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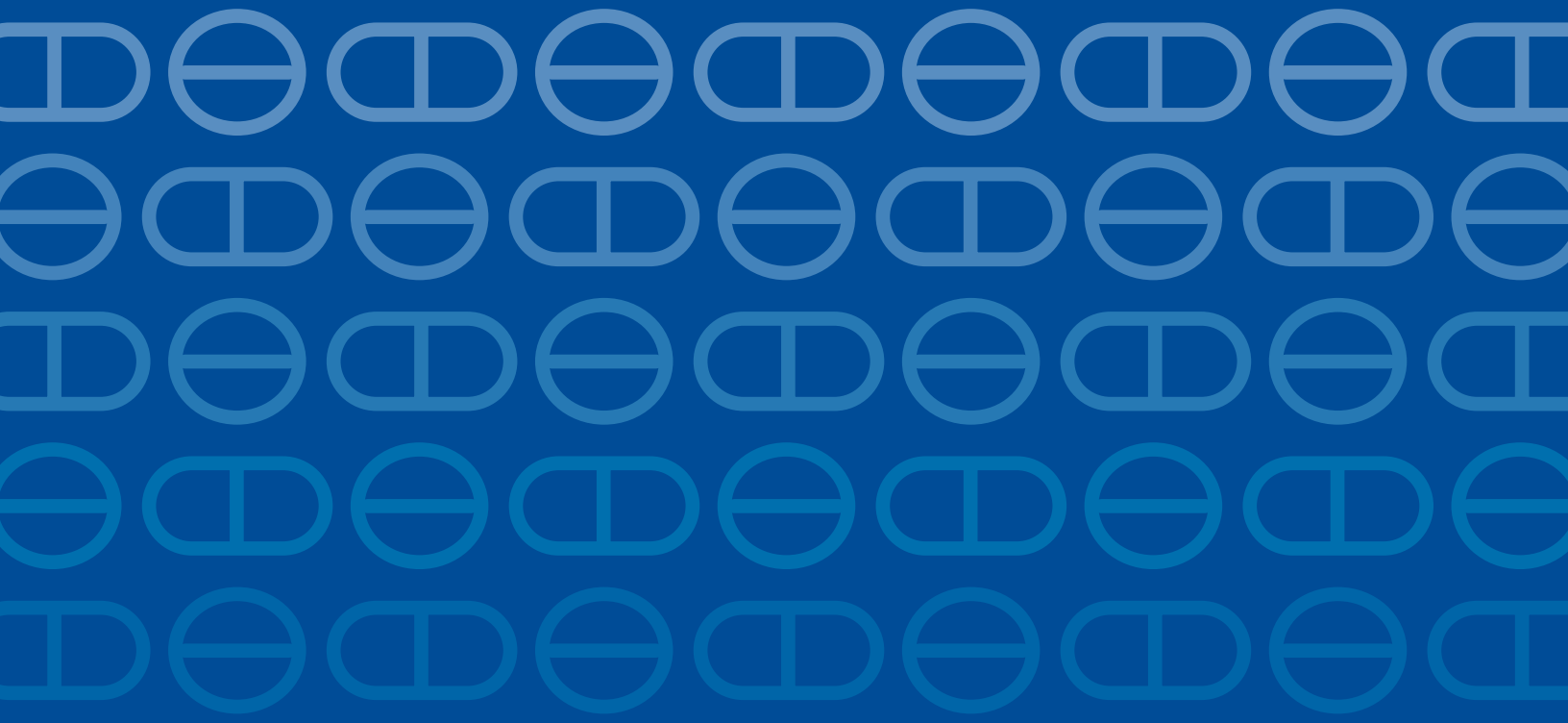
Managing depression in older patients

A guide to the most current evidence



Managing depression in older patients

A guide to the most current evidence

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Alosa Health

Managing depression in older patients

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Activity Overview:

The goal of this activity is to educate prescribers about the most recent evidence relating to defining and diagnosing depression in older adults, implications of addressing depression on comorbid conditions, as well as different treatments used to manage the condition.

The educational program has several components, which include:

- Written evidence report (print monograph)
- Summary document of the top 4-5 key messages
- “Academic detailing” educational sessions in clinicians’ offices with trained outreach educators (pharmacists, nurses, physicians) who present the material interactively
- Reference cards for easy access to key materials
- Patient education information (brochure/tear-off sheets)

This program works to synthesize the current clinical information on this topic into accessible, non-commercial, evidence-based educational material, which is taught interactively to providers by specially-trained clinical educators.

Target Audience:

The educational program is designed for primary care physicians practicing internal medicine, primary care, family practice, and geriatrics, and other health care professionals who deliver primary care.

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Apply standardized screening and diagnostic tools to identify depression in older adults
- Choose individualized treatment options based on symptom severity and patient preference
- Describe treatment monitoring, including treatment response, side effects, and dose titration or switching if no or low response.
- Provide a comprehensive risk assessment for suicide and develop a plan using the SAFE-T framework.
- Describe when to refer to a specialist.

Disclosure Policy:

All individuals in a position to control the content of this activity have been asked to disclose any relationship they have with ineligible companies whose primary business is producing, marketing, selling, re-selling, or distributing healthcare products used by or on patients. All relevant financial relationships have been mitigated.

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The activity will take approximately **1.75** hours to complete.

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Please email any questions to **cme@alosahealth.org** or call **(617) 948-5997.**

Table of Contents

Introduction

The word depression conveys feelings of frustration and intense sadness or disappointment in nearly everybody. However, while nearly everybody has been exposed to the concept of depression, the clinical syndrome of depression is a symptomatically defined and pathophysiologically complex entity.

Major depressive disorder (MDD), often referred to as clinical depression, is a disease defined by having 1) sadness or anhedonia with 2) four or more other symptoms of depression that 3) causes impairment in functioning and 4) lasts for at least 2 weeks.[1] Depression contributes to a variety of distressing emotional, cognitive, and physical problems and can decrease a person's ability to function in the way that they once did.

Over the past 20 years, the global burden of depression has remained high, with 3,440 cases per 100,000 persons in 2019.[2] In high-income North American countries, including the U.S., the estimated burden is higher at 4,270 cases per 100,000 persons (though it is unclear how much, if any, of this is due to differences in data availability between regions).[2] Estimates of the prevalence of depression in older adults vary based on the setting (Table 1). Two estimates from nationally representative samples of community-dwelling older adults suggest a prevalence of 3.8%-7.8% while another nationally representative survey of older adults living in the U.S. found that 11% were receiving treatment for the disease.[3-5] By contrast, rates of depression among patients living in medical or institutional settings are higher: >50% of older adults residing in long-term care facilities receive a depression diagnosis within their first year of being institutionalized.[6] Although symptoms of depression are common in persons who are aging or in poor physical health, it is not a normal part of aging.[7]

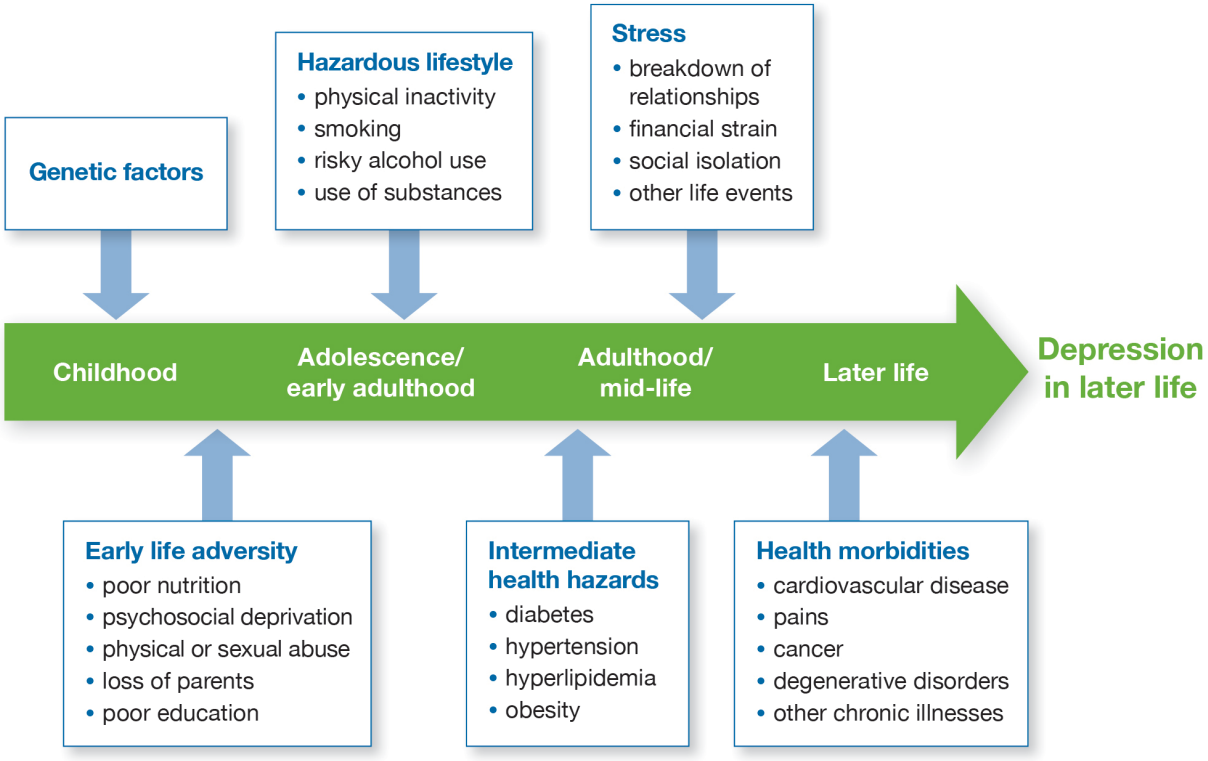
This document summarizes the evidence for identifying, diagnosing, and managing depression in older adults and addresses treatment challenges unique to this population. It will primarily discuss unipolar major depressive disorder (MDD) and persistent depressive disorder (previously called dysthymia). The terms depression and major depressive disorder will be used interchangeably throughout this document, and depressive symptoms will refer to those symptoms included in the *Diagnostic and Statistical Manual of Mental Disorders, 5th edition, text revision* (DSM-5 TR) criteria for depression. Although all patients with depressive symptoms have notable clinical concerns and potential related decrements in quality of life, not all of them meet criteria sufficient for major depression.[7-10] A depressive episode that occurs in older adults is referred to as late life depression.

Table 1: Prevalence of depression in older patients[7-10]

	Major depressive disorder	Depressive symptoms
Primary care	5-10%	25%
Hospital	≥20%	17-30%
Long-term care	≥20%	33-61%

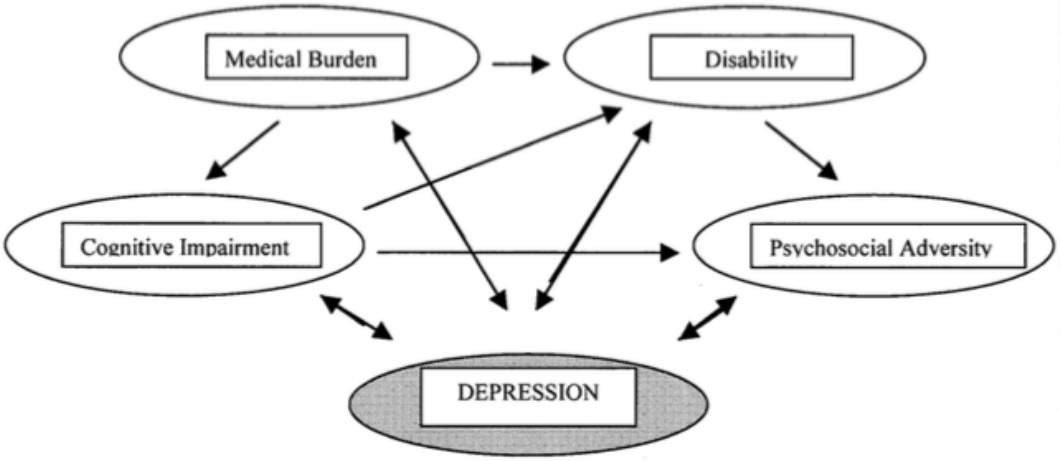
Risk factors for depression accumulate through life and encompass overall health, lifestyle, stress and adversity (Figure 1 next page).

Figure 1: Risk factors through the life span[11]



The complex interaction between depression and other health factors complicates management and prognosis for patients with late life depression. While comorbid conditions often play a role in worsening depression, depression itself may in turn exacerbate conditions such as cognitive dysfunction, disability, medical morbidity, and mortality (Figure 2).[8]

Figure 2: Health factors that contribute to late life depression[8]



Non-clinical effects of depression

In addition to the numerous impacts of depression on health outcomes (detailed later in this document), depression also increases financial costs, healthcare utilization, and caregiver burden. In 2018, depression in adults of all ages cost $326 billion in the U.S, alone due to absenteeism, medical, drug, and suicide-related costs.[12] The increased medical costs are not all related to treating depression itself: patients with significant depression have been found to have total health care costs roughly 50% higher than those without depression.[13,14] This extends to late-life depression when patients have nearly twice the number of doctor's appointments and spend nearly twice as many days in the hospital as those without depression.[15,16] Studies also suggest that caregivers report higher levels of depression and burnout when the patient for whom they are caring has depression.[17-19]

Undertreatment of depression

Depression in the elderly is under-recognized.[20] Comorbid medical conditions and lower functional expectations of elderly patients can obscure the degree of impairment associated with depression. Older patients do not always report depressed mood, and they may have less specific symptoms, such as insomnia, anorexia, fatigue, pain, irritability, or anxiety.[7,21] Elderly patients may also have more stigmatized attitudes about mental illness, which may prevent them from seeking care.[13,22]

In addition to diagnostic challenges that exist in older adults, many patients with a diagnosis of depression never receive treatment. In a study of the U.S. Medical Expenditure Panel Surveys with 46,417 respondents aged 18 years or older, only 28.7% who screened positive for depression received treatment. Moreover, when treatment was recommended, antidepressants were prescribed to over 80% of patients, but psychotherapy was utilized by only 20-30% of patients (with even lower utilization rates among older adults).[23] Unfortunately, even those that seek treatment for depression are at risk of being undertreated; for example, one simulation study estimated that only 9% of primary care patients are adequately treated for depression.[27] This is especially problematic given that the most cited estimates suggest that 60% of depression is treated in primary care.[24,25]

BOTTOM LNE: Depression is common in older adults, but it is not a normal part of aging. Late life depression is a heterogeneous illness that affects health and other outcomes. Despite its prevalence, depression is undertreated in primary care.

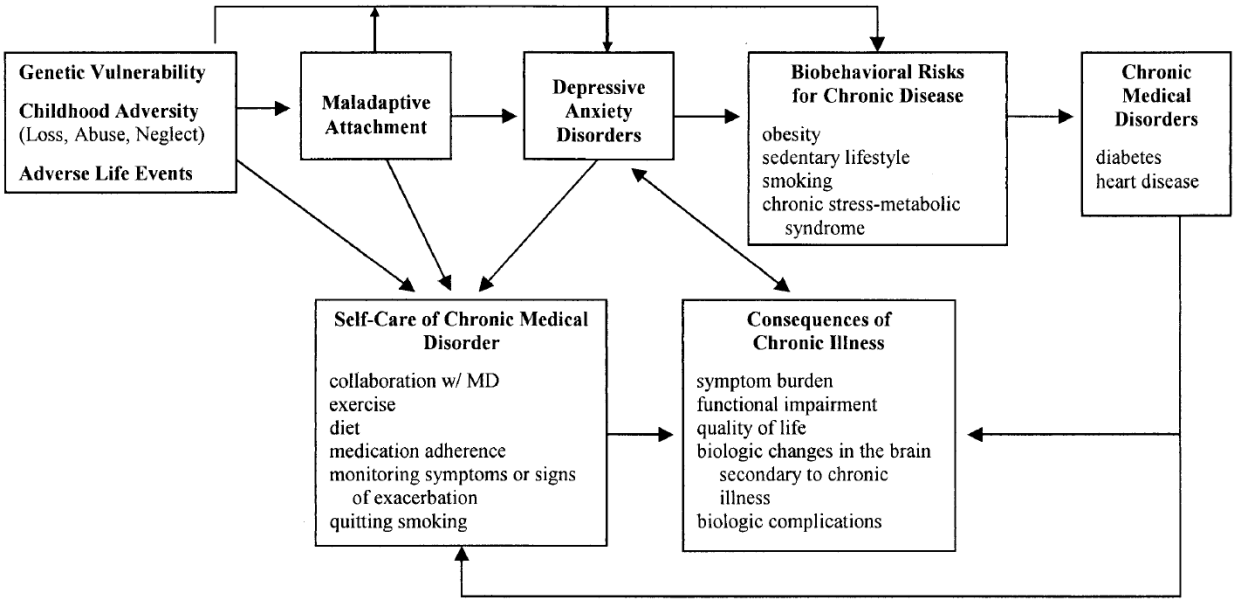
Impact of depression on health outcomes

Patients with depression in late life have worse health outcomes than patients without depression, including an increased risk of stroke, an increased risk of mortality in patients with comorbid coronary heart disease, and an elevated risk of suicide.[26-28] Late life depression is associated with cerebrovascular comorbidities, neurodegenerative pathologies, and biochemical changes.

