned in manuscript only)

Study	*N*	Location	Technology	Description	Comments
Nursing home					
Jones (1999)	2	USA	ISDN 128 KBS	Case reports	Able to provide care sooner and staff felt supported
Lee et al. (2000)	140	South Korea	T1	Prospective over 2 years: CDR, SBT, BDS	TP = in-person; nurses satisfied; caregiver distress reduced; improved patient behavior
Tang et al. (2001)	45	Hong Kong	ISDN 512 KBS	Prospective over 1 year	Satisfaction high with learning curve; some savings in costs
Johnston et al. (2001)	40	USA	ISDN 128 KBS	Descriptive study: MMSE	Satisfaction high; efficient use of psychiatrist's time
Lyketsos et al. (2001)	–	USA	Standard telephone	Descriptive study	Reduced hospitalization rate compared to past
Rabinowitz et al. (2004)	24	USA	ISDN 384 KBS	Pilot study: DCM	Satisfaction high; communication between providers and staff good
Yeung et al. (2009)	9	USA	ISDN 384 KBS	Descriptive study: CGI-I	Satisfaction high; significant improvement in 6/9
Rabinowitz et al. (2010)	106	USA	ISDN384 KBS	Descriptive study	Cost and time savings exceeded the start-up costs
Others					
Montani et al. (1997)	15, medical inpatient	USA	Coaxial cable	TP vs. in-person: MMSE, clock drawing	Nearly equal, with 0.95 correlation; all preferred in-person, though
Menon et al. (2001)	24, medical inpatient	USA	Standard telephone	In-person (twice) vs. in-person/video: HDRS, GDS-15	TP as reliable as in-person
Grob et al. (2001)	27, veterans home	USA	ISDN 384 KBS	In-person (twice) vs. in-person/video: BPRS, MMSE, GDS	TP as reliable as in-person
Saligari et al. (2002)	20, primary care	USA	ISDN 384 KBS	TP vs. in-person: MMSE, GDS	Equal, with MMSE 0.9 and GDS 0.78 correlation
Shore et al. (2004)	16, veterans home	USA	T1	TP vs. in-person: DSM-IV, clock drawing	TP equal to in-person
Loh et al. (2005)	20, community population	USA	ISDN 384 KBS	TP vs. in-person: MMSE, GDS	Nearly equal with 0.8 correlation for dementia
Collum et al. (2006)	33, primary care	USA	–	TP vs. in-person: MMSE, clock drawing, digit span	High correlations (> 0.60) for all, though only 0.48 for clock drawing
Turvey et al. (2007)	118, home	USA	Home monitoring system	Screening for depression with PHQ-2	96.6% completed the screen; helped with triage and treatment
Sheeran et al. (2011)	19, home	USA	ISDN 384 KBS	Descriptive: DCM, English and Spanish	For severe depression, all patients improved to mild depression
Conn et al. (2013)	294, home	Canada	Not available	Initial evaluations: dementia, depression, and mild cognitive impairment	Patient, provider, and staff evaluations positive. Focus groups indicated that barriers and challenges were manageable.
Vahia et al. (2015)	22, home, mono- or bilingual Spanish	USA	DSL with 512 KBS	Testing done by both TP and in-person: neurocognitive testing, MMSE, clock drawing, Hopkins verbal learning test	Equal results, controlling for impact of sequential testing

KBS kilobits per second, *CDR* Clinical Dementia Rating, *SBT* Short Blessed Test, *BDS* Blessed Dementia Scale, *CGI-I* Clinical Global Impressions-Improvement Scale, *MMSE* Mini Mental State Examination, *DCM* Depression Care Management module, *PHQ-2* Patient Health Questionnaire-2, *HDRS* Hamilton Depression Rating Scale, *GDS-15* Geriatric Depression Scale-15, *BPRS* Brief Psychiatric Rating Scale, *DSL* digital subscriber line (a digital option) (Adapted from: Hilty DM [37]. With permission of Springer Nature)

Caucasian provider. The patient spoke of many medications by color, stating that they "all helped very much," but he did not know which one was for depression. When asked about adherence with the medication, he complimented his provider, but then asked with trepidation, "It seems like a lot of medications to be taking." The PCP joined in the last 10 minutes. with an interpreter to ask questions and discuss the treatment plan. The medication was restarted—or continued but to be taken every day—and an open dialogue was encouraged.

