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GERIATRIC DISORDERS (W MCDONALD, SECTION EDITOR)

Late-Life Psychosis: Diagnosis and Treatment

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Abstract Psychosis is one of the most common conditions in later life with a lifetime risk of 23 %. Despite its high prevalence, late-onset psychosis remains a diagnostic and treatment dilemma. There are no reliable pathognomonic signs to distinguish primary or secondary psychosis. Primary psychosis is a diagnosis of exclusion and the clinician must rule out secondary causes. Approximately 60 % of older patients with newly incident psychosis have a secondary psychosis. In this article, we review current, evidence-based diagnostic and treatment approaches for this heterogeneous condition, emphasizing a thorough evaluation for the "six d's" of late-life psychosis (delirium, disease, drugs dementia, depression, delusions). Treatment is geared towards the specific cause of psychosis and tailored based on comorbid conditions. Frequently, environmental and psychosocial interventions are first-line treatments with the judicious use of pharmacotherapy as needed. There is an enormous gap between the prevalence of psychotic disorders in older adults and the availability of evidence-based treatment. The dramatic growth in the elderly population over the first half of this century creates a compelling need to address this gap.

Keywords Late-life psychosis · Geriatric psychosis · Psychosis · Geriatric · Elderly · Dementia · Neurocognitive disorders · Schizophrenia · Delirium · Primary psychotic disorders · Secondary psychotic disorders · Psychotic disorder due to another medical condition · Delusional disorder · Schizoaffective disorder · Major depressive disorder · Bipolar disorder · Substance/medication-induced psychotic disorder

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Introduction

Ernst von Feuchtersleben has been credited with introducing the term "psychosis" in 1845 by combining the Greek "psyche" (life, soul, mind) and "osis" (an abnormal condition thereof), although Karl Friedrich Canstatt apparently used the term as early as 1841 [1]. In modern medical parlance, "psychosis," according to the International Classification of Diseases, tenth revision (ICD-10), "simply indicates the presence of hallucinations, delusions, or a limited number of several abnormalities of behavior, such as gross excitement and overactivity, marked psychomotor retardation and catatonic behavior" [2]. The *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) aligns with the ICD-10, stating that psychotic disorders are defined by "abnormalities in one or more of the following five domains: delusions, hallucinations, disorganized thinking (speech), grossly disorganized or abnormal motor behavior (including catatonia), and negative symptoms." [3••]. However, in the appendix, the DSM-5 defines "psychotic features" as characterized by delusions, hallucinations, or formal thought disorder.

Late-life psychosis is strikingly prevalent in older adults, presenting in 5–15 % of elderly geropsychiatric inpatients, 10 to 62 % of nursing home patients, and as high as 27 % of community-dwelling psychiatric outpatients [4, 5]. The lifetime risk for psychotic symptoms in the elderly is up to 23 %, with dementia being the main contributing factor [4, 5]. Despite its widespread prevalence in older adults, late-onset psychosis frequently remains a diagnostic and treatment dilemma.

Diagnosis and Treatment of Secondary Late-Life Psychoses

Psychoses can be either *primary* (caused by a psychiatric disorder) or *secondary* (due to a medical or neurological

disorder). About three fifths of psychotic disorders in later life are due to a secondary condition [4, 5]. The estimated prevalences of the conditions most commonly associated with late-life psychosis are listed in Table 1.

History and Physical Examination

Accurate diagnosis of psychosis in the elderly is of critical importance, particularly given the presence of serious medical conditions that may masquerade as psychotic illness [6••, 7]. Because there are no pathognomonic signs to easily distinguish primary from secondary psychotic disorders, a primary psychotic disorder is the *final* consideration following the elimination of secondary causes of psychosis [3••]. A careful history and physical examination are the sine qua non of the workup of a psychotic disorder. Moreover, no diagnostic evaluation of late-life psychosis should be considered complete without collateral history.

A variety of risk factors associated with aging make older adults more prone to psychosis [8•]:

- Sensory deficits
- Social isolation
- Cognitive decline
- Medical comorbidities
- Polypharmacy
- Age-related changes in pharmacokinetics and pharmacodynamics
- Comorbid psychiatric illnesses such as dementia and delirium
- Age-related changes in cerebral structures such as frontotemporal cortices
- Neurochemical changes associated with aging

Clinical presentations that should raise suspicion of secondary causes of psychosis include [9] the following:

1. Unusual age of onset of the presenting psychiatric symptoms
2. An absence of family history of mental illness
3. An absence of past psychiatric history
4. Limited response to psychiatric treatment
5. Symptoms more severe than might be expected
6. Psychopathology developed following an abrupt personality change
7. Comorbid medical condition(s) with a known association with mental illness (psychosis)
8. Abnormalities of cognition, particularly memory and consciousness

There is no consensus approach for the initial diagnostic testing of psychotic illness in young or old adults [6••, 10]. Most clinicians conduct a complete blood count (CBC) and comprehensive metabolic panel (CMP) but also add thyroid-stimulating hormone (TSH), vitamin B_{12}, folate, rapid plasma regain (RPR), and erythrocyte sedimentation rate (ESR). Autoimmune antibody screens, HIV testing, and toxicology may be done when indicated. Often, a head MRI or CT scan is done; EEG and polysomnography are done if indicated by history.