It is important to note that the correlation between depression and chronic health conditions is bidirectional. There are decades of research showing that medical illness and incidence of depression are associated. For example, a 1988 study suggested that having at least one chronic medical condition was associated with a 30% increased risk of being diagnosed with depression,[29] and more recent evidence confirms this association.[30] This is likely due to a complex and not yet fully elucidated feedback loop

between depression and physical health. For example, depression can lead to decreased motivation for exercise, which can cause obesity, which may lead to heart disease. Arthritis can lead to inability to exercise, which can lead to molecular changes (such as decreased brain-derived neurotrophic factor among many other signaling pathway alterations), which are associated with increased risk of depression.[30-32] Note that this is in addition to medical conditions that are known to directly cause depressive symptoms, such as hypothyroidism. A simplified representation of this interplay is presented below.[33]

Figure 3: Interplay between medical conditions and depressive symptoms[33]



*Collaboration with MD includes any clinician involved in the chronic medical care of a patient

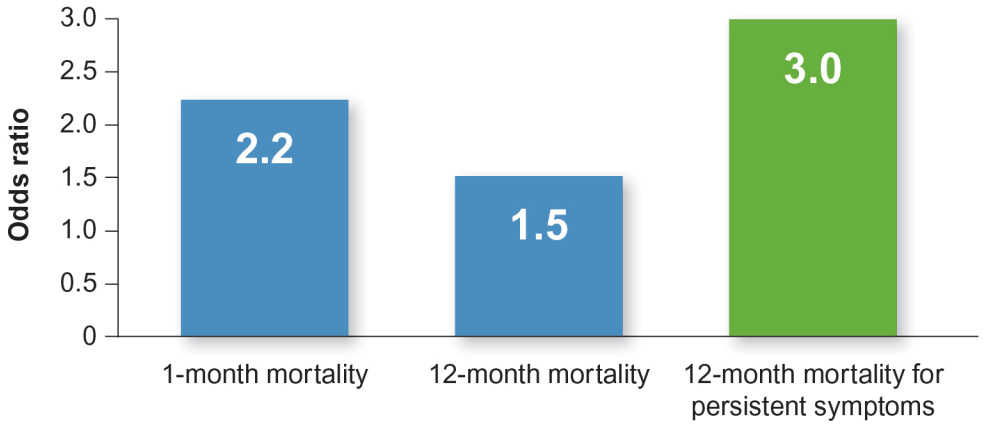
Most of the evidence presented in the subsequent sections will review the many associations between depression and health outcomes. However, while not studied as extensively, there is only limited evidence that treating depression can prevent or improve these poor health outcomes. For example, one cohort study followed 235 patients aged ≥60 who had been a part of the **Improving Mood-Promoting Access to Collaborative Treatment (IMPACT)** randomized controlled trial. While the original trial was conducted to study the impacts of different treatment modalities on depression, the 8-year follow-up assessed whether there was a significant interaction between depression treatment and baseline cardiovascular risk in terms of subsequent cardiovascular events. Patients without baseline cardiovascular disease who received treatment for depression had a 48% lower risk of a subsequent cardiovascular event (28% vs. 47%, hazard ratio [HR] 0.52; 95% CI: 0.31–0.86).[34] While this study was underpowered, future work from the group is anticipated.[35] As another example, while most evidence speaks only to a correlation between early-life depression and Alzheimer's disease, one study followed 755 patients with mild cognitive impairment who had previously carried a diagnosis of depression and found that previous use of a selective serotonin reuptake inhibitor for >4 years was associated with decreased risk of progressing to dementia.[36] These types of results have not been widely replicated in other studies, but they do provide preliminary evidence that the neurological benefits to treating depression may transcend mental health.[37]

Impact of depression on cardiovascular disease risk and mortality

The link between depression in older adults and increased risk of adverse outcomes in cardiovascular disease is well-established.[38-41] One meta-analysis of 21 studies with 47,625 older people (mean age of 74 years) who were followed over a median of 8.8 years compared patients without depressive symptoms to patients with depressive symptoms and found the latter group had a higher risk of stroke (HR 1.36; 95% CI: 1.18–1.56) and all-cause mortality (HR 1.44; 95% CI: 1.35–1.53), but not of myocardial infarction (MI) (HR 1.08; 95% CI: 0.91–1.29). In this same meta-analysis, patients with an apathy subset of MDD symptoms (defined as disrupted motivation resulting in reduced goal-driven behavior, cognition, and emotional responsiveness [see page 12 for more on apathy]), had a 21% higher risk of MI (95% CI: 1.08–1.36), a 37% higher risk of stroke (95% CI: 1.18–1.59), and a 47% higher risk of all-cause mortality (95% CI: 1.38–1.56).[42]

Depression has also been associated with an increased risk of cardiovascular mortality and all-cause mortality in patients with heart disease. A prospective cohort study followed 1,035 older adults (mean age 81.4 years) undergoing transcatheter or surgical aortic valve replacement for all-cause mortality at one and 12 months. At baseline, 31.5% of patients undergoing surgery had depression as determined by the Geriatric Depression Scale Short Form (GDS-15), though only 8.6% had a recorded diagnosis of depression. After adjusting for confounders, baseline depression was associated with all-cause mortality at one month (odds ratio [OR], 2.2; 95% CI: 1.18-4.10) and at 12 months after the procedure (OR 1.5; 95% CI: 1.03-2.24). Patients with persistent depression (baseline depression that was still present six months after the procedure) had a three-fold increase in mortality at 12 months (95% CI: 1.08-8.20) (Figure 4).[43]

Figure 4: Depression and increase in all-cause mortality after cardiac valve replacement surgery[43]



All findings are statistically significant.

Interplay between depression on other chronic disease

While the link between cardiovascular disease and depression is among the most well-studied, there are also associations between depression and multiple other chronic diseases. A non-exhaustive list sample of these associations are described below.

Type 2 diabetes is linked with increased risk of developing depression. A meta-analysis of nearly 48,808 patients with type 2 diabetes but without depression found that the risk of incident depression was 24%

higher than in controls without diabetes.[44] However not all associations between chronic diseases and depression are necessarily bidirectional; in the case of diabetes, several studies suggest that diabetes control is not necessarily worse among patients with depression,[45-47] though other observational studies suggest that having depression may be associated with severe hyperglycemic episodes.[48]

Some observational data suggests that depression could be both a result and cause of worsening outcomes in chronic obstructive pulmonary disease (COPD). For example, an observational study from the United Kingdom found that between 1995 and 2005, the prevalence of diagnosed depression was higher in individuals who went on to develop COPD (23.1% versus 16.8% who did not develop COPD). Furthermore, those who developed severe COPD had twice the odds of developing depression compared with others in the cohort (OR 2.01; 95% CI: 1.45-2.78). This suggests that depression could be both correlated with developing COPD and that poorly-controlled COPD could be correlated with developing depression.[49]

Chronic kidney disease (CKD) is another condition that has been associated with depression. One prospective cohort study followed 274 patients with CKD and found that approximately 20% of patients had comorbid depression at the time of cohort entry, which was independent of CKD stage.[50] Furthermore, in patients with end-stage renal disease (ESRD), having a diagnosis of depression is associated with increased hospitalizations[51] and even death.[52]

As mentioned above, there is likely a complicated interplay between chronic disease and depression. Unfortunately, to date there is very little evidence about whether treating depression can ameliorate poor physical health outcomes.

Interaction of cognition and depression in late life

Late life depression is associated with cognitive deficits and increased risk for cognitive decline. Depressive symptoms can involve loss of executive function, attention, verbal learning, motor speed, and processing speed.[53] Cognitive impairment has been detected in 40–60% of non-demented individuals with late life depression.[54] The correlation between depression and cognitive decline is complex and multifactorial. Late life depression may potentially be both a risk factor and early symptom of dementia.[53,55]

Attempting to clarify this complex correlation, a prospective cohort study examined trajectories of depressive symptoms and the risk of new dementia diagnosis over a 5-year period in 2,488 community-dwelling older adults (mean age 74 years). At five years, the proportion of patients who were diagnosed with dementia increased with higher severity of depression symptoms: 12% in patients with consistently minimal symptoms, 17% in patients with moderate and increasing symptoms, and 21% in patients with high and increasing symptoms. In this study, adults with high and increasing depressive symptoms were at increased risk of dementia (adjusted HR 1.94; 95% CI: 1.30-2.90) compared with those with consistently minimal symptoms, but no difference in dementia risk between moderate and high and increasing depression symptoms was observed.[56] Tracking the depressive symptoms of older adults over time may help identify those at greatest risk for dementia.

Unfortunately, remission of depression in older adults does not eliminate the risk of cognitive decline. For example, a longitudinal study of late-life depression in 273 depressed and 164 never-depressed community-dwelling adults aged 60 years or older followed patients for an average of five years and assessed for cognitive decline. Older adults with depression had more cognitive decline, especially for episodic and working memory, than never-depressed older adults. This difference was not modified by

whether the depressive symptoms remitted.[55] This is in contrast to some evidence suggesting treatment of early-life depression may limit later cognitive decline.[36] It remains best practice to treat both dementia and depression in patients who carry both diagnoses.

Risk of suicide

Compared with other age groups, older adults have the highest rate of suicide with depression being a major risk factor.[57] One out of every eight people who takes their own life is aged 65 years or over, and more men aged over 75 years attempt suicide than any age group.[58,59] Older Caucasian men in particular have the highest suicide rate of all demographic groups.[28,60] Although men are significantly more likely to complete suicide, women are more likely to attempt suicide than men. Suicide completion depends on the methods used: men are more likely to utilize a firearm, while women are more likely to attempt overdose using medications.[61]

Access to a firearm is one modifiable suicide risk factor assessed in several studies. Suicide attempts by firearms were more effective than any other means of suicide, with 80%-90% of attempts being successful.[62,63] Access to firearms increases the risk for completed suicide three-fold (OR 3.24; 95% CI: 2.41-4.40).[62] More than 50% of completed suicides utilize a firearm while other common means, namely suffocation and poisoning, account for 26% and 15% of completed suicides, respectively.[64] Risk factors for firearm suicide are varied and include substance use, dementia, prior suicide attempt, chronic pain, and poorly-controlled mental illness.[65] Survey studies of individuals being treated for mental illness support voluntary firearm safety interventions with the hope of reducing firearm suicide.[66] There is some evidence that healthcare interventions to treat depression and distance patients from lethal means reduce the risk of completed suicide.[67]

Among patients with major depressive disorder, the incidence of suicide attempts varies markedly depending on the severity of depression and is highest during major depressive episodes. A longitudinal prospective 5-year evaluation of 249 psychiatric patients with major depressive disorder found that the incidence of suicides was 7.5 times more likely during major depressive episodes and four times more likely during partial remission compared with full remission. While previous attempts and poor social support were found to be risk factors, the time spent depressed was the major risk factor determining overall long-term risk (HR 7.74; 95% CI: 3.40-17.6).[68]

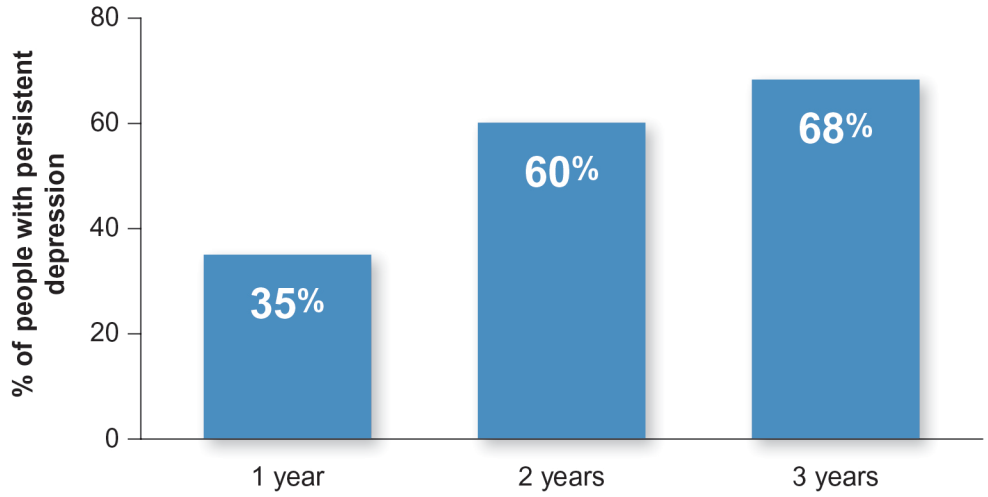
Compared to younger adults, older adults who attempt suicide are more commonly in contact with their primary care providers for any reason in the time leading up to suicide. A review of 40 studies examining the rates of contact between suicide victims and their care providers revealed that while 3 in 4 individuals who died from suicide had contact with primary care providers within the year of the attempt, only 1 in 3 of them had contact with mental health services. About 58% of older adults who attempted suicide had contact with primary care provider within a month before their suicide.[69] Healthcare professionals must be alert to the warning signs of instability and suicidality in patients (see Screening tools for suicidality on page 18 for more information on these signs).

Prognosis for depression in older adults

Many patients with depression remain symptomatic or have delayed remission despite availability of pharmacologic and psychosocial treatment.[70] Different studies provide different estimates for how many older adults will recover from depression. Remission is likely contingent on many patient-level factors such as comorbidities, other medications, depression history and other factors. One longitudinal primary

care cohort study of 234 patients (aged ≥55 years) with a major depressive disorder investigated the duration of depression, recovery over time, and predictors of prognosis. The median duration of a major depressive episode in this population was 18 months, with 35% of depressed patients remitting within one year, 60% within two years, and 68% within three years (Figure 5).[70,71] Of note, not all patients in this cohort received treatment despite having been given a diagnosis of depression, and receiving treatment for depression was not associated with prognosis. These data provide very similar estimates to those from a systematic review of 40 observational studies that followed patients between 9 months and 6 years and found approximately one-third of older adults with depression had a chronic course and another one-third of older adults achieved remission but then had recurrence of symptoms.[72] Unfortunately, multiple studies suggest depression is more likely to be chronic in course and relapse in older adults compared with other age groups.[73-75,]

Figure 5: Proportion of real-world primary care patients age 55 and over remitting from a major depressive episode[71]



Predicting the likelihood of treatment response could help direct treatment to those at highest risk of a poor prognosis, as well as manage expectations for patients and their families. Predictors of poor prognosis in patients with depression include longer duration of current episode, co-occurring anxiety symptoms, and poor executive dysfunction.[70,71] Factors predicting the chronicity of a depressive episode include comorbid medical illness, duration of depressive episode, and "double depression" (i.e., patients with persistent depressive disorder develop worsening symptoms and qualify for a major depression diagnosis as well), personality disorder, and neuroimaging abnormalities.[70,76] Unfortunately, there is little evidence regarding the effect of modification of these risk factors (where possible) or treating depression early in individuals at high-risk for poor prognosis affects likelihood of treatment response.