Follow-Up Adherence to medication and appointments was intact with the medication at follow-up at 2 months later (overall, month 6) with a partial response (leading to a dose increase), then again at 4 months (overall, 8 month) with full mood response at 20 mg/day and fewer somatic complaints. His number of scheduled appointments per year dropped from 9 to 3 the following year.

35.2.2 Case Analysis

There are several key elements to this case. There are patient-centered care principles, in finding a place, time, and context in which this gentleman could feel comfortable accessing care and sharing his concerns and preferences. In addition, telemedicine here is leveraging finite expertise—psychiatrist time, skill, and contextual understanding of the primary care setting as part of the larger subspecialty area of psychosomatic medicine—to a distant area with limited access. The focus on the patient and the provider—as the target for skill, attitude, and knowledge development—is not to be underestimated.

Finally, there were at least three issues related to culture. First, there was not an ethnic, language, and cultural match with the PCP, which may have caused some anxiety. Second, there was a generational difference between the patient and PCP. Third, raising a question was seen as confronting an authority figure regarding the number of medications.

35.3 Telepsychiatry Evidence Base for Geriatric Medical and Psychiatric Populations

35.3.1 Evaluation of Geriatric Telepsychiatry

Evaluation of TP/TMH—overall—has gone through three phases, beginning with a review of its effectiveness in terms of increasing access to care, being well accepted, and having good educational outcomes [2]. Second, a transition—into validity and reliability of clinical care compared to in-person services [2]. The building of rapport relies on detection of nonverbal cues and openly paced conversation. In addition to comparison (or "as good as") studies, telepsychiatric outcomes are not inferior to in-person care (i.e., non-inferiority studies) [2]. Third, frameworks to approach its evaluation are helpful [8, 17] though costs/economic assessments are very complex [3]. TP has been used with a variety of models of care (i.e., collaborative care, asynchronous, mobile, telemonitoring) with equally positive outcomes [2, 3].

Since the concordance for culturally competent care is rarely possible, telemental health (TMH) and other e-mental health options may help [2]. Different approaches have been described to face many challenges of Hispanics/Latinos and Asians, Native American, Eastern European, and other populations (e.g., deaf patients using sign language). One model international project is launched care for ethnic minorities who had long waiting times (3–6 months at private practitioners and even 12–36 months at specialized centers for treatment of refugees and torture victims), a lack of bilingual resources, and services using interpreters [18]. Programming allowed patients to use their own language, enhance reliable assessment, and provide valid treatment. High satisfaction regardless of ethnicity or educational level was noted, and furthermore, all participants preferred TMH compared to in-person care with a translator, partly due to perceived higher anonymity, confidence/trust in providers, and self-efficacy to express intimate thoughts and feelings without a third person involved.

35.3.2 Patient Evaluation by Telepsychiatry

Geriatric TP starts with a good geriatric mental health history, which includes the patient's point of view and collateral information from all other stakeholders and medical providers [19]. This is largely dependent on where the patient generally resides and who cares for them (e.g., home, family and caregiver, nursing home, staff). Cognition, pain severity, physical and other limitations, and environmental factors that may affect assessment are important to understand. Screening of geriatric patients via self-report questionnaires or clinician-rated instruments (e.g., Patient Health Questionnaire, 9 items; Geriatric Depression Scale, 30 items) is virtually the same as for in-person assessments [20, 21].

The geriatric psychiatry evaluation via TP includes important additional items to consider with older adults [19], including:

- Pre-visit event summary: an accounting of general events and the patient's attitude, comments, complaints, sources of information, and clinician observations (e.g., olfactory/vision/hearing limitations, gait/balance problems, others) need to be communicated before the patient enters the room.
- The clinical examination, in general: this may require staff assistance (often a nurse facilitator) to complete, particularly if a patient is delirious, combative, or agitated, has a low level of formal education, or suffers from aphasia, poor hearing, or vision impairment.
- Cognitive examination: may require item substitution if clock drawing or sentence writing cannot be uploaded to view or be visually positioned in front of the camera; again, clinic staff are better in assisting in such situations so as to not answer questions for the patient.

- Physical examination: camera control at the far end enables easy wide angle, closeup, and focused viewing to detect tremors, micrographia, and other abnormalities, but on-site staff may need to be trained to check for extrapyramidal side effects such as cogwheel rigidity.
- Encouraging family member(s) to attend in general and when there is significant cognitive impairment can promote patient acceptance. Families are very welcoming of TP interventions and are grateful for the extra time and effort put forth to facilitate a TP encounter [12].
- It is recommended that most or all TP encounters for nursing home residents or elders in similar environments include a member of the social work staff to provide input on family of origin, family dynamics, and past family and social history [12].