A useful way to think about the diagnosis of psychotic disorders is to use the "six d's" approach, that distinguishes disorders based on the timeline of their presentation (see Table 1). In the sections that follow, we address each of the "d's".

Delirium

Except for some minor rewording, the diagnosis of delirium in the DSM-5 has not changed from the DSM-IV-TR. It is a condition which often goes unrecognized and contributes to excess morbidity and mortality. A recent review by Inoue et al. noted a prevalence rate as high as 50 % among the hospitalized elderly in the intensive care unit [11••]. This same review and another recent meta-analysis by Witlox and coauthors [12] found that delirium had an appreciable impact on the relative risks of mortality, diagnosis of dementia, institutionalization, functional decline, and falls.

Perceptual disturbances are common during a delirium, with 40 to 70 % of elderly patients experiencing hallucinations

Table 1 "Six d's" of psychotic disorders [3••, 4, 123]

	Course	Proportion of all causes of psychoses	Type of psychoses
Delirium	Days to weeks	10 %	Secondary
Drugs, alcohol, toxins	Days to months	11 %	Secondary
Disease	Days to months	10 %	Secondary
Depression and other affective disorders	Weeks to months	33 % (depression) 5 % (bipolar)	Primary
Dementia	Months to years	40 %	Primary
Delusional disorder and schizophrenia-spectrum disorders	Months to decades	Delusions (2 %) Schizophrenia (1 %)	Primary

and 25 to 79 % experiencing delusions, depending on the subtype of delirium and the population being sampled [13••, 14, 15]. Psychosis is more common with patients experiencing the hyperactive variant of delirium; however, a recent study of oncology patients found prominent perceptual disturbances (50 %) and delusions (43 %) in hypoactive delirium [13••].

Factors that predispose to delirium include dementia, cognitive impairment, a previous history of delirium, a history of functional impairment, visual impairment, hearing impairment, comorbidities/severity of illness, depression, history of TIA/CVA, alcohol use disorders, and age >75 years [11••]. Importantly, a delirium episode is often the first sign of dementia. Rahkonen and colleagues [16] observed that dementia was diagnosed immediately after delirium symptoms had subsided in 27 % of patients and was present in 55 % of individuals on 2-year follow up.

The prompt diagnosis of the underlying etiology of delirium is essential. Validated screening tools for delirium such as the Confusion Assessment Method (CAM) and CAM-Severity (CAM-S) can be used [17, 18••]. EEG and neuroimaging need not be done routinely but should be ordered as indicated by the clinical features of a particular case. EEG has a typical pattern in delirium of diffuse slowing with increased theta and delta activity and poor organization of background activity, but this provides little insight into the underlying etiology [19]. Ordering an EEG may be most useful in difficult-to-evaluate cases, evaluating sudden deterioration in patients with dementia, and evaluating for non-convulsive status epilepticus or atypical partial complex seizures [11••].

Environmental and behavioral treatment strategies are best employed initially, with antipsychotic medications reserved only for severe agitation rather than as a standing medication [10]. If necessary, the best evidence suggests the use of oral or IM haloperidol or olanzapine for optimal patient outcomes and cost-effectiveness [20]. However, there is no FDA-approved pharmacologic treatment of delirium. Prevention and treatment strategies are covered extensively by guidelines (e.g., NICE, APA, and others) and recent review articles [11••, 21–24, 25•].

Disease

In DSM-5, all conditions attributable to other medical causes have been renamed from "[Condition] due to a general medical condition" to "[condition] due to another medical condition." [3••]. The DSM-5 diagnosis of a psychotic disorder due to another medical condition requires the presence of delusions or hallucinations that are attributable through history, physical examination, or testing to another medical condition [3••]. The diagnosis is further specified according to the etiology and whether it is "with delusions" or "with hallucinations." The prevalence is exclusive of delirium and dementia. History and physical and neurological evaluations remain crucial to accurate diagnosis and treatment. While physical and neurological examinations are non-specific for primary psychoses, they may point to a secondary etiology of psychosis or conditions that may be exacerbating the primary disorder [26]. Table 2 lists potential medical etiologies of late-life psychoses. The acronym "MINE," outlined in Table 2, is a useful mnemonic for recalling the principal medical etiologies. For an exhaustive reference on the diagnosis and potential causes of psychosis across the lifespan, we recommend the excellent book by Cardinal and Bullmore, *The Diagnosis of Psychosis* [27•].