BOTTOM LINE: Patients with depression are less likely to have control of physical health conditions, with associated higher mortality rates. In later life, depression can manifest as cognitive decline. Older patients have particularly high rates of completed suicides relative to younger patients.

Screening for depression in the elderly

In both 2016 and under-review 2022 guidelines, the U.S. Preventive Services Task Force (USPSTF) recommends screening all adults for depression.[77,78] It is important to note that screening alone is not effective for managing depression, and screening without a follow-up confirmatory evaluation can lead to false positive diagnoses and unnecessary treatment.[7,79] Screening needs to be implemented with support systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up.

Screening tools for depression

Numerous validated questionnaires are available for depression screening. Commonly used depression screening instruments include the Patient Health Questionnaire (PHQ) and the Geriatric Depression Scale (GDS). All positive screening results should lead to additional assessment that considers comorbid psychological problems, alternate diagnoses, and medical conditions.[77] The USPSTF does not currently recommend use of any one specific tool.[78] The tools that we recommend are easy to use in primary-care settings and have acceptable test characteristics.

The PHQ-2 is a short screening tool that has been shown to be efficacious in predicting depression in older adults. It consists of two questions:

1. During the past two weeks, how often have you been bothered by feeling down, depressed, or hopeless?
2. During the past two weeks, how often have you been bothered by little interest or pleasure in doing things?

The accuracy of the PHQ-2 for older adults was examined in a systemic review that compared it with 15 other screening instruments for depression in 46,651 participants from 133 studies (Table 2). The PHQ-2 showed comparable performance with other instruments, including clinician-rated scales.[79]

Table 2: Comparison of screening tools for depression[79]

	PHQ-2	PHQ-9	GDS-15
Sensitivity	84.6	83.4	84.4
Specificity	79.3	85.8	77.4
Time to administer	<5 min	5 min	5-10 min

The PHQ-9 and GDS-15 are longer scales that can be used to establish depression severity, and they can be repeated periodically to monitor treatment response.[80] As Table 2 suggests, the PHQ-9 may perform slightly better than the GDS-15 in older adults. Specifically, in one comparative study, 502 older adults seeking primary care completed the PHQ-9, the GDS-15, and had a Structured Clinical Interview for Depression (SCID); the PHQ-9 showed *very* good discrimination for depression (area under the receiver operator curve 0.85 [95% CI: 0.73-0.96]) while the GDS-15 showed only *good* discrimination (area under the receiver operator curve 0.71 [95% CI: 0.55-0.87]), although the study was not appropriately powered to determine if this difference was statistically significant.[81] It is also unclear if these minor potential differences in performance are clinically significant, as there is little reliable

evidence that using one scale over another to target treatment leads to better outcomes. One potential benefit of the GDS is that its questions are in “yes/no” answer format which may be easier to complete for those with some cognitive impairments.

See Appendices 1-3 for examples of these questionnaires. Once a patient screens positive for possible depression, further assessment to confirm and clarify the diagnosis is indicated.

Diagnosing depression in older adults

Patients with depression constitute a heterogenous group of individuals with symptoms that may fall anywhere from subsyndromal mood disorder to major depression.[1] However, the term “depression” largely refers to major depressive disorder (MDD) as defined by the DSM-5-TR.[1,82] The diagnostic criteria for depression are the same for all adults, as the DSM does not identify different criteria based on age.[1] It is important to note that the DSM-5-TR, published in 2022, has no substantive changes regarding diagnosing depression in most primary care settings. The only notable changes made to the definition involve slight wording changes clarifying how depression with psychotic features versus psychotic disorders with superimposed depression should be considered.[83,84]

Definitions of depressive disorders

Major depressive disorder

The predominant symptoms of major depressive disorder are anhedonia (a loss of interest in activities one used to enjoy) and a depressed mood through most of the day. The diagnostic criteria for major depression in the DSM-5-TR include the presence of sadness and/or anhedonia with a total of five or more symptoms (Table 3).[1]

Table 3: Diagnostic criteria for major depressive episode according to DSM-5-TR criteria[1]

Major depressive episode
Either one or two of the following must be present: • depressed mood • markedly diminished interest or pleasure in (almost) all activities **Plus other symptoms to make a total of five:** • significant weight gain or loss (when not dieting) or decrease or increase in appetite • insomnia or hypersomnia • psychomotor agitation or retardation • fatigue or loss of energy • feelings of worthlessness or excessive or inappropriate guilt • diminished ability to think or concentrate or indecisiveness • recurrent thoughts of death, suicidal ideation, or a suicide attempt or a specific plan for committing suicide

Major depressive episode
In addition, • symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning • the episode is not attributable to — the direct physiological effects of a substance (e.g., a drug of abuse, a medication) — a general medical condition (e.g., hypothyroidism) • symptoms are not better described by schizophrenia, delusional disorder, or other psychotic disorders, and there has never been a manic or hypomanic episode

Depressive episodes with insufficient number of symptoms or too short in duration (i.e., less than two weeks) to meet the criteria for major depression can still have significant clinical effects. Subsyndromal depression, or late life prevalence of depressive symptoms without MDD, has comparable disease burden to major depression, such as poor health and social outcomes, functional impairment, and higher healthcare utilization.[10] Late life subsyndromal depression is more prevalent than major depression.[85] Outcomes of subsyndromal depression are similar to those of major depressive disorder. A review of published studies found that a median of 27% of older adults with subsyndromal depression achieve remission after ≥1 year. Additionally, the disease can evolve, with approximately 8–10% of older persons with subsyndromal depression developing major depression every year. Efforts to treat depressive symptoms can prevent progression to MDD (see treatment section of this document on page 23).[10,86]

Bipolar depression

It is especially important to differentiate bipolar disorder from unipolar depression and other manifestations of depression as the medications used to treat unipolar depression can precipitate manic episodes in individuals with bipolar disorder. A bipolar disorder diagnosis requires that a person have at least one manic episode (persistently elevated, expansive, or irritable mood with increased activity or energy, lasting at least one week) or at least one hypomanic episode (similar symptoms but lasting only four days). Additional criteria for the diagnosis of bipolar disorder include at least three or four (if the manic episode is characterized only by irritable mood with increased energy) of the following:

- inflated self-esteem
- decreased need for sleep
- more talkative than usual
- flight of ideas or thoughts that are racing
- distractibility
- increase in goal-directed activity or psychomotor agitation
- excessive involvement in activities with high potential for painful consequences

These manic periods should not be attributable to substance use or another medical condition. Many patients with bipolar I disorder (e.g., mania with or without depression), and all patients with bipolar II disorder (e.g., hypomanic episodes with depression), experience depression and need to be adequately diagnosed to receive proper treatment. Even for those without particularly severe depression, the presence of a bipolar disorder diagnosis would affect the choice of medication, which is beyond the scope of this review.

Major depressive disorder with psychotic features

Psychotic major depression in patients older than 60 years is highly prevalent in inpatient settings and is a difficult-to-treat condition that causes great suffering and disability.[87] It is characterized by unipolar major depression with psychotic features such as delusions, fixed false beliefs, and/or hallucinations (most commonly false sensory perceptions). Psychotic depression can represent a psychiatric emergency due to elevated suicide risk or diminished ability to care for self. Timely referral to a psychiatrist is important to mitigate safety risks and to distinguish psychotic depression from other etiologies of psychosis (e.g., dementia).[87]

Persistent depressive disorder

Known previously as dysthymia, persistent depressive disorder is a chronic form of depression diagnosed when the mood disturbance continues for at least two years. This diagnosis is a new designation in the DSM-5-TR and includes both the diagnostic categories of chronic major depression and dysthymia from the DSM-IV (Table 5).[1]

While treatments for persistent depressive disorder will not be discussed separately, it is treated much like MDD in practice using a combination of both psychotherapy and medication. Small randomized trials show the most benefit for pharmacotherapy or a combination of pharmacotherapy and psychotherapy with less evidence for psychotherapy alone.[88-91] However, some trials have showed decreased effect of medications in older adults.[92] As such, with treatments that are at best only marginally superior to placebo, persistent depressive disorder has been identified as a particularly difficult disease to treat in older adults.[93]

Table 5: Diagnostic criteria for persistent depressive episode according to DSM-5-TR criteria[1]

Depressed mood for most of the day, more days than not, for two years **Plus two or more of the following:** • poor appetite or overeating • insomnia or hypersomnia • low energy or fatigue • low self-esteem • poor concentration or difficulty making decisions • feelings of hopelessness
In addition, • During a 2-year period, person has not been without above symptoms for more than 2 months. • There has never been a manic or hypomanic episode; criteria not met for cyclothymic disorder. • Symptoms are not better explained by schizophrenia or other psychotic disorder. • Symptoms are not attributable to substance use disorder or another condition. • Symptoms cause clinically significant distress or impairment in important areas of functioning.

Substance or medication-induced mood disorder

For a diagnosis of substance-induced depressive disorder, a patient needs to have.[94]:

- any number of depressive symptoms
- depressive symptoms causing impairment of function
- depressive symptoms beginning during substance/medication use or immediately after ceasing use of the substance/medication, and improvement with time off the substance.

Epidemiological studies have suggested that as few as 1% of patients with mood disorders have only substance-induced mood disorder. The vast majority of patients with mood symptoms and substance/medication use have both substance use (with or without substance-induced mood disorder) and an additional mood disorder (such as depression).[95] This supports an assessment for substances that could be contributing to mood disorders but also being mindful of assessing whether additional depression, bipolar, or other primary psychiatric illness exists and should be treated as well.

Clinicians should be aware of specific common substances that have the potential to cause or worsen depression and other psychiatric illness. These may include cannabis, tobacco, alcohol, opioids, and other medications. While numerous medication classes have been implicated in causing medication-induced depression, perhaps most notably beta-blockers and finasteride,[96,97] the evidence is largely mixed about the link for most of these classes. For example, the largest systematic review and meta-analysis on the topic of beta-blockers and depression found that in 53,533 patients, beta-blocker use was not associated with increased odds of MDD.[98] As such, while many medications may have the ability to induce depressive symptoms, and while all patients should be monitored for side effects and tolerability when starting any medication in accordance with usual care, there is not strong evidence to avoid specific classes of medications in most people for fear of causing medication-induced depression.

Depressive disorder due to a medical condition

For a diagnosis of depression due to a medical condition, a patient needs to have:

- any number of depressive symptoms
- depressive symptoms causing impairment of function
- depressive symptoms beginning after the start of a medical condition and improving with treatment.

Note that there must be evidence that the disturbance is the direct pathophysiological consequence of a medical condition, and the disturbance cannot occur exclusively during the course of a delirium episode.[94] One common example is hypothyroidism, which has a pathophysiologic mechanism for causing depression, and symptoms resolve with treatment of the thyroid disease.[99] While many patients that receive a new medical diagnosis report depressive symptoms, these experiences are often more appropriately classified as an adjustment disorder with depressed mood (i.e. symptoms in response to an identifiable stressor occurring within three months of the onset of the stressor) rather than MDD.[100] A more complicated example is depression associated with cerebrovascular disease, which is sometimes called vascular depression (though it does not appear in the DSM-5 TR as an official diagnosis). Cerebrovascular disease may be a stressor that causes depressive symptoms, but there are also numerous pathophysiological mechanisms by which cerebrovascular disease may cause depression.[101]

When clearcut, such as the case of hypothyroidism, treatment for this type of mood disorder is usually limited to managing the underlying medical condition. When the stress of an illness causes depressive symptoms, or where there is likely to be a more complex interplay between illness physiology and social stress caused by a medical condition (e.g., cerebrovascular disease), multimodal treatment (i.e., team-based social support, pharmacotherapy aimed at depression, pharmacotherapy aimed at physical disease, and psychotherapy) is recommended.

Other factors relating to depression

Bereavement and significant loss

Many older individuals experience the loss of loved ones, and there are also frequently age-related losses in physical ability, social status, mobility, independence, ambitions, and financial income. These changes can be associated with a range of feelings, such as denial, disbelief, sadness, anger, despair, guilt, or yearning. However, although these losses can induce great suffering, they do not typically induce major depression, according to DSM-5 TR definitions. It is not uncommon for symptoms of bereavement to be prolonged, and Prolonged Grief Disorder, or bereavement lasting more than 1 year in adults, is now recognized in the DSM-5 TR.[102] It is important to consider bereavement and major depressive disorder as two separate conditions, which can occur together but do not need to. When the conditions do occur together, the depressive symptoms and functional impairment tend to be more severe, and the prognosis is worse compared with bereavement that is not accompanied by major depressive disorder. Bereavement symptoms can also be the catalyst of a clinically significant major depressive episode.[1]

DSM-IV excluded those with a recent bereavement episode from the definition of major depressive disorder, but this is no longer the case in DSM-5 and DSM-5 TR. The American Psychiatric Association (APA) removed the bereavement exclusion for two main reasons: 1) there is no evidence that depression following bereavement is any different in nature or outcomes from depression in other contexts; 2) disqualifying a patient from a major depression diagnosis simply based on bereavement may leave the person untreated for major depression, which is associated with high suicide risk.[1] It is important to distinguish major depression from bereavement and to ensure appropriate treatment for both (Table 4).

Unfortunately, despite anecdotal reports of the benefits of selective serotonin reuptake inhibitors for patients with grief or bereavement in isolation from other psychiatric comorbidities,[103] there are few studies assessing the efficacy of medications to treat bereavement without an accompanying MDD diagnosis. The benefit of psychotherapy is also unclear in cases of bereavement in the absence of other psychological disorders, such as depression. In 2013, the World Health Organization recommended against the routine use of structured psychotherapy programs for bereavement alone.[104]

Table 4: Distinguishing bereavement from major depression[1,105]

	Bereavement	Major Depression
Predominant affect	• feeling of emptiness or loss	• persistently depressed mood • inability to anticipate happiness or pleasure
Timing/Intensity	• decrease in intensity with time; occurs in waves ("pangs of grief")	• persistent, unremitting
Associated Factors	• symptoms connected to thoughts/ reminders of the deceased. • can be accompanied by positive emotions and humor	• symptoms connected to pervasive unhappiness
Thought Content	• preoccupation with memories of the deceased • self-esteem preserved • may have a passive desire to "join" the deceased, but not suicidal thoughts	• self-critical or pessimistic • self-loathing or feelings of worthlessness • thoughts of one's own death, focused on worthlessness, undeserving of life, or unable to cope with the pain depressive thoughts

Apathy

Apathy is broadly defined as disrupted motivation, resulting in reduced goal-driven behavior, cognition, and emotional responsiveness. Apathy can be variably characterized by reduced interests or emotions that cannot be attributed to diminished level of consciousness, cognitive impairment, or emotional distress.[106] Symptoms of apathy can occur in the context of depression, neurocognitive disorders, or independently as an isolated syndrome of disturbed motivation (Table 6, next page).[42] Apathy treatment is dependent on the underlying pathology (e.g., depression versus Alzheimer's disease versus Parkinson's disease),[107] but unfortunately there is limited evidence that pharmacologic therapy has significant effects in older adults with apathy symptomatology independent of depression.[108]

Table 6: Differential diagnosis of apathy and depression by exclusive and overlapping symptoms[106]

Apathy symptoms	Apathy/depression overlap symptoms	Emotional symptoms of depression
• reduced initiative • decreased participation in external activities unless engaged by another person • loss of interest in social events or everyday activities • decreased interest in starting new activities • decreased interest in the world around him or her • emotional indifference • diminished emotional reactivity • less affection than usual • lack of concern for others' feelings or interests	• psychomotor retardation • anhedonia • anergia • less physical activity than usual • decreased enthusiasm about usual interests	• sadness • feelings of guilt • negative thoughts and feelings • helplessness • hopelessness • pessimism • self-criticism • anxiety • suicidal ideation

Assessing for depression

A positive screen for depression is the starting point for a thorough evaluation. A patient assessment should elicit information regarding the duration and severity of the depressive symptoms, associated social and functional impairment, history of depressive and manic episodes, alcohol or other substance use/misuse, and the presence of cognitive dysfunction and/or psychotic symptoms. Because older adults are less likely to have depression or anxiety as the presenting problem, and symptoms of depression can co-occur with memory problems, obtaining additional information from a family member or caregiver is important when possible.[80]

Patient history

In older adults, a patient's medical history should be carefully reviewed, as somatic illnesses can induce or worsen depressive symptoms.[80] Critical elements of psychiatric history include psychosis, bipolar disorder, mania, suicidality (ideation/plan/intent), and problems with memory and functional ability. Assess patients' social environments because social factors, such as support (emotional and practical), can influence daily routine and symptomatology as well as affect the ability and desire to take medications consistently and correctly. Other important details include family history of suicidality, mood, or memory disorder, details of prior medication trials (duration and response), and prior treatment with psychotherapy.[7]

As suicide rates are high in older adults, the presence of suicidal thoughts should be carefully investigated when evaluating depression in these individuals.[7] In particular, the patient's sense of usefulness, feeling of social disconnectedness, and psychological pain associated with chronic physical illness should be assessed in older adults because of their strong association with suicidal behavior.[28]

Inquiries should include whether they have thoughts of death, wish to be dead, or even have a specific suicide plan.[80] (See more about assessing for suicide on pages 18).