35.3.3 Types of Geriatric Telepsychiatry Interventions

TMH to geriatric populations is increasingly common:

- Nursing home TMH non-randomized studies have demonstrated effectiveness for depression or major neurocognitive disorder, making evaluation easier and enhancing efficient use of consultant time [22].
- Assessment, cognitive intervention, and outcomes have been similar to in-person, and a new development is telemonitoring of depression in the home, which facilitates connectedness [12].
- One study showed that neurocognitive assessment via TP using a Spanish-language battery was comparable to in-person testing for rural Latino patients [23].
- Adding a geriatric nurse practitioner to an outpatient diagnostic multidisciplinary facility for patients with cognitive disorders may improve the primary care provider concordance rate of the advice from the decision-making tools and reduce subjective burden of the informal caregiver [24].
- Telehealth problem-solving therapy (tele-PST) for low-income homebound older adults in a 6-month, randomized controlled trial showed that both tele-PST and in-person PST reduced depression and disability, but tele-PST outcomes were sustained significantly longer than those of in-person counterparts [25].
- An integrated telehealth care for chronic illness and depression in geriatric home care patients compared in-home nursing with education to a telehealth nurse intervention (conducting daily telemonitoring of symptoms, body weight, and medication use; providing eight weekly sessions of problem-solving treatment for depression; and providing communication with participants' primary care physicians, who also prescribed antidepressants) [25]. Depression scores in individuals who received telehealth nurse intervention were 50% less at 3- and 6-month follow-up, with problem-solving and medical care self-efficacy improved as well.

35.4 Telepsychiatry Models: Pros and Cons

35.4.1 Introduction to Models

TMH models of clinical care and education have pros and cons, including their level of overall intensity, cost, feasibility, and depth of the relationship between the TMH provider, the PCP, and patient. These models can be conceptualized in three levels:

1. *Low-intensity* models include tele-education [26], formal case review, and in-person, telephone or e-mail doctor-to-doctor "curbside" consultations. A multi-specialty phone and e-mail physician-to-provider consultation system for adults and children with developmental disabilities used a 24-hour warm line [3].
2. *Moderate-intensity* models include an integrated program of MH screening, therapy on site, and telepsychiatric consultation (phone, e-mail, or video), with continuing medical education and training on screening questionnaires [3] or asynchronous telepsychiatry (ATP) to primary care in English- and Spanish-speaking patients in primary care [27, 28].
3. *High-intensity* models include implementing a disease management module for depression [29] and collaborative care for depression or posttraumatic stress disorder [16, 30] by TP. The collaborative care model uses a long-term approach to build relationships with PCPs through continuing education and medication co-management. Integrated care and TP are being more thoroughly evaluated [31].

Newer models involve new and old technologies. This is driven by consumers or persons at large, before they become patients in traditional services, and transitions our thinking from clinic-based care past patient-centered care to person-centered care known as participatory medicine [3]. MH-related, technology-based services exist on a continuum: self-help/support groups with well-prepared materials for patient psychoeducation and provider professional education tips for assessment and self-care (e.g., depression), informal provider consultation online, asynchronous communication with providers, MH services with professionals like teleMH (TMH) care, or Internet-based CBT [32]. Nationally, 79% of caregivers have access to the Internet, and of those, 88% search online for health information. Education (89% of those with a college degree vs. 38% who have less than a high school) and income (95% of adults with household income $75,000+ vs. 57% with household income less than $30,000) affect use [32].

35.4.2 Studies of Older Adults and Technology

Many studies—in MH and other fields—have demonstrated positive results and suggest technology will be used even more with older adults.