Table 2 Common medical causes of psychosis in older persons [8••, 19, 27•, 123, 124]

Metabolic	• Vitamin B_{12} deficiency • Folate deficiency • Electrolyte abnormalities ○Sodium ○Potassium ○Calcium ○Magnesium • Acute intermittent porphyria • Hepatic encephalopathy • Uremic encephalopathy • Other nutritional deficiencies • Anoxia/hypoxia • Hypercarbia
Infections	• Meningitides • Encephalitides (e.g., herpes, etc.) • Neurosyphilis • HIV/AIDS • Pneumonia
Neurological	• Parkinson's disease • Epilepsy ○Temporal lobe epilepsy ○Grand mal ○Non-convulsive status epilepticus • Subdural hematoma • Cerebrovascular events • Huntington's disease • Multiple sclerosis • Amyotrophic lateral sclerosis • Tumors ○Temporal lobe—auditory hallucinations ○Occipital lobe—visual hallucinations ○Limbic—delusions ○Hypothalamus—delusions • Limbic encephalitides • Autoimmune[reference] ○Paraneoplastic syndromes ○Systemic lupus erythematosis ○Vasculitides • Sleep disorders (narcolepsy) • Other genetic/heritable conditions ○Likely to have been diagnosed in childhood
Endocrine	• Hypo-/hyperthyroidism • Adrenal disease • Hypo-/hypoglycemia • Hypo-/hyperparathyroidism

The treatment of these conditions should be based on addressing the underlying medical condition. Behavioral and environmental strategies should be first-line treatments for these psychoses; however, short-term treatment with antipsychotic medications may be indicated due to symptom severity. This treatment should be time limited and dose limited and medication choice tailored to the needs of the specific patient.

According to general expert guidance on medication choice in the elderly, for patients with major metabolic conditions (diabetes, dyslipidemia, obesity), it is best to avoid clozapine, olanzapine, and conventional antipsychotic medications [28]. In the case of congestive heart failure or prolonged QTc, clozapine, ziprasidone, and conventional antipsychotics should be avoided [28]. Risperidone (first line) and quetiapine (second line) are the medications of choice in cases with comorbid obesity, cognitive impairment, diabetes, diabetic neuropathy, xerostomia, xerophthalmia, or dyslipidemia [28].

Drugs, Alcohol, and Toxins

The problematic use of substances (illicit or prescribed) remains an under-recognized problem in the elderly [29]. While drug and alcohol use might continue to be less prevalent than in other age groups, the overall prevalence in the elderly is rising [30••, 31]. Recent predictive modeling estimates that the prevalence of substance use disorders in adults 50 and over (across genders, race groups, and age groups) will double from 2.8 million (average) in 2002–2006 to 5.7 million by 2020 [31]. This is attributable to the aging of the baby boomers who have a higher lifetime rate of alcohol and drug use than previous generational cohorts [31].

According to DSM-5, psychosis resulting from substance use is termed a substance/medication-induced psychotic disorder [3••]. Multiple substances have been associated with psychosis according to DSM-5. The diagnosis of a substance/medication-induced psychotic disorder is established by the presence of delusions and/or hallucinations and is attributable to substance intoxication or withdrawal through a plausible substance/medication mechanism [3••]. Screening for problematic drug and alcohol use is vital to accurate diagnosis in this population. The CAGE consists of only four questions but is a useful and validated tool for detecting alcohol misuse in elderly populations [32]. Urine toxicology should be conducted to evaluate for drug usage.

During *intoxication*, the following substances and substance classes are considered psychotogenic [3••]:

- Alcohol
- Cannabis
- Phencyclidine
- Other hallucinogens
- Inhalants
- Sedatives, hypnotics, or anxiolytics
- Stimulants (inclusive of amphetamine-type substances, cocaine, or other unspecified stimulants)
- Other/unknown substances

During *withdrawal*, the following substances/classes of substance have been implicated [3••]:

- Alcohol
- Sedatives, hypnotics, or anxiolytics
- Other/unknown substances

In theory, any medication that crosses the blood-brain barrier could induce psychotic symptoms; however, certain medications and classes of medications have been more commonly associated with psychosis [8••]:

- Antiparkinson drugs
- Anticholinergic drugs
- Cimetidine
- Digoxin
- Antiarrhythmic drugs
- Corticosteroids
- Interferon

There are no controlled studies on the treatment of substance/medication-induced psychotic disorders in the elderly. Whenever possible, the safe withdrawal (or dosage decrease) of the offending substance/medication should be initiated as first-line treatment. Psychosocial interventions should be encouraged such as motivational enhancement therapy, CBT, and support groups for substance cessation although many of these approaches are not validated in the elderly population [33••]. Of the pharmacologic approaches for substance cessation, naltrexone has the most evidence supporting its use in the elderly [33••].