Cognitive testing

Cognitive assessment should always be part of the routine evaluation of older adults, because depression is often associated with cognitive impairment.[80,82] The Mini-cog, Montreal Cognitive Assessment (MoCA), and Mini-Mental State Examination (MMSE) are examples of commonly used screening tests for cognitive dysfunction. Cognitive screening may reveal deficits in specific components of cognitive processing, such as visuospatial processing or memory, even if the total score is normal in range.[7] While screening tools differ slightly in their ability to detect cognitive impairment (which is beyond the scope of this review), studies have validated multiple tools for screening for dementia in patients with depression.[109] It is important to be aware that depression has been shown to be correlated with lower performance on these scales (especially for executive function and attention) as compared with healthy controls.[110] However, no cognitive screening tool can completely disentangle the contributions of a dementia process or depression to the cause of cognitive impairment.[111] In particularly unclear cases, formal neuropsychiatric testing may be needed.[112]

More generally, for patients with multimorbidity, frailty, or polypharmacy, a comprehensive geriatric assessment can be useful. This systematic evaluation of older persons encompasses multiple domains, including medical history, cognition, mood, functional capacity, fall risk, polypharmacy, nutrition, and social support. This permits primary care physicians to develop an integrated plan for treatment and long-term follow-up and can be effective in improving survival and function in older persons.[80]

Differential diagnosis

The differential diagnosis of late life depression is broad (Table 7). Physical examination and cognitive screening may be useful to rule out common conditions that are often confused with depression and to assess commonly co-occurring diseases.[82]

Table 7: Differential diagnosis of late-life depression[82]

Category	Examples
Central nervous system disorders	dementia, Parkinson disease, and neoplastic lesions
Related psychiatric disorders	persistent depressive disorder, bipolar, anxiety, and substance-induced mood disorders
Endocrine disorders	hypothyroidism, hyperthyroidism, and hyperparathyroidism
Adverse events of some pharmacological agents	β-blockers, centrally active antihypertensive medications, steroids, H2-blockers, sedatives, certain chemotherapy agents
Life circumstances	grief, bereavement, or financial loss
Infectious and inflammatory diseases	HIV encephalopathy, systemic lupus erythematosus
Sleep disorders	obstructive sleep apnea

Laboratory testing

There is no consensus on which laboratory tests should be obtained when evaluating depression in older patients.[80] Some sources recommend obtaining blood counts to test for anemia, measurement of blood glucose levels, and measurement of thyroid stimulating hormone, since hypothyroidism can mimic depressive symptoms. Measurement of serum levels of vitamin B_{12} are also commonly recommended because vitamin B_{12} deficiency can cause neuropsychiatric symptoms and its prevalence increases with age. Other tests, such as folate levels, can be obtained in patients with known risk factors for deficiencies (e.g., dietary restrictions or macrocytic anemia).[7]

Establishing severity and monitoring

Once the diagnosis of depression is made using the DSM-5 criteria, one needs to establish the baseline severity:

One approach to describe severity is to utilize PHQ-9:

- minimal symptoms: PHQ9 score ≤4
- mild to moderate: PHQ9 score 5-14
- moderately severe to severe: PHQ9 score 15-27

In patients with diagnosed depression, using the PHQ-9 can have several advantages. First, it has been extensively validated for assessing depression in general,[113] and it has specifically been proven to be a useful measure to monitor response to treatment.[114] Furthermore, depression severity as assessed by the PHQ-9 has been associated with meaningful clinical outcomes; for example, in one analysis of 280,145 patients with depression, worsening PHQ-9 scores were associated with increased risk of short-term hospitalization.[115] It is less clear if severity based on PHQ-9 modifies the relationship between treatment modality (i.e., therapy versus medication) and outcomes.[116]

BOTTOM LINE: Screen older adults for depression with a short tool such as the PHQ-2. Follow-up positive results with a thorough history that includes a cognitive assessment and then use DSM-5 criteria to make the diagnosis. A more comprehensive screening tool (e.g., PHQ-9) can establish depression severity and help clinicians monitor the response to treatment.

Assessing suicide-related safety of patients with depression

While there is a large range of risk considerations in the care of older vulnerable patients, such as the risks associated with driving, or falling, the risk of suicide is particularly prominent in patients with depression.

Evaluating safety of the patient

Most older patients, who are at highest risk of suicide, are seen by primary care physicians rather than psychiatrists.[69] All clinicians who care for older adults should be able to assess and manage suicide risk

in their patients and effectively identify patients who should be referred to mental health providers or who need to be sent to the hospital for emergency care.

Although routine screening for suicidality is not common practice, nearly 4% of adults experience suicidal ideations each year, and clinicians will therefore frequently encounter patients who may have thoughts of death or self-harm.[117] The frequency of depressive symptoms on the PHQ-9 in primary care settings has been linked to a risk of suicide attempts. An analysis of 207,265 PHQ-9 responses from 84,418 patients with depression (aged ≥13 years) over three years found that responses to item 9 of the PHQ-9 ("How often have you been bothered by thoughts that you would be better off dead, or of hurting yourself?") remained a moderate predictor of subsequent suicide attempts and deaths. The cumulative risk of suicide attempt over one year increased from 0.4% among outpatients reporting no thoughts of death or self-harm to 4% among those reporting thoughts of death or self-harm "nearly every day." Similarly, the cumulative risk of suicide death over one year increased from 0.03% among those reporting no thoughts of death or self-harm ideation to 0.3% among those reporting such thoughts "nearly every day." This excess risk emerged over several days and continued to grow for several months, suggesting that suicidal ideation was an enduring vulnerability rather than a reflection of short-term crisis.[118] Note that subsequent analysis have confirmed the association between reporting suicidal thoughts on a PHQ-9 and risk of completed suicide in the subsequent months to years in all age groups including older adults.[119]

Screening tools for suicidality

Primary care providers should inquire about suicide to identify those at greatest risk. Despite the importance of detecting suicidality in depressed individuals, there is no clear optimal screening tool. This is in part because too few studies are conducted to develop reliable test characteristics to be able to compare tools by efficacy.[120] We present some of the most cited tools below:

- The Columbia Suicide Severity Rating Scale (C-SSRS) is a validated and reliable instrument that measures current and past suicidal ideation, suicide attempts, preparatory behaviors, and non-suicidal self-injury (a deliberate self-harm behavior performed with no intent to die).[121] This tool is available online and through webapps and can be used to triage individuals at high-risk of suicide to emergency services (e.g., mdcalc.com).

- Suicide Assessment Five-step Evaluation and Triage (SAFE-T) is a 5-step assessment of suicide risk that guides clinicians to identify risk and protective factors, inquire into suicidal ideation, determine risk level, and choose an appropriate intervention. SAFE-T incorporates the American Psychiatric Association Practice Guidelines for suicide assessment and provides guidance about subsequent management.

Because SAFE-T provides more detailed guidance on screening and triaging patients, this tool is discussed in further detail below. The five steps in SAFE-T are: 1) Identify risk factors; 2) Identify protective factors; 3) Conduct suicide inquiry; 4) Determine risk level/intervention, and 5) Document and provide a safety plan.[121,122]

SAFE-T Step 1: Identify risk factors

Enhancing protective factors and reducing risk factors are the core of treating patients at risk for suicide. Multiple factors can increase one's risk for suicide, and there is no one factor or set of factors that is predictive of suicide with high reliability. Risk factors include demographics, psychiatric symptomatology, psychiatric illness and comorbidity, family history, personality disorder/traits, substance use/misuse,

severe medical illness, life stressors, suicidal behavior, psychological vulnerability, and access to weapons or potentially lethal doses of unused prescription medications. Identifying modifiable risk factors is key to risk reduction (Table 8).[122]

Table 8: Risk factors for suicide[121,122]

Risk factor	Description
Current/past psychiatric disorders	mood disorders, psychotic disorders, alcohol/substance use disorders, attention deficit hyperactivity disorder, post-traumatic stress disorder
Suicidal behavior	history of prior suicide attempt, aborted suicide attempt, or self-injurious behavior
Suicide history	suicide or suicide attempt of a family member
Change in treatment	discharge from a psychiatric hospital, change in usual outpatient providers
Access to lethal methods	access to firearms or other means (e.g., medications, razor blades)
Precipitants/ stressors/ interpersonal	• triggering events leading to humiliation, shame or despair • ongoing medical illness (e.g., central nervous system disorders, pain) • intoxication • family turmoil/chaos • history of physical or sexual abuse • social isolation
Key symptoms	anhedonia, hopelessness, anxiety/panic, insomnia, command hallucinations, impulsivity, executive dysfunction

SAFE-T Step 2: Identify protective factors

Variables that decrease the likelihood of suicide include both internal and external factors such as children in the home, sense of responsibility to family, pregnancy, religiosity, life satisfaction, reality-testing ability, positive coping skills, positive problem-solving skills, positive social support, and positive therapeutic relationships. One of the most critical protective factors is a connection to significant others, such as loved ones, friends, and/or family.

SAFE-T Step 3: Suicide inquiry

The third step of the SAFE-T process in determining suicide risk is a detailed and thorough suicide inquiry. Broaching the issue of suicidal ideation may be a relief for the suicidal patient by opening a discussion for communication. However, not all patients will report having suicidal ideas even when such thoughts are present.[123]

First, it is often helpful to begin with questions that address the patient's thoughts and feelings about living and dying, such as, "How does life seem to you at this point?" or "Have you ever felt that life was not worth living?" or "Did you ever wish you could go to sleep and just not wake up?".[123]

If the patient's response is affirmative, this leads to more specific questions about whether the patient has had specific thoughts or plans of death or suicide. Examples include asking about plans for the future or about recent acts or thoughts of self-harm, such as "Is death something you've thought about recently?" or "Have things ever reached the point that you've thought of harming yourself or committing suicide?".[123]

It is important to focus on the nature, frequency, intensity, and duration of suicidal thinking in the last 48 hours, as well as the worst or most intense ideation ever experienced. These factors can be a useful guide in determining the patient's propensity towards suicide. If suicidal ideation is present, it is useful to ask about the specific plans for suicide and whether any steps have actually been taken toward carrying out the plan. An inquiry will follow about the patient's understanding of the potential lethality of the method chosen and the expectation that he/she will carry it out.[123]

For patients who have thoughts of self-harm or suicide without a plan, traditional teaching has been that it is not typical for a patient rapidly to progress from ideation to attempt (Table 9). This is because the escalation in risk (starting with ideation then progressing to plan, behaviors, intent, and then attempt) has traditionally been taught as occurring over a period of time.[124] However, there are data that as many as 1 in 3 adults attempt suicide without ever endorsing a plan.[125] As such, the process model in which one progresses from suicidal ideation through numerous steps to attempt over a period is not applicable to all patients. Ultimately, patients with any suicidal ideation or a desire for death are likely highest risk for attempting suicide and should be treated as highest risk.[126] For those who have suicidal ideation who seek medical care, the largest reductions in ideation often occur within months of beginning treatment.[120]

Table 9: Assessment of suicidality, by stage of suicide risk progression[124]

Stage	Description
Ideation	• Have you ever felt that life was not worth living? • Have you ever wanted to go to sleep and not wake up? • Have things ever reached the point where you have had thoughts about harming yourself or committing suicide?
Plan	• Have you made a specific plan to harm or kill yourself? (If so, what does the plan include?) • What do you envision happening if you actually killed yourself? (e.g., escape, reunion with significant other, rebirth, reactions of others)
Behaviors	• Have you made any particular preparations? • Have you ever started to harm (or kill) yourself but stopped before doing something?
Intent	• Why do you want to harm yourself? • What means would you use to harm yourself? • Have you ever acted impulsively in the past?
Attempt	• Have you ever had a suicide attempt? • When? Triggers? What was the act? Did you seek help?

If depressive symptoms (especially anhedonia, anxiety, and insomnia) are severe, or if clinical presentation seems inconsistent with a denial of suicidal thoughts, then additional questioning can be indicated. Asking additional questions, such as asking about thoughts on the future, desire to die, or past acts of self-harm, can be useful to elucidate the underlying processes within initially reticent patients.[123,124]

SAFE-T Step 4: Determine risk level and select intervention

Once a clinician has understood the context surrounding a particular patient's case, including his or her risk factors, protective factors, and suicidality, risk level can be determined (Table 10). The more intense and specific the answers in the suicide inquiry and the more desperate, hopeless, agitated or impulsive the patient, the more likely it is that emergent treatment is needed. Patients who refuse to answer questions or who present as guarded in the suicidal inquiry may be the most concerning of all and likely warrant additional, immediate evaluation.[123]

Table 10: Levels of risk

Risk level	Suicidality	Intervention
High	recent suicide attempt or persistent ideation with strong intent or suicide rehearsal	• hospitalization likely indicated
Moderate	suicidal ideation with plan, but no intent or behavior	• develop a crisis plan if things get worse and provide crisis resources • can consider hospitalization or intensive outpatient program depending on history and risk factors
Low	thoughts of death; no plan, intent or behavior	• treatment of depressive disorder • provide crisis resources

Patients at high risk for suicide may be those who have made a potentially lethal suicide attempt in the past or have strong intent, have psychiatric disorders with severe symptoms, or have an acute precipitating event. Emergency treatment is required in patients who are highly symptomatic and have persistent thoughts of suicide, with a potential plan and/or means. Conversely, low risk patients may have thoughts of death, but have no associated plan, intent, or behavior. These individuals often have modifiable risk factors and strong protective factors.[123,124]

Whenever a clinician is concerned about suicide risk in a patient (even a lower risk patient), involving loved ones in data collection and treatment planning can be crucial. Providing patients and caregivers with resources, support, and a plan for how to manage thoughts and intents at home is also a crucial aspect of proper care.[123,124]

Resources include:

- **National Suicide Prevention Lifeline 988 or 1-800-799-4889** (deaf/hard of hearing)
- Online support at: suicidepreventionlifeline.org

SAFE-T Step 5: Documenting the assessment and providing a patient with a safety plan

The final step in a suicide assessment is documentation that includes the risk level, rationale for the assigned risk level, chosen interventions to reduce suicide risk, and plans for follow-up and treatment. Documentation should include the following elements:

- assessment of immediate risk
- rationale behind the treatment/follow up plan
- documentation of contact with loved ones and consultation with current or previous providers
- treatment plan being implemented to address modifiable factors, such as mood symptoms and/or psychosis
- how protective factors have been enhanced
- how available means of harm have been made less accessible

Suicide risk can be difficult to judge. Always seek support and obtain consultation from the most appropriate party available if you are concerned about a patient's risk of suicide, even if it is an emergency room evaluation.