- Telehealth to "digital illiterate" patients (i.e., no interest in using, or capacity to use, computers and smartphones) found digital pens for daily reporting of their health state (in the form of a virtual health diary easy to use and caregivers felt that improved contact led to more "security" at home [33].
- Older adults may be challenged to use new technologies due to aging-related physical changes, lack of experience, and different attitudes toward their use. One-on-one training/instructions and use of a telemonitoring application help older adults and caregivers adapt to new healthcare technologies in the treatment of major neurocognitive disorders [34, 35].
- Nonmental health examples include geriatric (mean age 80) outpatients with heart failure with an average ejection fraction of 46%, randomly assigned to a telemonitoring system (oxygen saturation, heart rate, and blood pressure readings) vs. control over 6 months with office-hours telephonic support provided by a geriatrician. The program was feasible and hospitalizations and risk of death were reduced for the intervention group [36].
- A review of Internet-based interventions for medical and MH disorders showed that approximately two-thirds of open or randomized controlled trials reduce caregiver stress and improve quality of life [37]. Family caregivers located in rural areas found e-health support to be beneficial in comparison with conventional caregiver support. Interventions range from interactive communities to bulletin board therapy groups. The population of patients cared for varied from mental health (e.g., major neurocognitive disorder, schizophrenia, anorexia) to medical (e.g., older adults/aging, heart transplant, traumatic brain injury, hip fracture, cancer, stroke). Significant improvements in caregiver outcomes were detected while caregivers were satisfied and comfortable with various support services delivered via technology (e.g., cell phone). Services included webcasts, discussion boards, online classes, learning modules, and chat rooms.

35.5 How to Employ Telepsychiatry: Basic Information, Implementation, and Training

35.5.1 Basic Considerations

The main requirements for a clinical TP encounter are a room equipped with a computer processor, camera, screen, microphone and speakers, and a method of conveying the information between the respective TP stations. It is also useful to have a telephone if an interpreter with a common language is not available on site. There are a number of considerations when choosing equipment. In the past, cost was likely to be a limiting factor for videoconferencing services, but a proliferation of low-cost systems is now available dramatically reducing cost. Many services use computers with a built-in video camera, videoconferencing software (e.g., Skype Business, LifeSize Softphone), a remote control camera, and encryption safeguards. Additional options preferred by professionals are a mobile laptop computer with an external camera and microphone that can go from site to site or home to home. This also enables the healthcare professional to have consultation with a senior colleague.

The model that is most expensive, but in the exchange offers many more options without compromising with the quality, is the use of so-called "stand-alone" video cameras. While these are more expensive, they do not require additional use of computers and are more safe and stable. Stand-alone cameras should be connected to the TV screen and to the Internet. Typically, stand-alone video cameras may also be remotely controlled. This enables the telepsychiatry consultant to move the patient's video camera (e.g., zoom-in and zoom-out in order to observe body language or check for involuntary movements) during the consultation.

Development of a routine or protocol is suggested. This includes a brief discussion about the care, use of technology, and a few nuances as part of the informed consent process by the clinician or one of his/her designees. Most programs have written information about the service, which can be provided to the patient prior the TP encounter, with attention to clinical care, legal, privacy, and other issues. It is critical to assure patients that sessions are not going to be recorded and that the Internet connection is encrypted/safe. Written consent should be obtained, documenting that the patient is voluntarily involved with TP, as well as provisions for the patient to terminate the TP encounter at any point during the course of treatment.

35.5.2 The Telepsychiatry Interview

At the beginning of the each session, the patient should be introduced to any/all provider(s) at the distant TP station. Enabling a wide-screen view of the entire room will reassure patients of confidentiality in that no one else (out of camera range) is observing the interaction. If the patient speaks loudly, he/she should be informed that the microphone is sensitive and it is not necessary. Most community-based settings utilize a tele-presenter (often also the telemedicine coordinator) in the telemental health encounters for both quality care and for reimbursement requirements. The provider should determine the scope of the presenter's assistance before the session (with scheduling, paperwork, and socialization to the behavioral health system) and after the session (with implementing recommendations, facilitating referrals, and coordinating with the system of care).

If care is delivered in a traditional clinic setting, the TP provider shall alert staff to any identifiable risks to the patient's safety so that they can be aware of need to assist or notify security or other resources. On occasion, a presenter may be needed during the session (with technical and clinical support, including taking vital signs and assisting in emergency situations). The provider may decide when to include the presenter in the session (e.g., if the presenter is outside

of the room, the provider should determine how he/she will be contacted to join the sessions should there be a need for assistance).

Involved clinicians should receive preliminary training in the operation of the equipment. They should be aware of local policy regarding the actions that should be taken in the event of accidental equipment failure. In such case, clinicians should have the option to use the telephone and speak to the patient while technologic issues are being addressed. More detailed aspects of necessary clinician competencies will be reviewed later in this chapter.