Dementia (Now: Neurocognitive Disorders)

Psychosis is found most commonly among persons with neurocognitive disorders. In the instances in which patients present with cognitive changes and psychotic illness, reversible causes of cognitive decline and associated psychosis must be addressed initially. Moreover, during the evaluation of a neurocognitive disorder with psychotic symptoms, careful attention must also be paid to the presence of sensory deficits, particularly visual impairment, that may contribute to the presence of psychotic symptoms [34•].

There have been extensive changes in the DSM-5 nomenclature [3••]. Previously called "dementias," the neurocognitive disorders are classified according to neurocognitive domains and the characteristic deficits of these

domains within specific disorders. Deficits must be present in at least one of the following neurocognitive domains:

- Complex attention
- Executive function
- Learning and memory
- Language
- Perceptual motor
- Social cognition

The diagnosis has been subdivided into "major" and "mild" forms. The diagnostic criteria of a major neurocognitive disorder are based on a significant decline of cognitive function from the previous level of performance in one or more of the cognitive domains whereas mild neurocognitive disorder requires a less severe decline in at least one neurocognitive domain with no appreciable decline of function.

The prevalence of psychotic symptoms in Alzheimer's disease ranges from 16 to 70 % (median 37 %) for delusions and 4 to 76 % (median 23 %) for hallucinations [35, 36, 37•, 38]. The rates of psychoses vary by the stage of illness. It is found most commonly in the middle stages of the illness, with a 20 % rate in the early stages of Alzheimer's disease and up to 50 % by the third or fourth years of illness (overall 30 to 50 %) [35, 36, 37•, 38].

Visual hallucinations are the most common type of hallucination in Alzheimer's disease patients, followed by auditory and, less commonly, other types (olfactory, tactile, gustatory) [36]. This differs from primary psychoses where auditory hallucinations are most common. The hallucinations experienced most commonly involve people from the past (e.g., deceased relatives), intruders, animals, and objects. The most frequent types of delusions experienced during the course of Alzheimer's disease are false beliefs of theft, infidelity of one's spouse, beliefs of abandonment, believing that their house is not their home, and persecution [36]. Delusions tend to decreases in later stages. Some symptoms, although appearing to be delusions or hallucinations, may be misidentifications due to cognitive deficits, e.g., mirror sign (mistakes self in mirror for someone else) and TV/magazine sign (belief that people on TV or in magazines are present and real) [36].

There is increasing evidence supporting a subtype of Alzheimer's disease based on the presence of psychotic symptoms that has an association with dopamine receptor gene alleles, an increased density of plaques and tangles in the prosubiculum and frontal cortex, APOe genotypes, and differences in neurotransmitter concentrations [39, 40••]. The anterior cingulum has recently been implicated in the presence of certain neuropsychiatric symptoms, particularly irritability, apathy, agitation, dysphoria, and nighttime behavioral disturbances [41•, 42•].

Psychosis associated with vascular dementia has been found to be epidemiologically similar with some phenomenological differences. The Cache County study found the prevalence of hallucinations to be similar between Alzheimer's disease and vascular dementia, while delusions were found to be more prevalent in Alzheimer's disease versus vascular dementia (23 vs 8 %) [43].

Neurocognitive disorder with Lewy bodies (NCDLB) also known as dementia with Lewy bodies has three main classes of neuropsychiatric symptoms: visual hallucinations, misidentification syndromes, and delusions [44]. Most common are visual hallucinations with prevalence rates of 25 to 83 %, while delusions have reported rates between 13 and 75 % of patients [45]. Recent studies have reported 29 to 50 % rate of misidentification syndromes such as Capgras syndrome or phantom boarder syndrome in NCDLB [45–47]. The rate of misidentification syndromes was found to have a 4 % point prevalence and 22 % period prevalence for patients with Alzheimer's disease, making this a useful clinical diagnostic indicator [47]. Approximately 43 % of patients with NCDLB have visual hallucinations in the earliest phases of the illness. Early visual hallucinations with or without clinically meaningful cognitive decline should always raise the suspicion of Lewy body disease [45].