BOTTOM LINE: Suicide and self-harm are serious risks in patients with depression, particularly those of advanced age. Clinicians should use standardized, systematic tools to assess suicide risk.

Treatment options for depression

A simple diagnosis of depression does not give information about the cause, nor about the best interventions. Clinicians should think about the four "P's" to guide them to understand the presenting mood concern and develop an individual-specific treatment plan.[127]

- **Predisposing**: Why is the patient vulnerable to developing the problem? Identify possible biological contributors, genetic vulnerabilities, environmental factors and psychological or personality factors that may increase the risk of developing depression.
- **Precipitating:** What triggered or exacerbated the problem? Look for the presence of significant events preceding the onset of depression, such as substance use, or interpersonal, legal, occupational, physical, or financial stressors.
- **Perpetuating:** What factors are maintaining or worsening the problem? Be vigilant for ongoing substance use, repeating behavioral patterns, biological patterns, or cognitive patterns such as attentional biases, memory biases, or hypervigilance.
- **Protective factors:** What strengths can be drawn upon or enhanced? Identify strengths or supports that may mitigate the impact of the disorder such as social support, skills, interests, and some personal characteristics.

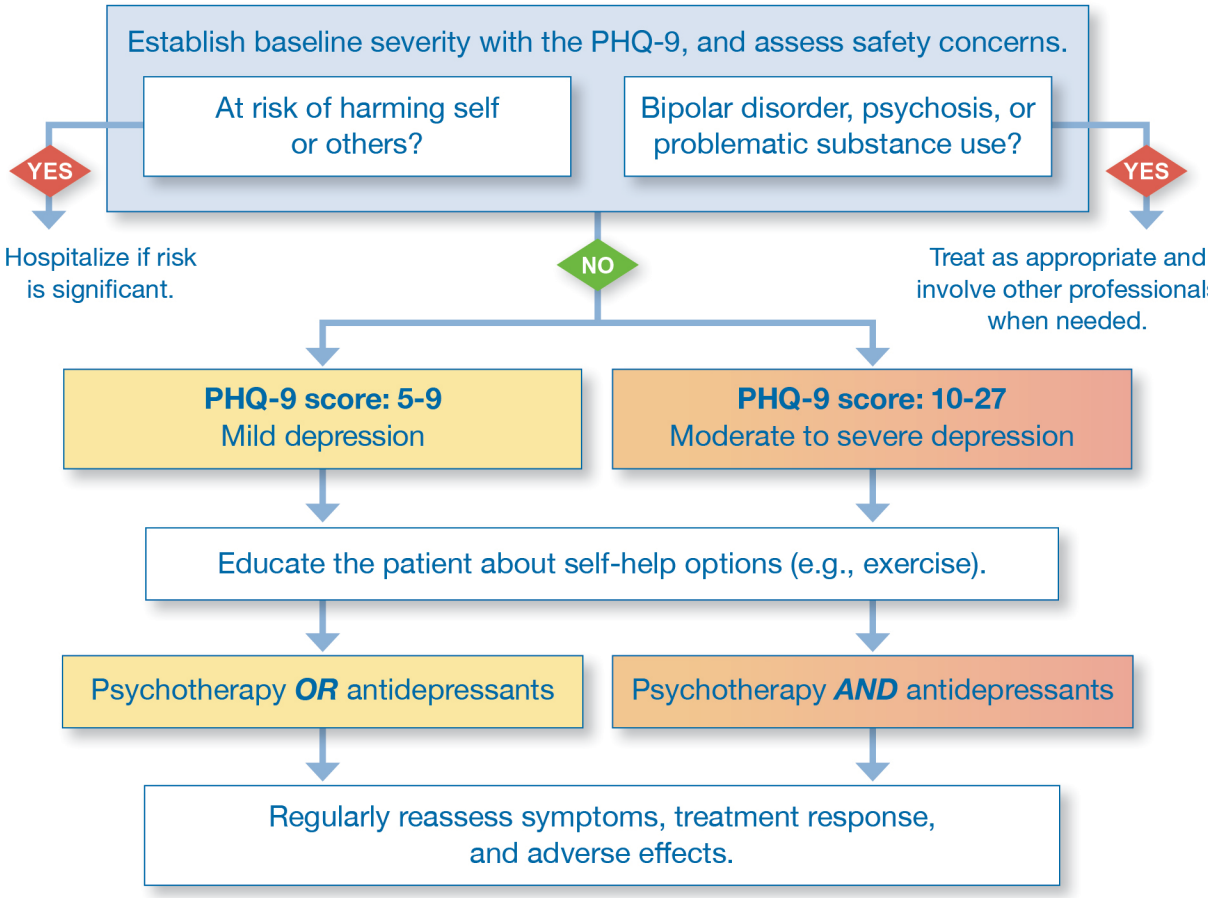
Management goals for depression in older adults should include increasing availability of treatment, improving the efficacy of the treatment plan, and preventing relapse and recurrence of depression.[8] The choice of treatment will depend on severity of depression, contraindications, access to care, and patient

preference.[8,128] Combining screening information, medical and psychological histories, diagnostic criteria, severity, and the four "P's" creates a framework for managing patients with depression and recommending evidence-based treatment options (Figure 7).

In general, depression in older patients is approached in the same way as it is for younger patients.[80] Various treatment approaches can be used to manage depression, such as psychotherapy, exercise, and pharmacotherapy; these strategies can be used alone or in combination with each other.[77,129] Effectively treating depression can reduce disability and improves quality of life.

Response to treatment (typically defined as a 50% reduction in measured symptom severity) can be quantified using tools such as the PHQ-9. Remission from depression is difficult to define consistently and may mean different things for different patients and is sometimes quantified as a PHQ-9 score <5. Full remission should mean that the patient has experienced the resolution of all symptoms of depression and the restoration of everyday functioning. When patients achieve full remission, they have a lower risk of relapse than patients who are considered to be in remission but have some minimal residual symptoms.[130]

Figure 7: Algorithm to evaluate and manage depression symptoms[131,132]



Older adults view and discuss depression in different terms than younger adults.[133] One of the most important tenets regarding successful treatment is to first address common misperceptions held by patients regarding medication for depression. An analysis of responses from 42 participants with negative attitudes toward medication for depression revealed four major themes: fear of dependence, resistance to viewing depressive symptoms as a medical illness, concern that antidepressants will prevent natural sadness, and prior negative experiences with medications for depression (especially sedation). Identifying and addressing these and other perceptions can facilitate patient-provider dialog around treatment selection. Setting realistic expectations can increase adherence with treatment.[128]

Addressing preconceived notions, providing education, and setting expectations regarding the time frame and impact of medications can be helpful in developing a therapeutic alliance. These approaches may also encourage the patient to take the medication long enough to experience the benefit, especially in the first one to two weeks when side effects might feel greater than the improvement. Discussing the medication and time to response may improve patient adherence.

Non-pharmacologic therapy

Psychotherapies

While more severe episodes of depression may require medication therapy, psychotherapies (the backbone of non-pharmacologic therapy for depression) represent effective first-line treatment for many patients. A meta-analysis of 30 studies with 5,159 patients with depression showed improved depression scores for face-to-face cognitive behavioral therapy versus control among primary care patients (standardized mean difference -0.30, 95% CI: -0.48 to -0.13).[134] Another meta-analysis of six trials including 698 patients with treatment-resistant depression similarly found better outcomes when psychotherapy was a part of the treatment regimen versus usual care alone (i.e., antidepressants) (standardized mean difference of depression scores -0.40; 95% CI: -0.65 to -0.14). While these standardized mean differences, which are used because different scales are used in different depression studies, represent only small-moderate improvements in depression over control, these modest improvements are nonetheless consistently found.[135]

A wide range of evidence-based psychotherapy options are available for patients with depression. Almost all therapies aim to ameliorate symptoms and improve function, change maladaptive thoughts, behaviors, and relationships, provide support, and enhance capacity for psychological and behavioral change. The most commonly studied psychological intervention is cognitive behavioral therapy (CBT). Additional non-pharmacologic interventions with evidence to support their use in patients with depression include other psychotherapies, including problem-solving therapy, interpersonal therapy, supportive therapy, psychodynamic psychotherapy, dialectal behavioral therapy, reminiscence/life review therapy, and family therapy as well as motivational interviewing and exercise.

Many therapists integrate elements of a variety of evidence-based therapy strategies into their practice. If a patient is amenable to trying psychotherapy and it is feasible for the patient to obtain this care, it is generally reasonable to refer a patient to any accessible therapist – even if a structured course of CBT is not what is being offered.

Effectiveness of psychotherapy

As mentioned above, psychotherapy interventions effectively improve depression in many adults, including older patients. A systematic review and meta-analysis of 27 randomized controlled trials (RCTs) with 2,245 patients aged 55 years or older with acute-phase depressive disorder found a moderate-to large-effect: a standardized mean difference of 0.73 (95% CI: 0.51-0.95) supporting psychotherapy. Interventions in the analysis included multiple therapy modalities, including common types such as CBT, problem-solving therapy, and interpersonal therapy. When the analysis was limited to trials that only included major depressive disorder, the effect size was 0.64 (95% CI: 0.42-0.87) – similarly in favor of psychotherapy.[136]

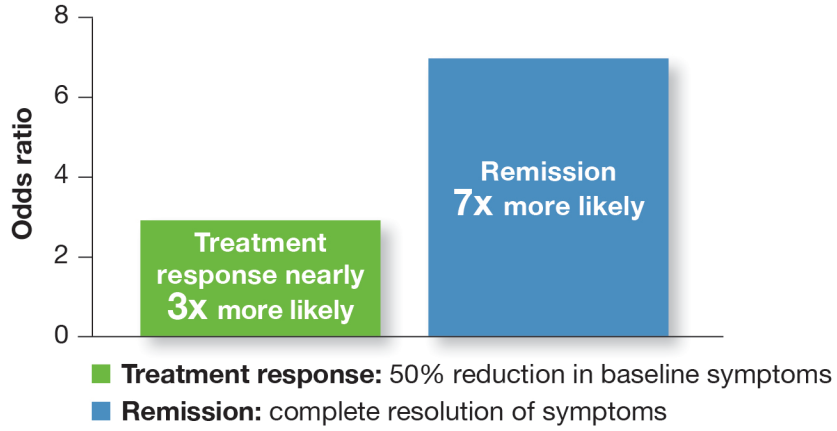
For older adults in particular, psychotherapy may be as effective as antidepressant therapy. A meta-analysis of 44 studies with 4,409 patients compared psychotherapy to drug therapy and found no benefit in one over the other (Hedges' g -0.11; 95% CI: -0.54 to 0.33). Another review found that the number of older adults with depression needed to be treated with psychotherapy for one patient to benefit could be as low as three.[137] In a few studies that looked at psychotherapy plus antidepressant therapy versus antidepressant therapy alone, there were only statistically non-significant findings that suggested possible benefit in the combined group (Hedges' g 0.41; 95% CI: -0.05 to 0.88). These studies may have been underpowered to clearly answer the research questions, and further work is needed to comment definitely on the topic.

There are myriad psychotherapy modalities. We highlight two of the most studied and widely used in the following sections.[138]

Cognitive behavioral therapy

CBT helps people understand how their thoughts, moods and behaviors are all affected by each other. Negative thoughts can generate negative feelings and precipitate maladaptive behaviors. Patients are taught to identify this connection and use this to change the way they feel by changing the way they think and behave. This is a structured therapy that can be administered using manuals/sheets. There is robust evidence that CBT reduces depression symptoms in adults; for example, one meta-analysis of 115 studies showed a moderate effect for CBT alone and in combination with medication for achieving reduction in depressive symptoms.[139] In older adults specifically, CBT has been shown to improve treatment response and lead to remission of depressive symptoms.[140] For example, a meta-analysis of 23 RCTs with 1,803 older patients (age ≥50 years) with depressive symptoms found CBT was significantly more effective at reducing depressive symptoms than treatment as usual or being on a waiting list (pooled standardized effect size six months after CBT -0.5; 95% CI: -0.95 to -0.05). CBT improved the likelihood of treatment response (pooled OR 2.87; 95% CI: 1.25–6.59) and remission (pooled OR 6.98; 95% CI: 3.04–16.02) vs. usual care or wait-list controls (Figure 8). Overall, CBT was as effective as other active treatment (e.g., antidepressant) (pooled clinician-rated effect size -0.22; 95% CI: -0.89 to 0.44).[141]

Figure 8: Improved depression response and remission with CBT vs. control



Due to many reasons, access to CBT programs may be limited. Electronic options to access CBT-based programs are in development, but there is currently limited evidence for use in older adults, who may be less familiar with computers and technologies. Analysis of computerized CBT programs in younger adults suggests benefit in adults with depression.[142,143] Furthermore, there is evidence, mostly collected during the height of the COVID19 pandemic, that electronically delivered CBT has positive effects on depressive symptoms across all ages.[144] For example, in one trial published in 2022, 175 primary care patients with depression were randomized to computer-assisted CBT versus usual care; at the end of a 6-month follow-up period, PHQ-9 scores were 3.2 points lower (95% CI, −4.5 to −0.8; P = .007) in the computerized CBT group. However, access to computerized CBT options may be limited in certain parts of the U.S. and may also not be as feasible where broadband internet access is more limited (e.g., rural areas). Future developments include accessible computerized online programs and applications that can assist in providing mental health services with known efficacy compared to face-to-face services.[142,145,146]

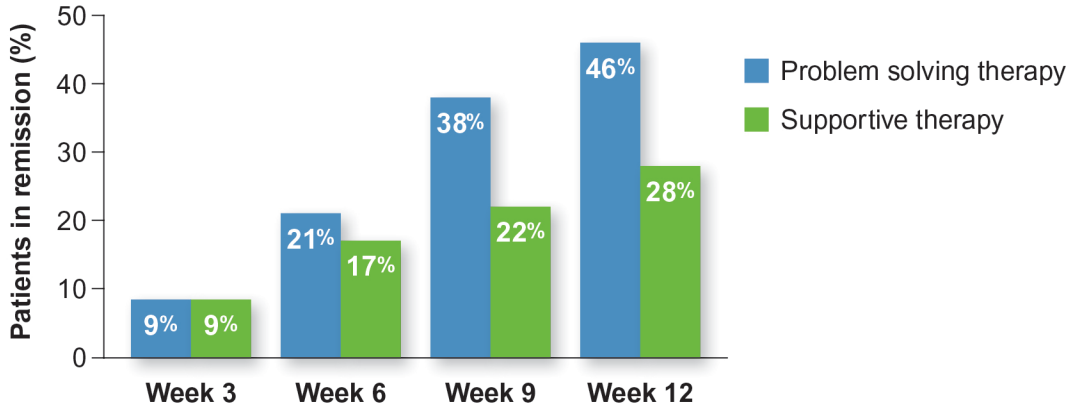
Problem-solving therapy

Problem-solving therapy is a psychotherapy intervention focused on helping patients become better managers of their lives. This therapy trains patients to identify problems central to their well-being and provides a method for selecting and implementing problem-solving plans. Participants set goals, discuss and evaluate different ways to reach goals, and create action plans. Follow-up includes evaluating effectiveness in reaching their goals and repeating the process. Problem-solving therapy has been shown to be effective in depressed older adults with executive dysfunction and those receiving home health care.[147]

A two-site RCT examined whether problem-solving therapy is an effective treatment in 221 adults aged 60 and older (mean age 73) with major depression and executive dysfunction. Participants were randomly assigned to 12 weekly sessions of problem-solving therapy versus supportive therapy and were assessed periodically over 12 weeks. Although reduction of depressive symptom severity was comparable for the two treatment groups during the first six weeks of treatment, at weeks nine and 12 the problem-solving therapy group had a greater reduction in symptom severity, a greater response rate and a greater remission rate than the supportive therapy group (Figure 9).[147] However, like most studies of

psychotherapy, these results are only generalizable to patients who have sufficent interest, motivation, and ability to remain engaged in the weekly therapy.[147]

Figure 9: Rates of remission of depression among older adults treated with problem-solving therapy[147]