35.5.3 Implementation Intangibles

A host of factors affect perception of the telepsychiatry visit and communication by participants [38]. This is particularly relevant when considering implementation for geriatric patient care. The presence of others in the room (e.g., family members, nurses, tele-coordinators) is important. Many patients feel they are being videotaped when they are not—a big deterrent to disclosure and spontaneity. Other important clues to the patient's challenges may be evidenced before they appear on screen: the time and behavior of the patient's arrival, conversations and other interactions with the telemedicine coordinator, and initial anxiety and distraction due to the equipment and/or self-consciousness seeing oneself on the screen.

The positioning of camera relative to the screen is an important factor. It is commonplace for the TP user to naturally look at the image of the person they are communicating with on the screen/monitor rather than directly into the camera (i.e., if the camera may be on top of the unit or elsewhere). This can give the impression to the remote viewer that the individual is not making eye contact. This happens even with laptop built-in cameras. In addition, a camera placed below the screen gives the remote viewer the sense that they are being "looked down on." It is common practice for the camera to be placed on top of the screen, and if the users sit a little farther away from the camera (approximately 2–4 m), this reduces the angle between eye, camera, and screen; this improves the impression of eye contact. The camera should be set up to capture a head and shoulders view for most interactions.

The room size, appearance, and layout are important and significantly influence the user's perception of the system. The room should appear as much as possible like a normal consulting room. It should preferably have windows for natural light and have adequate heating or air conditioning. Above all, it should be pleasant to use, as negative attitudes toward TP can develop based on experience of the working environment rather than on the quality of the interaction. This is particularly important for practitioners who spend a large part of their clinical day in TP. The room background should be plain and uncluttered. Too much backlight from a window will silhouette the appearance of the individual on camera, and background movement seen through a window or glass pane in a door will be distracting. The color of the background should be neutral although some still suggest blue-colored background.

The clinician should maintain a professional appearance even if practicing TP from home. Similar to television broadcasts, clothes with solid colors and, for gentlemen, ties without striking patterns are visually less distracting. Overall, telepsychiatrists may "need" to be an additional 15–20% more active and attentive, clinically and administratively, and in overall efforts to connect at a distance [38].

A critical variable in communication is telemedicine's ability to simulate real-time experiences, at least in terms of image and interaction. A speed of transmission of 384 KBS suffices for most encounters; the technology must be adequate for the clinical task at hand (e.g., on-site staff to address an emergently suicidal patient; engaging an on-site PCP, nurse or physician extender to assess for tremor). A concept that bears on communication is presence, defined as " . . . the fact or condition of being at the specified or understood place" [39]. The physical, virtual, and imagined environments affect presence. In a physical environment, informational cues may be incorporated into conversation without conscious awareness (e.g., a patient walks in a reticent way). Participants in the virtual environment created by telemedicine may not realize all cues in the physical environment. Therefore, being observant and listening carefully may be more important [38, 39]. Videoconferencing provides "enough" of the physical environment to facilitate decision-making one-on-one and a "social presence" for participants to share a virtual space, get to know one another, and discuss complex issues [40].

35.5.4 Training for Residents and Attendings

A call for training in TP has come forward from many. A survey of psychiatry residency programs reported 12 (26.1%) having a TP curricula and 21 (45.7%) with either formal or informal TP experiences [41]. In a national survey of psychiatry trainees published in 2013, 19% reported direct patient care experiences in telepsychiatry and 21% were offered didactic exposure. Only 18% of psychiatry residents and fellows reported providing direct patient care through telepsychiatry. However, 72% of the respondents were "interested" or "very interested" in telepsychiatry [42].

A survey of 270 physicians in psychiatric training programs throughout the USA, including 123 residents and fellows, was completed [43]. This included general psychiatry (54%), child and adolescent (33%), and other fellowships (13% forensic, geriatric, psychosomatic, and addiction). Geographically, 76% of responders were practicing in an urban setting, 5% practiced in a rural setting, and 19% were from both settings. Overall, the most common concerns and reasons that participants viewed TP as challenging, daunting, and/or difficult to implement were that the following:

- Poor Internet connection is a roadblock to implementing TP (52%).

- Liability risks involved with TP are unknown (47%).
- Certain cultures will be less accepting (39%).
- Nonverbal cues are missed (36%).
- Privacy is an issue (33%).
- TP is not as effective as to in-person psychiatry (32%).
- One cannot manage emergencies related to safety with TP (30%).
- Residency is insufficient for one to become competent in TP (30%).
- Paranoid patients do not like TP (26%).