Psychosis is also a common sequelae of Parkinson's disease and neurocognitive disorder due to Parkinson's disease. While the hallucinations of Parkinson's disease (approximately 25 %) have been described as benign hallucinosis and remarkable for retained insight, the hallucinations of neurocognitive disorder due to Parkinson's disease (previously Parkinson's disease with dementia or PDD), seen in about 60 % of these patients, have been described as more complex and distressing, and present with a general loss of insight [48]. Visual hallucinations are more common than delusions in PDD patients [49]. As with the other neurocognitive disorders, these symptoms worsen prognosis, intensify caregiver distress, and increase the likelihood for institutionalization [50]. It is important to underscore the need to rule out extrinsic causes of hallucinations, i.e., antiparkinson's medication/dopaminergic agents.

Given the multitude of studies that have described issues with the safety profiles of medications used to treat psychosis in the elderly, the consensus across the varied guidelines is a uniform recommendation for first-line non-pharmacological approaches [51••, 52••]. Every effort should be made to institute these treatments first, particularly in cases in which patients themselves are without subjective distress related to their psychotic symptoms. Moreover, it is important to alleviate "unmet needs" such as sensory deficits (e.g., hearing aids, glasses), social isolation of patients, environmental over- or under-stimulation, and so forth [51••, 52••].

Psychosocial strategies for dementia with the strongest evidence at present include alleviating caregiver burden (caregiver education, support systems), music therapy, cognitive stimulation therapy, Snoezelin therapy (multisensory stimulation), behavioral management (by professionals), and staff

training/education [51••, 52••]. Less convincing evidence exists for strategies such as reality orientation, caregiver-instituted behavioral management, validation therapy, reminiscence therapy, therapeutic activity programs, and physical environment stimulation strategies [51••, 52••].

When these first-line approaches have failed, and moderate or greater symptoms remain, pharmacologic approaches should be considered. This remains the consensus recommendation despite the associated risks of these approaches. The first step of a rational, evidence-based psychopharmacologic approach to psychotic symptoms in dementia should include the appropriate use of acetylcholinesterase inhibitors (donepezil, rivastigmine, galantamine) and memantine. Beyond their modest benefits for cognition, these medications have been shown to reduce behavioral symptoms (including psychosis) and possibly decrease the need for additional pharmacologic agents [53, 54, 55••].

When initial treatments fail, consideration should be given to the use of antipsychotic medications. Following the 2005 publication of a large meta-analysis noting an increased (OR 1.7) risk of mortality in patients with dementia with psychosis treated with atypical antipsychotic medications, the FDA issued a black box warning regarding the use of antipsychotic medications in this population [56]. It should be noted that the absolute increase in mortality is approximately 1 in 50 to 1 in 100 patients. Principal causes of mortality are cardiovascular, infectious, and cerebrovascular causes [56, 57]. There is controversy in the literature with some studies finding no increases in mortality, that the mortality risk may be associated with higher doses of medication, and that some medications may be safer, e.g., quetiapine has the lowest associated mortality rates [58, 59••]. Of note, data from the CATIE-AD trial have revealed an increased decline in cognition in those treated with atypical antipsychotics versus those treated with placebo [60••].

Perhaps due to a dearth of effective alternatives and the modest effectiveness of some of these medications, their carefully weighed use continues to be a part of expert guidelines [61–64]. The neuropsychiatric symptom domains which appear to improve differentially with antipsychotic treatment are anger, aggression, and paranoid ideation while functional abilities, care needs, and quality of life do not seem to improve [65].

Recommendations for antipsychotic treatment in the elderly include (ranging from starting dose to maximum target dose) [66, 67••] the following:

- Risperidone 0.25 to 1.5 mg daily
- Olanzapine 2.5 to 10 mg daily
- Quetiapine 12.5 to 200 mg daily
- Aripiprazole 2.5 to 12.5 mg daily

Antidepressant medications have shown promise, particularly sertraline and citalopram, for the treatment of behavioral disturbances in neurocognitive disorders and are tolerated well when compared to antipsychotic medications and placebo [68••]. Carbamazepine has show utility in small studies for the treatment of agitation in neurocognitive disorders, but potential adverse effects frequently outweigh benefits [69, 70]. Prazosin has one positive study for the treatment of agitation in neurocognitive disorders, but further research is needed [71].