Problem-solving therapy also reduces suicidal ideation in depressed older adults with executive dysfunction. In a secondary analysis of the RCT described above, 61% of participants reported suicidal ideation at baseline. The supportive therapy group had a lower rate of improvement in suicide ideation than did the problem-solving therapy group (44.6% vs 60.4%, p=0.031) at 12 weeks. This difference in reduction in suicidal ideation for the problem-solving therapy group versus supportive therapy group was sustained at 36 weeks.[148]

Lifestyle changes

While prescribing lifestyle interventions is often not thought of as a treatment for depression like it is for hypertension or other chronic medical diseases, depressed older adults should nonetheless be encouraged to live a healthy lifestyle as doing so may have positive effects on their depressive symptoms. Reasonable behavioral recommendations include improving nutrition, increasing engagement in pleasurable activities and social interactions, improving sleep hygiene, and increasing exercise. However, because depression increases the challenge of initiating lifestyle changes, these recommendations are generally accompanied by other interventions, such as pharmacotherapy or psychotherapy.[7]

Exercise

Among these lifestyle interventions, exercise has the most evidence for its effect on reducing depression. One systematic review and meta-analysis of seven RCTs with 519 patients evaluated exercise as it specifically relates to depression in older people. This study found that exercise, which most often included both strength and endurance training tailored to individual ability, modestly reduced depression severity at 3-12 months of follow-up (standardized mean difference of depression scores -0.34; 95% CI: -0.52 to -0.17).[149]

Aerobic exercise, which is often recommended to older adults for cardiovascular benefits, has also specifically been shown to improve depression. A 16-week RCT in 156 patients 50 years or older with major depression (80-90% with recurrent depression) assessed the effectiveness of an aerobic exercise

program compared with antidepressants. Participants were assigned to a program of aerobic exercise (three supervised sessions per week for 16 weeks), an antidepressant (sertraline), or combined exercise and antidepressant. Although antidepressant treatment resulted in a more rapid initial therapeutic response than exercise, after 16 weeks of treatment exercise was equally effective in reducing depression. The groups did not differ statistically on HAM-D or Beck Depression Inventory (BDI) scores (p=0.67), and all treatment groups experienced statistically and clinically significant reductions in both depression scores. Among patients receiving combination therapy, those with less severe depressive symptoms initially showed a more rapid response than those with more severe symptoms. Patients assigned to exercise or combination therapy had a greater improvement in aerobic capacity.[150]

Diet

There is less evidence for the impact of other healthy lifestyle behaviors, such as diet, on depression. For example, the small SMILES trial was conducted to assess whether nutritional interventions might impact depression. This trial randomized 67 patients to receive either nutrition counseling by a dietician or social support and found those who received the nutrition counseling had significantly greater reductions in their depression scores at the end of the 12-week study period.[151] This trial has several limitations, including an implausibly large effect size of the nutrition counseling (larger than most other interventions for treating depression), a small sample size, and problems with subject recruitment.[152] There have also been subgroup analyses of larger trials aimed at assessing the impact of diet on depression, but most have not found convincing evidence of a link between the two. For example, a subgroup of the PREDIMED trial, which was designed to study the impact of a Mediterranean diet on cardiovascular disease outcomes, did not find a link between randomization to the intervention diet and reduced odds of incidental depression during follow-up.[153] Instead, most evidence linking diet and depression is purely associative and comes from observational studies at very high risk of bias.[154,155] While healthy lifestyle should be recommended to all patients, it is not considered adequate counseling for addressing depressive symptoms.

BOTTOM LINE: Psychotherapy is an effective first line treatment for depression in older adults. Psychotherapy can encompass many evidence-based interventions, such as CBT and problem-solving therapy. Exercise should be encouraged in all patients with depression. Dietary changes alone for depression treatment are not recommended.

Antidepressant medications

The role of medication for the management of depression depends on the severity of depression. Antidepressants are effective for the treatment of moderate to severe depression. For patients with mild depression, psychotherapy may be preferred over medication to avoid potential medication side effects.

Mechanism of action of antidepressants

Consistent with the hypothesis that one or more neurotransmitters (serotonin, norepinephrine, and/or dopamine) are depleted in patients with depression, the classic action of antidepressants is to block one or more of their transporters and allow these neurotransmitters to increase concentration in intercellular spaces. Different classes of antidepressants work by different variations on this general principle (Table 11). However, it is now accepted that changes in neurotransmitter levels induced by antidepressant medications also have numerous downstream effects on protein and gene expression, which explains why it takes antidepressants several weeks to reach their full effect.

Table 11: Most common antidepressant drugs, listed by class

Class	Examples	Mechanism of action
Selective serotonin reuptake inhibitors (SSRIs)	citalopram (Celexa) escitalopram (Lexapro) fluoxetine (Prozac) paroxetine (Paxil) sertraline (Zoloft) fluvoxamine (Luvox)	selectively inhibits the reuptake of serotonin (5-HT) at the presynaptic neuronal membrane
Serotonin norepinephrine reuptake inhibitors (SNRIs)	venlafaxine (Effexor, Effexor XR) desvenlafaxine (Pristiq) duloxetine (Cymbalta) levomilnacipran (Fetzima)	combines the selective reuptake inhibition of the SSRIs with inhibition of the norepinephrine transporter
Atypical antidepressants	bupropion (Wellbutrin) mirtazapine (Remeron)	bupropion – structure related to amphetamine, inhibits presynaptic reuptake of dopamine and norepinephrine mirtazapine - blocks presynaptic central alpha$_2$-adrenergic autoreceptors, resulting in increased neurotransmission of noradrenaline and serotonin; also blocks post-synaptic 5-HT$_2$ and 5-HT$_3$ receptors
Serotonin modulator	trazodone (Desyrel, Oleptro) vilazodone (Viibryd) vortioxetine (Trintillex)	act as antagonists and agonists at postsynaptic serotonin receptors, inhibits reuptake of presynaptic serotonin

First-generation antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) are rarely used to treat depression because second-generation antidepressants like SSRIs, SNRIs, and serotonin modulators have fewer adverse events and lower potential for toxicity, with similar efficacy.[129]

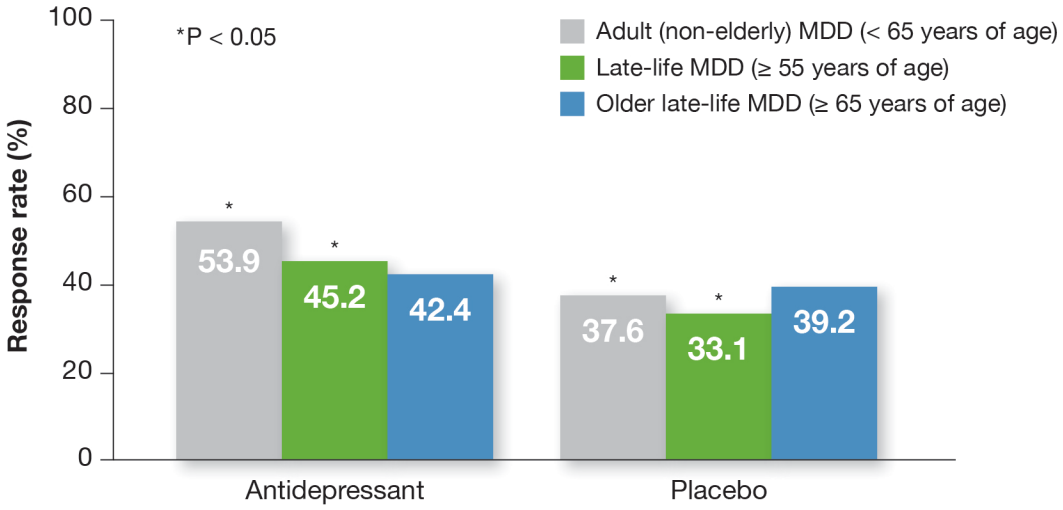
One additional antidepressant recently approved by the U.S. Food and Drug Administration (FDA) is a combination of dextromethorphan and bupropion (so it is both a glutamatergic and a monoamine modulating medication).[156] In 2022, the GEMINI trial randomized 327 patients with depression to receive dextromethorphan-bupropion or placebo. After six weeks of follow-up, clinical response was 54% in the medication group compared with 34% in the placebo group (treatment difference, 20.0%; 95% CI, 8.4%-31.6%).[157] An additional trial compared dextromethorphan-bupropion with bupropion alone and found that the combination medication led to remission of depression in 46.5% of patients compared with only 16.2% in group treated with bupropion alone (treatment difference 30.3%; 95% CI: 11.2%- 49.4%).[158] This medication has been marketed as the first “rapid-acting” antidepressant because trials showed evidence of improvement in depressive symptoms in as little as one week. However, given that the medication has just been approved, questions about the efficacy over other pharmacotherapy options, and lack of guideline recommendations involving its use (in addition to uncertainty about insurance coverage), it is not yet clear how widely, or in what patient population, this medication should be used over existing first line therapies.

Efficacy of antidepressant medications

Antidepressant medications are more effective than placebo at achieving improvement or remission of depressive symptoms. A recent systematic review and network meta-analysis analyzed 522 double-blind RCTs of 21 antidepressants versus placebo for the acute treatment of 116,477 adults with moderate to severe major depressive disorder (all ≥18 years old, mean age 44 years). Standardized mean differences for all antidepressants (the summary effect size) was 0.3 (95% credible interval 0.26-0.34) for remission (defined as the absence of depression). All antidepressants were found to be more effective than placebo, with OR for treatment response (i.e., improvement in depression symptom score by at least 50%) ranging between 2.13 (95% credible interval 1.89-2.41) and 1.37 (credible interval 1.16-1.63). Most antidepressants were equally well-tolerated based on dropout rate compared with placebo.[159]

Response to antidepressant therapy in older adults is not as robust as in younger adults. A meta-analysis of more than 20,500 older patients in 74 placebo-controlled trials, including 15 trials of patients aged 55 years and over, found that as age increased, antidepressant response rates dipped (Figure 10). In contrast to adults <65 years of age, late life depression in older adults was not responsive to antidepressants. However, response to placebo was similar across age groups.[160]

Figure 10: Comparison of antidepressant and placebo response rates according to patient age[160]



Older adults may be more likely to require longer treatment with antidepressants than younger patients. According to one meta-analysis of 10 trials with 4,165 patients 60 years and older with MDD treated with antidepressants, patients had a higher response in trials lasting 10 to 12 weeks (OR 1.73; 95% CI: 1.42-2.09) than in the six- to eight-week trials (OR 1.22; 95% CI: 1.05-1.43). This effect is has also been observed in real-world settings, where older patients (especially with co-occurring anxiety) may require more time to respond to antidepressants than their younger counterparts.[161]

Antidepressants may not have a legacy effect. That is, patients are at higher risk of experiencing relapse of their depressive symptoms if they stop their antidepressants than if they continue them. For example, one trial of 478 patients (not limited to older adults) with well-controlled depression who were on citalopram, fluoxetine, sertraline, or mirtazapine, randomized participants to either taper off their medication or continue it. At the end of the 52 week trial, relapse occurred in 39% of the medication

maintenance group and 56% of the medication-tapering group (hazard ratio 2.06; 95% CI: 1.56-2.70; P<0.001).[162] While 44% of patients were able to stop their medication without problems, this finding suggests that shared-decision making conversations about deprescribing antidepressant medications should include discussion of the elevated risk of relapse after stopping medication.

Safety

The frequency and severity of side effects can limit tolerability of these medications (see Table 12 for most common adverse effects). More than 60% of patients have at least one adverse event during treatment with a second-generation antidepressant.[163] Although most adverse events are minor, they may lead to discontinuation of treatment.

Antidepressants may have more serious adverse effects on older people compared with younger groups because of higher levels of comorbidity, age-related physiological changes, and polypharmacy. As older populations are often underrepresented in clinical trials of antidepressants and existing trials are generally short-term in duration, the risk of adverse events in the older age group is difficult to quantify precisely.[164]

Table 12: Adverse events of antidepressant drugs

Class	Adverse events
SSRIs	nausea, diarrhea, dyspepsia, headaches, drowsiness, insomnia, sexual dysfunction, falls, weight changes (typically weight gain), bleeding, orthostasis and bradycardia (especially in the elderly)
SNRIs	nausea, diarrhea, headaches, sexual dysfunction, diaphoresis, dry mouth, increased blood pressure (except duloxetine)
Atypical antidepressants	bupropion - jitteriness or agitation, headaches, tremors, lower seizure threshold mirtazapine - dry mouth, sedation, increased appetite and significant weight gain, increase in cholesterol
Serotonin modulators	trazodone - sedation, orthostatic hypotension, headache, dizziness, priapism vilazodone - diarrhea, nausea, dizziness, sexual dysfunction vortioxetine - nausea, constipation, vomiting

Table 13 outlines the starting and therapeutic doses for the various antidepressant medications, as well as side effect comparisons.

Table 13: Summary of side effects of antidepressants and considerations regarding use in older adults

MEDICATIONS	STARTING DOSE	THERAPEUTIC DOSE	PRESCRIBING TIPS
Selective serotonin reuptake inhibitors (SSRIs)			
citalopram (Celexa)	20 mg	20 mg	• first-line medications because of a better safety profile compared to other antidepressants • citalopram and escitalopram can cause QTc prolongation
escitalopram (Lexapro)	5-10 mg	10-20 mg	
sertraline (Zoloft)	25-50 mg	50-200 mg	
fluoxetine (Prozac)	10 mg	4-60 mg	• long half-life may lead to accumulation
paroxetine (Paxil)	10 mg	50 mg	• anticholinergic effects limit use in older adults
Serotonin norepinephrine reuptake inhibitors (SNRIs)			
duloxetine (Cymbalta)	20-30 mg	60 mg	• effective for co-occurring neuropathic pain
levomilnacipran (Fetzima)	20 mg	40-120 mg	• monitor for increase in blood pressure
venlafaxine (Effexor)	37.5-75 mg	150-225 mg	
desvenlafaxine (Pristiq)	25-50 mg	50-100 mg	
Atypical antidepressants			
bupropion XL (Wellbutrin XL)	150 mg	300 mg	• can improve energy and concentration • lowers appetite • helps with smoking cessation • avoid in patients with seizure risk
mirtazapine (Remeron)	7.5 mg	30 mg	• can improve appetite and sleep • may cause thrombocytopenia
Serotonin modulators			
trazodone (Desyrel)	75-150 mg	400 mg	• helps insomnia at low doses
vilazodone (Viibryd)	10 mg	20 mg	• limited data in older adults
vortioxetine (Trintellix)	5 mg	5-20 mg	
Tricyclic antidepressants (TCAs)			
amitriptyline (Elavil)	25 mg	100-300 mg	• may cause QTc prolongation, hypotension • anticholinergic side effects limit use in older patients
nortriptyline (Pamelor)	25-50 mg	75-100 mg	

In addition to the factors above, some antidepressants have significant drug-drug interactions. Especially in patients who take multiple medications, it is important to ensure the antidepressant selected will not affect management of other conditions.