The findings of this survey are in three distinct areas. First, interest in TP is high and increases with exposure. Second, education/training is not seen as adequate, but now with TP competencies and methods delineated, programs may add clinical experiences (e.g., via subcontract) and perhaps utilize online modules. Third, concerns of residents/fellows, program directors, and faculty members appear to shift perspectives based on exposure/experience, with increased interest and reduced concerns about effectiveness (e.g., nonverbal cues, engagement).

35.5.5 Skills and Competencies

Telepsychiatry has been integrated into clinical care with educational components being facilitated by the release of telepsychiatric competencies [44]—the first telemedicine competencies worldwide—based on Accreditation Council of Graduate Medical Education (ACGME) milestones movement and the evidence-based CanMEDS framework [45]. The competencies provide outcomes mainly in the form of skills, with suggested teaching, supervisory and program evaluation steps. For published TP competencies [3], a three-level stratification fit across disciplines and learner levels:

- Novice or advanced beginner (e.g., advanced medical student, early resident, or other trainees).
- Competent/proficient (e.g., advanced resident, graduating resident, faculty, attending, or interdisciplinary team member).
- Expert (e.g., advanced faculty, attending, or interdisciplinary team member).
- At the level of medical students, the American Association of Medical Colleges outcomes are evidence-based, including the domains of medical knowledge, patient care skills and attitudes, interpersonal and communication skills and attitudes, ethical judgment, professionalism, lifelong learning and experience-based improvement, and community and systems-based practice.

The ACGME specifies patient care, medical knowledge, practice-based learning and improvement, systems-based practice, professionalism, and interpersonal skills and communication competency domains. The CanMEDS framework describes the knowledge, skills, and abilities that specialist physicians need for better patient outcomes, based on the seven roles that all physicians play: medical expert, communicator, collaborator, leader, health advocate, scholar, and professional.

The most important area described in the TP competencies is patient care. It is divided into two parts: (1) clinical—history, interviewing, assessment, and treatment; and (2) administrative-based issues related to care—documentation, electronic health record, medico-legal, billing, and privacy/confidentiality. Systems-based practice includes outreach, inter-professional education, providers at the medicine-psychiatric interface, geography, models of care, and safety. Attitude, integrity, ethics, scope of practice, and cultural and diversity issues were grouped within professionalism. An additional domain, technology, was added to include some behavioral, communication, and operational aspects. Communication, knowledge, and practice-based learning are included for completeness, although many skills in this domain are similar to skills needed for in-person care.

35.6 Key Points: Geriatric Telepsychiatry: Opportunities, Models, and Outcomes

- Telepsychiatry is as effective as in-person care in terms of outcomes. It leverages a wide range of treatments at a distance to clinics, nursing homes, and patient homes.
- Geriatric TP is more similar to, than different from, in-person care and TP for other age groups.
- The clinician needs to consider the patient population, model of care, collateral sources of information, and a range of cultural issues including language.
- Geriatric patients are as open to using TP as other populations and report high satisfaction. Telemedicine innovations, in general, may be inroads for TP services for patients, providers, and caregivers.
- There is steady growth of the TP evidence base. More formal TP research studies and health services effectiveness studies are needed for geriatric patients in culturally diverse populations, team-based or interdisciplinary care, and stepped or integrated care inter-professional models.
- TP is effective and moving into mainstream care for all patients. Its clinical relevance is growing with many additional technologies that are reshaping service delivery. Indeed, TP is only part of a larger spectrum of clinical care based on how technology is now being used (the e-MH care spectrum), and competencies will grow in importance.
- TP competencies for trainees and clinicians grounded in healthcare, business, and andragogy will help learner objectives align with patient-based evaluation. Cross-sectional and longitudinal evaluation of nearly all participants is needed iteratively to improve the process. Exposure to TP care in training and opportunities for clinicians to train at the bedside or via interactive educational programs may yield a greater impact. Outcome, learner, and program evaluation that drives the training—rather than is tacked on to it—is needed.

- The institutional context is critical to the uptake of technology-mediated healthcare. Stakeholders have to be convinced that technology significantly contributes to patient care and population health in order to gain buy-in. If only one group champions the value of TP, adaptation of new competencies is unlikely.
- Leaders adapting to changes related to e-MH care may need to consider a change management plan to streamline clinical service delivery consider building/upgrading an integrated e-platform. Such a path considers current and emerging infrastructure like wireless options.
- Start-up, ongoing, and context-specific funding is crucial and the use of TP could leverage clinical resources (i.e., specialists, interpreters, social workers) and offset costs.

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Supplementary Information

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