Targeted treatment for patients suffering from Parkinson's disease (PD) or NCDLB and secondary psychosis must be initiated cautiously due to a much-heightened risk of extrapyramidal symptoms in these patients. It is critical to adjust antiparkinson's medications *before* initiating antipsychotic medications, starting with medications with the least effectiveness, as many of these medications may induce psychosis [72, 73••]. Typical antipsychotic medications should not be used in these patient populations. Clozapine has the most consistent evidence for efficacy in the PD population although its use has been limited by concerns about agranulocytosis, anticholinergic side effects, orthostatic hypotension, and the need for blood monitoring [72, 74]. Quetiapine has inconsistent evidence for its benefit in this population but is still used preferentially over clozapine because of the aforementioned concerns [72, 74]. Dosing ranges recommended for PD and NCDLB patients are [52••] the following:

- Clozapine 6.25 to 50 mg
- Quetiapine 12.5 to 150 mg

Donepezil and rivastigmine have shown some benefits for the treatment of psychosis in the PD population [72]. Recently, pimavanserin, a serotonin inverse agonist, successfully completed phase 3 trials and has been shown to have a greater decrease in Scale for Assessment of Positive Symptoms in Parkinson's Disease (SAPS-PD) scores compared to placebo [75••].

Diagnosis and Treatment of Primary Late-Life Psychoses

The diagnosis and treatment of primary late-life psychotic disorders should proceed only after the evaluation for secondary late-life psychotic disorders is complete. Clinicians should remember the pre-diagnostic probability in the elderly—three fifths of psychoses are secondary psychoses—and be willing to revisit their assessments as more information becomes available.

Depression and Other Affective Disorders with Psychotic Features

Major Depressive Disorder

Major depressive disorder (MDD) is common in the late life, with roughly 4 to 7 % aggregate prevalence in adults 55 years

old and older [76, 77•, 78]. Data from the National Comorbidity Survey Replication indicates a 12-month prevalence of 2.6% and a lifetime prevalence of 9.8 % in adults 65 years and older [78]. When MDD was combined with minor depression and depression treatment status in adults 71 years and older, overall prevalence of clinically meaningful depressive symptoms rose to 11 % [79]. In the DSM-5, the presence or absence of psychoses is indicated with a diagnostic specifier, "with psychotic features" that may be further detailed using the specifiers "with mood [*congruent*] psychotic features" or "with mood [*incongruent*] psychotic features [3••].

Older persons with MDD are more likely to have psychotic features and be resistant to treatment than their younger counterparts [80, 81]. Psychotic depression occurs in 20 to 45 % of hospitalized elderly depressed patients and 15 % of community-dwelling depressed persons. Rates of psychosis do not seem to differ between those elderly subjects with an early-onset (before age 60) and those with a late-onset (age 60 and above) depression. Delusions are the most common psychotic symptom in late-life depression with psychotic features, and they are most often mood congruent, e.g., delusions of guilt, delusions of deserved punishment for moral or personal inadequacies, delusions of nihilism, somatic delusions, and delusions of poverty. Auditory hallucinations are less common and not easily described by patients, e.g., vague derogatory voices [82].

A complete medical workup should be conducted, and alternative psychiatric diagnoses should be ruled out prior to this diagnosis. The differential diagnoses rely heavily on patient and collateral history. Hearing the voices of lost loved ones is very common in the bereaved elderly and in some cases has been reported to be a helpful phenomenon [83]. Once the diagnosis is established, treatment must be considered. In older adults, electroconvulsive therapy (ECT) may be most effective and limit the need for additional pharmacotherapy; however, research is necessary before a definitive statement can be made [84]. In particular, the greater the degree of frailty, the more likely ECT should be chosen as a first-line treatment [85].

When ECT is not possible, the best evidence for the pharmacologic treatment of the psychotically depressed elderly is combination therapy of an antidepressant and an antipsychotic medication. The only RCT that has been published on this topic noted the superiority of olanzapine plus sertraline in obtaining remission in the elderly [86]. Augmentation with psychotherapy and psychosocial treatments should be considered. Cognitive behavior therapy, problem solving therapy, interpersonal therapy, and supportive therapy are the most often cited, while CBT is the most studied and has the best evidence for its effectiveness [87].

Bipolar Disorder

The prevalence of bipolar disorder in the elderly is estimated to be between 0.25 and 1 % [88–90]. There are two peaks for bipolar illness [91]. A majority of cases are diagnosed in the second to fifth decades of life, and a second peak occurs at age 65 and over [91]. In elderly inpatients with bipolar disorder, the mean prevalence of late-onset mania was 44 % [91]. Those patients with late-onset bipolar disorder may represent a distinct subset of bipolar disorder [92, 93]. Studies of psychosis during late-life bipolar disorder are limited and conflicting, with one study finding increased depressive episodes with psychotic features and another finding no difference in the prevalence of psychosis between late-life patients and their younger counterparts [94, 95].

