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].

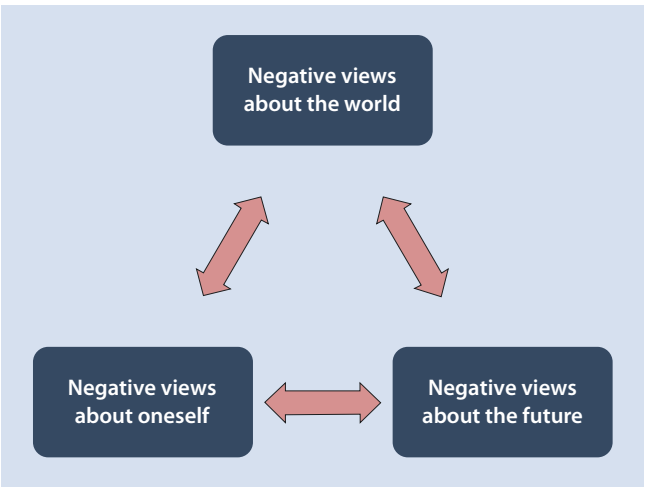

Fig. 10.1 Aaron Beck's cognitive triad

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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