Hyponatremia

Defined as serum sodium <135 mmol/L, hyponatremia associated with antidepressant use is an adverse event that disproportionally affects older patients. The clinical spectrum includes general symptoms such as nausea, fatigue, muscle cramps, and headache as well as serious neuropsychiatric symptoms of cerebral edema (e.g., confusion, restlessness, gait abnormality, lethargy, seizures, coma). Hyponatremia tends to occur within the first few weeks of treatment.[165] Older patients taking SSRIs have a 52% increased risk of hyponatremia compared to those who are not taking antidepressants.[164]

The risk of hyponatremia is the highest with SSRIs but is not confined to this class.[166,167] Older age is also a major risk factor for hyponatremia, as well as concomitant use of other hyponatremia-eliciting drugs such as thiazide diuretics, or laxatives (Table 14).[165]

Table 14: Risk factors for hyponatremia[165]

Type	Factor
Demographic	• elderly age • female sex
Co-medication	• diuretics (thiazides) • angiotensin converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) • laxatives
Comorbidity	• heart failure • kidney failure • cirrhosis • low body weight • hypothyroidism

Clinicians should be aware of the risk of hyponatremia in older adults taking antidepressant medications. Obtaining a sodium level within the first few weeks of treatment is prudent in high-risk individuals, particularly those with a history of hyponatremia. Sodium levels should be checked in all elderly patients with abrupt/unexplained mental status changes when being treated with antidepressants. In patients who develop hyponatremia while receiving treatment with an SSRI or SNRI, mirtazapine and bupropion are reasonable potential alternative agents, as they are associated with lower risk for hyponatremia.[165]

Increased risk for bleeding

Antidepressants, particularly SSRIs, may increase the risk for abnormal bleeding, particularly gastrointestinal (GI) bleeding and intracranial hemorrhage.[168,169] Bleeding is thought to be due to the blocking by SSRIs of serotonin reuptake by platelets, leading to impairment of the platelet hemostatic response.[164]

Risk factors for increased upper GI bleeding include increased age, past history of upper GI bleeding or peptic ulcer disease, and use of certain medications associated with increased bleeding risk (non-steroidal anti-inflammatory drugs (NSAIDs), oral anticoagulants, antiplatelet drugs or systemic corticosteroids). The combination of any of these factors is expected to have an additive effect to further increase the risk.[170]

Many observational studies have found an association of SSRI with increased GI bleeding when compared with not taking an antidepressant. As an example, a large observational cohort study of 60,746 people 65 years and over with late-onset depression found a significantly increased risk of upper GI bleeding for both SSRIs and other antidepressants:[164]

- SSRIs: HR 1.22 (95% CI:1.07-1.40)
- Other antidepressants: HR 1.37 (95% CI: 1.08-1.74).

Acid-suppressing medications, particularly proton pump inhibitors, reduce the risk of upper GI bleeding associated with SSRI use and in patients with concomitant use of SSRIs and NSAIDs. It may be prudent in patients at highest risk for GI bleeding to prescribe proton pump inhibitors with antidepressants, though this has not been explicitly studied in trials.[170,171]

SSRI exposure has been associated with increased risk of brain hemorrhage, largely due to intracerebral bleeding. In one meta-analysis of 16 controlled observational studies comprising 506,411 patients, SSRI use was associated with a 17% increased risk for intracranial hemorrhage (95% CI: 1.02-1.35), and was highest during the first 30 days of use.[168,169] However, the risk of intracranial hemorrhage is rare, with roughly one additional event for every 10,000 treated per year.[168]

Falls and fractures

Older patients on antidepressants may have an increased risk of falls and fractures versus older patients without antidepressant use. For example, one observational study found an association between SSRIs and falls and fractures (HR 1.66; 95% CI: 1.58-1.73).[164] However, these types of studies are significantly confounded by indication (i.e., the need for an antidepressant) and should be interpreted with caution. If patients begin to have falls after starting a new antidepressant medication, evaluating whether the medication could be the cause is reasonable.

Whether SSRIs directly contribute to skeletal changes, such as reduced bone mineral density, is not well established. It is premature to conclude a causal relationship or establish SSRIs as a secondary cause of osteoporosis.[172]

QTc prolongation

It is estimated that up to 3% of all prescriptions are for medications that may prolong the QTc interval. A meta-analysis of 16 prospective studies with 4,292 adults found that SSRIs were associated with an increase in QTc interval compared to placebo (+6.10 milliseconds; 95% CI: 3.47−8.73), and TCAs were associated with a significantly greater QTc increase than SSRIs (+7.05 milliseconds; 95% CI: 3.84−10.27). High-dose citalopram (>40 mg) was associated with significantly greater QTc prolongation than sertraline, paroxetine, and fluvoxamine.[173]

Several additional risk factors for QTc prolongation have been suggested and include: age >65 years, female sex, concomitant use of a QTc-prolonging drug or concomitant use of a drug that influences the metabolism of a QTc-prolonging drug, cardiac disease, excessive antidepressant dosing, and specific electrolyte disturbances (hypomagnesemia, hypokalemia, or hypocalcemia).

Despite mounting evidence about the impact of antidepressant use on QTc prolongation, the clinical significance of QTc prolonging properties of antidepressants is unclear and there is no clear guidance on how to manage this risk. Reasonable strategies at this time include

1. In patients with risk factors for QTc prolongation, choose an SSRI other than citalopram as first-line treatment for depression.[173]

2. Consider electrocardiogram screening and monitoring before and following the start of QTc-prolonging antidepressants if the patient is vulnerable to QTc prolongation or if two or more risk factors are present.[118]

Selecting antidepressant therapy

The **Sequenced Treatment Alternative to Relieve Depression study (STAR*D)**, a large multi-year clinical trial published in 2006, remains the best evidence base regarding pragmatic treatment strategies for routine-care patients with depression.[174] STAR*D enrolled 4,041 outpatients, ages 18-75 years, from both specialty care settings and primary medical care settings. The goal of each treatment step was the remission of depression symptoms. In this trial, patients were started on citalopram (step 1), doses were increased based on response, and then patients who did not become symptom-free after 14 weeks could proceed to the next step of treatment (step 2), where they were randomized to either switch medication or augment their treatment. Those with partial response went on to augmentation of their treatment (step 3).[175]

STAR*D used a stratified randomized design in which at steps 2 and 3 the patient could choose either to switch therapies (stop the current drug and receive one of several different treatments) or to augment their current therapy by adding one of several treatments. The design of this study reflects clinical practice, as it allowed participants to choose their own treatment and limited the randomization of each participant only to their individual range of acceptable treatment strategies.[175]

Overall in STAR*D, 48.6% of patients responded to citalopram at six weeks (i.e., had a decrease in depression symptoms by at least 50%), with 36.8% fully remitting. The average duration of treatment required to achieve remission was seven weeks. Only 16% of patients reported intolerance to treatment.[174]

Switching therapy

In patients who did not respond to treatment with the initial SSRI in STAR*D approximately one in four patients had a remission of symptoms after switching to another antidepressant. (Note that bupropion was avoided in those patients with seizure risk.) Response and remission rates were similar among the three switching options (Table 15).[174]

Table 15: Remission and response rates of switching options in STAR*D (Step 2)

Antidepressant	N	Remission (%)	Response (%)
sertraline	238	26.6	26.7
bupropion SR	239	25.5	26.1
venlafaxine XR	250	25	28.2

In practice, switching to another SSRI is a reasonable next step. In STAR*D, some of those failing to remit with citalopram went on to remit on sertraline. SSRIs differ considerably in chemical structure and

responses may vary on individual level. After trying another SSRI, the next course of action would be switching to a non-MAOI antidepressant in a different class with a different mechanism of action, such as an SNRI. In some cases, switching to bupropion or mirtazapine is also reasonable based on individual patient characteristics and evidence that many antidepressants have similar efficacy in older adults. When switching, the first drug should be withdrawn gradually over a few weeks as the second drug is gradually titrated.[176,177]

Augmentation

For patients in STAR*D who went on to augmentation with either bupropion, buspirone, or psychotherapy (CBT), the response and remission rates were not statistically different from one another (Table 16). Buspirone is an anxiolytic agent that is a partial serotonin 1A receptor agonist and it tends to be generally well-tolerated in older individuals. Adding a drug was more rapidly effective, while augmenting with CBT was better tolerated. However, fewer patients accepted CBT augmentation as a treatment option.[174]

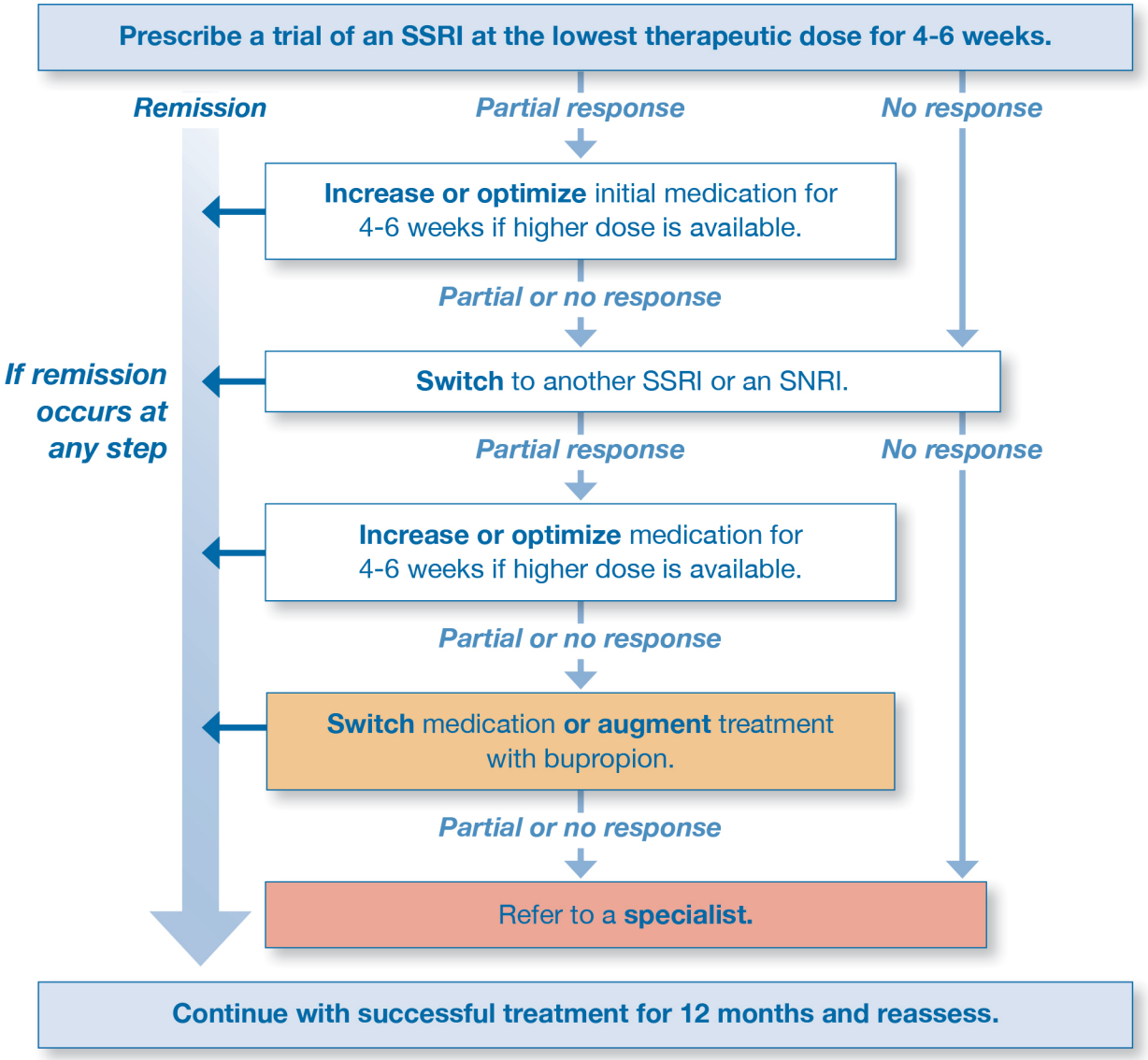
Table 16: Remission and response rates of augmentation options in STAR*D (Step 2)

Antidepressant	N	Remission (%)	Response (%)
bupropion SR	279	39	31.8
buspirone	286	32.9	26.9
CBT	85	29.4	34.1

By the completion of step 2, 50% of patients responded to treatment. With persistent and vigorous treatment, most patients entered remission in the study: after step 4, two out of every three patients were in full remission (absense of depression).[174,175]

Based on the strategies from the first two steps of the STAR*D trial, Figure 11 outlines an approach for how to start medication for depression and how to proceed if initial treatment fails.

Figure 11: Evidence-based approach to initiating antidepressants and modifying therapy



Other augmentation strategies:

- buspirone
- lithium
- antipsychotics

Specialist referral is appropriate for persistent treatment resistant depression or at any stage if:

- psychotic features
- substance use disorder
- suicidal risk

Augmentation may be selected instead of switching following an initial partial response.

Know the risks of antipsychotics. Monitor for extrapyramidal symptoms, tardive dyskinesia, and metabolic changes.

STAR*D and relevance to older adults

Although no clearly superior treatment choice was revealed, results from STAR*D confirm the benefit of following a stepwise plan of care. This includes giving antidepressants in adequate doses, monitoring patient symptoms and side effects, and appropriate adjustment of the regimen according to response after an adequate trial. Switching agents or augmenting with a second medication is reasonable. For many patients, remission will require repeated trials of sufficiently dosed antidepressants for a sufficient period of time. However, after ≥2 adequate medication trials, the likelihood of remission substantially decreases. These patients should be referred to a psychiatrist for consultation when possible.

STAR*D was not specifically focused on late life depression and had an upper age cutoff at 75 years old. In the study, 4% of participants were ≥65 years old and 24% were ≥50 years old. One secondary analysis of STAR*D separated participants into five age cohorts, and compared groups based on sociodemographic and clinical factors. Older patients (51–65 years and 66–75 years of age) had longer durations of illness, more major depressive episodes, a later age at onset of their first major depressive episode, and more general medical comorbidities. Older patients had more insomnia, less irritability, and less hypersomnia. They were less likely than younger study participants to hold negative views of themselves, report previous suicide attempts, or to endorse symptoms consistent with generalized anxiety disorder, social phobia, panic disorder, and drug abuse.[133]

The self-reported age at onset of the first depressive episode was not found to be related to clinical outcomes for older patients in STAR*D. A post-hoc analysis of STAR*D evaluated whether the age at onset of the first major depressive episode was related to clinical outcomes in a subgroup of 574 older patients (aged 55-75 years). Remission rates, response rates, and time to reach remission were not different for those with earlier-onset depression (before or at age 55) vs. those with late-onset depression (after age 55). The late-onset group had more participants who reported intolerance to citalopram (21.9% versus 11.4%, respectively; p=0.001). Doses of citalopram in STAR*D could be increased up to 60 mg as this study was conducted prior to the FDA-imposed dose limit for citalopram of 20mg.[178]

For the vast majority of frail older individuals, SSRIs are the first-line therapy for unipolar depression (with the rare exception being those who are exceedingly sensitive to hyponatremia or bleeding). Halving the standard adult starting dose helps to compensate for decreased drug clearance, improve adherence to the medication, and minimize side effects. The dose can then be increased to the minimal effective dose after one to two weeks as tolerated. It is especially important to start at a very low dose with depressed patients with anxiety, as these individuals tend to have more difficulty with tolerability when first starting medication. Although this is often referred to as the “Start low, go slow” method, it is also important to remember “Don’t stall,” as many older patients need to reach the same therapeutic dose range as younger patients to achieve remission.

After a patient starts taking an antidepressant medication, it is generally recommended to assess response and tolerability 2-4 weeks after treatment initiation – and then consider further dose adjustment based on tolerability, improvement, and dose limit.

In summary, general principles for treating older adults with depression include:

- **Start low, go slow, don’t stall.** Remember to titrate dose upward if there is a partial response to medication.
- Increase to a therapeutic dose.
- Provide adequate time for effect.

- Switching medications may be preferable in frail older adults to avoid the polypharmacy that results from augmentation.
- Be aware that medication treatment for other coexisting conditions may be affected by antidepressants.

Antidepressant medication management beyond STAR*D

Since the results of STAR*D were published, medication strategies for patients with depression have evolved, and with them, new avenues for treatment may be considered.

In STAR*D, extended-release venlafaxine was used as the representative SNRI. Since then, additional SNRI options have become available, such as duloxetine, desvenlafaxine, and levomilnacipran, which may have different effects on patients from venlafaxine. These other medications are generally considered more potent inhibitors of the norepinephrine transporter than venlafaxine. In addition, two new serotonin modulators (vortioxetine and vilazodone) have become available and have a wider range of impact on serotonin receptors outside of the classic serotonin postsynaptic reuptake inhibition.

There is growing evidence supporting the efficacy of newer antidepressants like duloxetine and vortioxetine, specifically for late life depression. However, the extent to which they compare to each other or to SSRIs has not been well established. While comparative effectiveness studies of both monotherapy and combination therapy of these new agents with older medications is awaited, it is often reasonable (given their mechanism of action) to use these same-class newer agents in place of older agents recommended by the STAR*D algorithm.