Because of the paucity of treatment studies in this age group, clinical interventions are extrapolated from those of non-elderly adult bipolar disorder. There is an on-going study of the treatment of acute mania, treatment of bipolar mania in older adults study (GERI-BD) examining the use of divalproex and lithium in the elderly [96]. To date, the GERI-BD study has revealed the positive effects of socialization on outcomes [97•]. It has also identified ethnicity (non-Hispanic Caucasian), symptom severity, and past psychopharmacologic treatments as factors increasing the likelihood of inpatient psychiatric treatment and a lack of associations between lifetime bipolar disorder and cognitive decline [98••, 99]. Another study examining age-group differences in bipolar disorder found a higher prevalence of disordered thought content in older adults versus a higher rate of aggression and irritability in younger adults [100•].

Sajatovic and Chen's review of geriatric bipolar disorder provides an excellent summary of the treatment literature [101]. To target psychosis occurring in the context of acute mania, all the current atypical antipsychotic medications (except clozapine) are indicated for use. The olanzapine-fluoxetine combination has strong evidence for its use in mixed bipolar patients.

Delusional Disorder and Schizophrenia-Spectrum Illnesses

Schizophrenia

An important change in the DSM-5 from previous editions was the elimination of the subtypes of schizophrenia (paranoid, disorganized, undifferentiated, residual, and catatonic) due to their "limited diagnostic stability, low reliability, and poor validity" [3••]. Also eliminated were the symptoms that established the diagnosis of schizophrenia by their sole presence such as bizarre delusions and Schneiderian hallucinations. When establishing the diagnosis of schizophrenia, special attention should be paid to differentiating other DSM-5 disorders with psychotic features (major depression, bipolar disorder, schizoaffective disorder), delusional disorder, and personality disorders (schizoid and schizotypal personality disorders).

A review of studies of late-onset schizophrenia found that approximately 20 to 25 % of patients with schizophrenia were reported to have experienced the onset of the disorder after age 40, while the remaining four fifths of elderly patients with schizophrenia experienced early onset [102, 103]. Today, with greater numbers of schizophrenia patients surviving into old age, the prevalence estimates for schizophrenia in adults aged between 45 and 60 are approximately 0.6 to 1 % and 0.1 to 0.5 % in persons aged 65 plus [104–108]. By 2025, about one fourth of persons with schizophrenia will be age 55 and over [109].

Although neither the DSM-5 nor ICD-10 distinguishes by age of onset, the International Late-Onset Schizophrenia Group proposed that schizophrenia be termed "Late-Onset Schizophrenia" and "Very Late Onset Schizophrenia-Like Psychosis" for disorders that begin with an onset between age 40 and 60 and after the age of 60, respectively [110]. The former is considered similar to the early-onset disorder although there is greater preponderance of women. The very late disorder has features that suggest a neurodegenerative component including more brain abnormalities and neuropsychological deficits and is also distinguished from the other two types by many more females; greater prevalence of persecutory and partition delusions; higher rates of visual, tactile, and olfactory hallucinations; lower genetic load; more sensory abnormalities; and the absence of negative symptoms or formal thought disorder [110].

Jeste et al. have described an exaggerated "paradox of aging" among older adults with schizophrenia [111•]. People with schizophrenia, when compared to the general population, have accelerated physical aging, including increased and earlier medical comorbidity and mortality; however, their cognitive aging rate remains normal following an initial, persistent occurrence of mild neurocognitive disorder [112]. Conversely, as these patients age, psychosocial function improves, psychosis decreases, relapse and hospitalization rates decrease, self-management improves, and they experience an improvement in their quality of well-being [112].

Schizoaffective Disorder

With the publication of DSM-5, the diagnosis of schizoaffective disorder was reformulated as a longitudinal condition, more in keeping with other major psychiatric disorders [3••]. The diagnosis now requires the presence of a major mood component during the "majority" of the lifetime duration of illness rather than only episodically as in DSM-IV-TR. The diagnosis is established once an uninterrupted period of illness includes a major mood episode concurrently with schizophrenia criteria. Delusions or hallucinations must occur in the absence of a mood episode for at least 2 weeks at any point during the course of the illness. The disorder is further classified into bipolar and depressed types.

The clinical features and risks of late-life schizoaffective disorder were first discussed in 1971 by Post, who noted their frequent treatment-refractory condition, risk of suicide, and severe illness [113]. A more recent retrospective chart review confirmed Post's original findings, further noting an increased risk of suicide attempts in depressed versus bipolar-type patients greater than 60 years old [114•].

Delusional Disorder

Delusional disorder, according to DSM-5, is diagnosed by the presence of one or more delusions for greater than 1 month [3••]. Diagnostic criteria for schizophrenia or schizoaffective disorder must not be met. Further classification is made by subtype of delusion, e.g., erotomanic, grandiose, jealous, persecutory, somatic, and mixed.

There is a paucity of literature regarding delusional disorders in the elderly. Studies indicate a prevalence of 0.03 % in the elderly, with women slightly more affected than men [115]. There are no clear neuroanatomical changes associated with delusional disorder. There is mixed evidence that hearing or visual abnormalities might play a role in the development of delusional disorder, with Maher observing that a subset of patients develops delusions in the context of sensory impairment [116].

Treatment

There has been a paucity of studies devoted to the pharmacological treatment of older adults with schizophrenia. A Cochrane review of antipsychotic medications for elderly people (age 65+) with schizophrenia found only three RCTs involving 252 persons. One involved drugs that are no longer available. The other studies found no differences between risperidone and olanzapine and olanzapine and haloperidol [117].

Evidence-based treatment of late-onset schizophrenia is based primarily on findings of early-onset individuals who survived into later life. The most recent Cochrane review conducted in 2012 found no "good quality" data to support the use of antipsychotic medications in the late-onset or very late-onset schizophrenia [118]. One trial was found "acceptable," a controlled study of risperidone and olanzapine, but did not provide enough usable data to make conclusions [118, 119].

On the other hand, there is considerable clinical experience using risperidone, olanzapine, aripiprazole, and clozapine for the treatment of late-life schizophrenia [28, 52••, 119]. Consensus guidelines currently recommended for schizophrenia in older adults are as follows [28]:

- *First line*: risperidone 1.25 to 3.5 mg/day
- Quetiapine 100 to 300 mg/day

- Olanzapine 7.5 to 15 mg/day
- Aripiprazole 15 to 30 mg/day

Starting dosages for late-onset persons should be at 25 % of the recommended adult dose and maintenance doses at 25–50 % of the adult dose. Often, effective doses for early onset can be 50–75 % of younger patients.

There are few specific treatment studies of late-life schizoaffective disorder, and most include this group with the treatment of late-life schizophrenia [118]. As noted above, a cautious approach is recommended with the smallest effective dosage of antipsychotic medication with adjunctive treatment based on their subtype of illness and according to the consensus guidelines for adults. Mood-stabilizing medications (lithium, divalproex, carbamazepine, lamotrigine) and antidepressants should be used judiciously and in the minimum effective dosages.

There are no available studies on the treatment of late-life delusional disorder. Expert consensus guidelines recommend the use of atypical antipsychotic medications as follows [28, 52••]:

- *First line*: risperidone 0.75–2.5 mg/day
- Olanzapine 5–10 mg/day
- Quetiapine 50–200 mg/day

The adage of geriatric psychiatry, "start low, go slow," should be heeded when initiating antipsychotic treatment. Elders are prone to adverse effects including cardiovascular, metabolic, sedation, anticholinergic burden, extrapyramidal symptoms, tardive dyskinesia, orthostatic hypotension, metabolic changes, falls, hyperprolactinemia, agranulocytosis, and neuroleptic malignant syndrome [52••, 120]. To ensure their safety, patients should be monitored regularly with a complete blood count, comprehensive metabolic panel, lipid panel, hemoglobin A1C, electrocardiogram, orthostatic vital signs, abnormal involuntary movement scale, and weight checks.

Psychosocial treatments should be used adjunctively to pharmacologic treatment in the elderly to better target deficits in social and occupational functioning. Recent studies have found that Functional Adaptation Skills Training, cognitive behavior therapy, social skills training, cognitive behavioral social skills training, and cognitive training (cognitive remediation) are useful approaches for the treatment of patients with schizophrenia [121, 122].

Conclusion

In summary, psychosis is among the most common experiences in later life with a lifetime risk of 23 % among older persons. Elderly patients with late-life-onset psychosis require careful evaluation. There are no reliable pathognomonic signs to distinguish primary or secondary psychosis. Primary psychosis is a diagnosis of exclusion, and the clinician must rule out secondary causes. Roughly three out of five older patients with newly incident psychosis have secondary psychoses. Thus, every new-onset psychoses or appreciable change in symptoms necessitates a medical workup. It is useful to remember the "six d's" of late-life psychosis (Table 1) in formulating a differential diagnosis and the acronym "MINE" to trigger a list of potential medical diagnoses associated with secondary psychosis (Table 2).

Treatment is geared towards the specific cause of psychosis and tailored based on comorbid conditions. Frequently, environmental and psychosocial interventions are first-line treatments in late-life psychoses. Caution should be exercised in all elderly patients when initiating pharmacotherapy for psychosis, particularly antipsychotic medications because of their association with increased morbidity and mortality. Each additional pharmacologic agent adds to the medication burden for elderly patients already at risk for adverse events because of polypharmacy.

Finally, there is a remarkable gap between the prevalence of psychotic disorders in older adults and the availability of evidence-based treatment. The dramatic growth in the elderly population over the first half of this century creates a compelling need to address this gap.

Compliance with Ethics Guidelines

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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