The strategy of augmentation of antidepressants with atypical antipsychotic medications has been explored in patients with unipolar, treatment-resistant depression since STAR*D (see page 44 for details). Atypical antipsychotics are now being examined in a larger number of studies than any other augmentation or treatment strategy. While these medications constitute a possible treatment modality, it is important to note that effect sizes may be modest and these medications carry considerable risks.

Pharmacogenetic testing

While there is growing interest in using pharmacogenetic testing to guide antidepressant treatment, it is currently not clear what benefit genetic analyses offer. In 2020, the FDA reviewed the evidence around this form of pharmacogenetic testing and concluded that they remained concerned about about the safe use of pharmacogenetic tests, since many claims by manufacturers were not supported by sound science.[179] More recently, the **PRIME trial** attempted to quantify the potential benefits of pharmacogenetic testing for depression. In this pragmatic trial, 1,944 patients were randomized to a have a pharmacogenomic-guided approach to medication therapy for depression versus usual care and were followed for 24 weeks. Patients randomized to receive the pharmacogenomic-guided approach to medication therapy were prescribed medications with lower potential drug-gene interaction (OR 4.32; 95% CI: 3.47-5.39; $P < 0.001$); however, there was no significant difference in depression remission rates.[180] Taken together, the current evidence suggests that pharmacogenetic testing should not be used routinely to guide treatments. However, in patients who have significant polypharmacy and have had adverse effects to medications in the past, or who have symptoms after starting treatment that make selecting medications for depression difficult, using pharmacogenetic testing may be helpful.

Maintenance of depression remission

Treatment of depression may evolve through different phases of response, which can be classified as acute, continuation, and maintenance.[129] In the acute phase, the goal of treatment is to work towards remission as much as possible, while the continuation and maintenance phases are then aimed at ongoing recovery and preventing relapse.[129]

Duration and continuation strategies for antidepressant therapy depend on the number of episodes of depression the patient has experienced. Discontinuation of antidepressants may be considered a year after remission is achieved in depressed, older patients who have had a single episode of depression. Patients who have had two episodes of depression should continue antidepressant therapy for two years. If a patient has had three or more episodes of depression, he/she should continue antidepressant therapy for at least three years or should possibly receive it indefinitely.[80] In general, we advise continuation of the same medications at the same doses as were needed to enter the maintenance phase..

Even if depression is well-controlled for a prolonged period of time, stopping medication has been associated with relapse in nearly all studies that have assessed this issue. If and when patients taper and/or discontinue antidepressant medication, providers should be vigilant and proactive in assessing for any symptoms of relapse.[181]

BOTTOM LINE: Antidepressant medications are more effective than placebo for managing depression. The STAR*D trial remains a foundation for stepped treatment strategy and is one of the best evidence-based guides for clinical management of depression to date. Treatment approaches should be tailored to patient response, and recurrence rates are relatively high for patients who taper therapy even if they've previously achieved clinical remission.

In older adults, start low, go slow, but don't stall in increasing to a therapeutic dose if the patient is not responding. The benefits of these agents must be balanced with the risks of adverse events. Based on evidence to date, there is a limited role for using pharmacogenetics to guide treatment choice,

Treatment-resistant depression

While many patients respond to treatment, one in three adults do not achieve remission.[174] Continued depression is associated with ongoing functional impairment, increased usage of health care resources, a greater risk of suicide, and overall increased mortality, especially in relation to cardiovascular disease.[182]

Treatment resistant depression is defined as the failure of at least two antidepressant treatments (of adequate dose and duration) from two distinct drug classes in a single major depressive episode.[182] In STAR*D, remission rates at each of the first two treatments were quite similar (37% and 31% for step 1 and 2, respectively) but decreased significantly after a failure of two treatments (14% and 13% for step 3 and 4, respectively).[174,182]

For patients with treatment-resistant depression, primary care providers should follow a few key steps:

1. Evaluate the safety of the patient and risk for suicide
2. (Re)establish the correct diagnosis

3. Consider barriers to adequate dose and/or duration of medication trials

If symptoms are persistent beyond these initial steps taken by a PCP, specialist involvement should be considered.

Evaluate the safety of the patient

Ask about risk of suicide and use the SAFE-T assessment as needed. See the section on assessing safety of patients with depression on page 18.

Re-establishing the correct diagnosis

Depression that is resistant to usual treatments often has multiple contributing factors that need to be addressed with an individualized treatment plan. As a first step, clinicians should confirm the primary diagnosis, assess psychiatric and medical comorbidities, and verify the adequacy of prior treatments. Diagnostic re-evaluation is necessary in cases where bipolar disorder, substance use/misuse, cognitive disorders, trauma, personality disorders, or other medical conditions are suspected.[183] This process assists with clarifying contributing causes and identifying comorbid conditions. This may reveal that a depression diagnosis was not accurate to start with or there was another comorbidity being inadequately addressed.

Referral to a psychiatrist can assist in evaluating for other psychiatric disorders. Misdiagnosis of bipolar disorder as unipolar depression may occur in nearly one-third of patients,[184] and in these cases antidepressants can be ineffective or lead to increased agitation and anxiety. Personality disorders can also contribute to treatment resistance and often are not adequately addressed. Even in the absence of a formal disorder, elements of personality are often driving forces in treatment resistance. Referral to psychotherapy, which is a mainstay of addressing personality disorders, can be a critical component of the treatment plan.[183] Inadequate treatment of any of these co-occurring conditions may be associated with treatment resistant depression. When needed and available, psychiatrists can assist in managing these complex psychiatric conditions.

Barriers to trials of medication

Barriers to adequate dose or duration of medication should be reviewed and may include factors related to both the patient and prescriber. Patient factors interfering with treatment may include side effects or practical issues such as problems obtaining medication at the pharmacy or organizing daily life to ensure adherence. Concerns, fears, beliefs, and preconceived notions on the part of patients and families about the medication as well as a patient's beliefs about their control over their own health may play a role in lack of adherence. Providers should try to elicit these concerns early in the treatment-planning process so they can be addressed.

In the same vein, medications are only effective if appropriately prescribed. Clinician factors that negatively affect provision of appropriate medication treatment include misconceptions regarding depression and aging, such as therapeutic nihilism (the belief that it is impossible to cure older people of their conditions). The quality of the clinician-patient therapeutic alliance also appears to be strongly associated with patient adherence to (and satisfaction with) treatment.[185] The limitations in ability to focus on depression due to competing medical/health priorities may also influence treatment resistance. Over-

adherence to the start low-go slow approach may stall adequate medication titration resulting in patients not receiving adequate doses for sufficient duration to be deemed a true treatment failure.

Referral to a specialist

Once a patient has failed several therapies, suicide risk has been re-evaluated, other possible diagnoses have been ruled out, and barriers to medication trials have been addressed to the extent possible, referral to a psychiatrist is indicated for additional switch or augmentation strategies or neuromodulation. While possible therapies are discussed below, they should generally be carried out in conjunction with a specialist.

Progression to switch or augmentation strategies

Psychiatrists utilize a variety of medication options that require careful evaluation of benefit and risk in older adults, and in general these medications are recommended to be used only by specialists.

Switching

Although evidence from STAR*D forms a foundation for how to proceed with treatment in patients who do not respond to initial strategies, there are important caveats to this strategy when it comes to treatment resistant depression in older patients.

In STAR*D, the response and remission rates were not statistically different for nortriptyline vs. mirtazapine, nor was the comparison of extended-release (ER) venlafaxine plus mirtazapine vs. tranylcypromine (an MAOI; Table 17). However, more patients did not tolerate the MAOI than the combination of venlafaxine ER and mirtazapine. Patients using the MAOI stopped all other serotonin-influencing medications in a 2-week washout period prior to the switch. Overall, MAOIs may be effective, but are poorly tolerated and need to be prescribed with extensive food and medication restrictions, so they are prescribed only with extreme caution given newer, safer options.

Table 17: Remission and response rates in STAR*D after augmentation therapy in treatment resistant depression (step 3)[174]

	Drug	Step	N	Remission (%)	Response (%)	Intolerance (%)
Switch	nortriptyline*	3	116	12.9	17.2	32.8
	mirtazapine	3	110	8.3	13.9	31.8
	tranylcypromine**	4	55	14.5	12.7	40
	venlafaxine ER and mirtazapine	4	50	16.0	24.0	20.0
Augment	lithium	3	63	14.5	16.1	20.6
	T_3	3	70	25.7	24.3	10

* Nortriptyline (Pamelor) is a TCA.

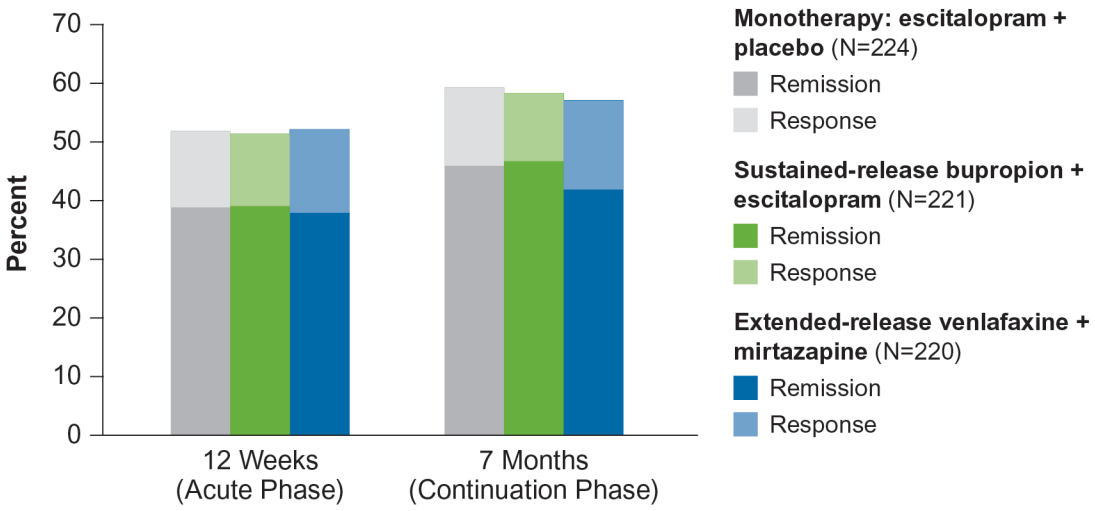
** Tranylcypromine (Parnate) is an MAOI.

Augmentation

Adding lithium or thyroid hormone, also called T_3 or liothyronine, did not achieve statistically different remission rates (Table 17). T_3 treatment was better tolerated than other strategies for treatment resistance. However, the long-term safety of T_3 in older patients with cardiovascular disease, arrhythmia, osteoporosis, and adrenal disease are not well characterized. Therefore, it is not routinely used in late life depression.[174]

When a second antidepressant is added to the first treatment, it is important to be aware that medication combinations may fare no better than monotherapy for recurrent or chronic depression and may increase side effect rates. In a follow-up trial to STAR*D, the CO-MED trial randomized 665 patients to three arms: 1) SSRI monotherapy plus placebo; 2) SSRI plus bupropion sustained release, and 3) venlafaxine ER plus mirtazapine. Remission and response rates were not different among the three treatment groups at 12 weeks and 7 months (Figure 12). At 12 weeks, the remission rates were 38.8% for escitalopram-placebo, 38.9% for bupropion-escitalopram, and 37.7% for venlafaxine-mirtazapine. At seven months, venlafaxine plus mirtazapine had a significantly larger side effect burden than monotherapy.[186]

Figure 12: Remission and response rates after progression to combination therapy (step 4)[186]



Atypical antipsychotic medications

Several atypical antipsychotic medications (APMs) are FDA-approved for augmentation in depression treatment, including aripiprazole (Abilify), brexpiprazole (Rexulti), quetiapine XR (Seroquel XR), and olanzapine with fluoxetine (Symbyax). As a class they are more different from one another and less selective in their action than antidepressants. These agents also carry a higher side effect burden than antidepressants. When APMs are used, increased monitoring for side effects is required. If these higher-risk medications are to be used in an older adult, the benefits need to be clear, robust, and consistent to outweigh the associated risks.

Efficacy

APMs may achieve response and remission for patients with depression who have failed at least one prior medication. A meta-analysis of 16 RCTs with 3,480 adults found that adjunctive APMs were significantly more effective than placebo in achieving response (OR 1.69; 95% CI:1.46–1.95; p<0.00001)

and remission (OR 2.00; 95% CI: 1.69–2.37; p<0.00001). The effect was not significantly different among the APMs.[187] A more recent RCT with 181 adults age 60 and over found a higher rates of remission in the aripiprazole group vs placebo (44% vs. 29%, p=0.03) when added to venlafaxine ER. Further, the resolution of baseline suicidal ideation was more marked with aripiprazole over placebo (73% vs. 44%, p=0.02).[188] Another recent trial of aripiprazole augmentation randomized 1,522 older adults who did not remit on one prior antidepressant to three groups: switching to bupropion alone, augmenting current antidepressant with bupropion, or augmenting current antidepressant with aripiprazole. Remission rates at 12 weeks were 22% for switching to bupropion, 27% for augmentation with bupropion, and 29% for augmentation with aripiprazole (relative risk of remission of augmentation vs. switching to bupropion 1.30; 95% CI: 1.05-1.60). Differences between other groups were not statistically significant. Relapse rates were similar across all groups.[189]

Safety

Atypical antipsychotic medications require additional monitoring, especially in older adults. A meta-analysis of RCTs found discontinuation rates due to side effects were significantly higher with APMs than placebo (OR 3.91; 95% CI: 2.68–5.72).[187] One RCT highlighted the increased risk of extrapyramidal symptoms, such as akathisia (reported in 26% of participants on aripiprazole vs 12% of those on placebo) and parkinsonism (reported in 17% of those on aripiprazole versus 2% of those on placebo).[188]

APMs are associated with extrapyramidal symptoms (EPS), which include:

- **Dystonia**: an acute, involuntary contraction of major muscle group (e.g., torticollis, retrocollis, oculogyric crisis, laryngospasm)
- **Akathesia**: Motor restlessness with a compelling urge to move and difficulty sitting still. A milder form is a subjective feeling of restlessness.
- **Parkinsonism**: Mask-like face, resting tremor, cogwheel rigidity, shuffling gait and psychomotor retardation (bradykinesia)

Tardive dyskinesia is a late side effect associated with APMs, which includes involuntary, repetitive, but irregular movements. These occur mostly in the oral, lingual, and buccal regions, and may include tongue protruding, puckering, chewing, and grimacing. Tardive dyskinesia may also occur in the hands, legs, feet, and trunk, and may be irreversible. Risk factors for tardive dyskinesia include older age, female sex, and other factors more common in older patients such as cognitive disturbance, diabetes, and treatment with antiparkinsonian agents.[190,191] While lower with atypical antipsychotic medications, rates of tardive dyskinesia increase with duration of APM use.[191]

A diagnosis of tardive dyskinesia can be made clinically, but, when the diagnosis is ambiguous, the Abnormal Involuntary Movement Scale (AIMS) is a commonly recommended screening tool and may be helpful in assessing the common areas that tardive dyskinesia occurs (face, extremities, and trunk) (Appendix 4). A rating of 2 or higher on the AIMS scale is evidence of tardive dyskinesia, which indicates either moderate severity movement in one or more body area or mild severity movement in two or more body areas.

Monitoring for other common adverse events is necessary. Metabolic changes with APMs can lead to weight gain, hyperglycemia, and hyperlipidemia. They can prolong QTc, affect blood pressure, and cause anticholinergic side effects (Table 18).

Table 18: Recommended assessments for patients on APMs[192]

What to assess	baseline	4 weeks	8 weeks	12 weeks	annually
Metabolic effects					
Weight (BMI)	X	X	X	X	
Waist circumference	X				X
Blood pressure	X			X	X
Fasting plasma glucose, or A1c	X			X	X
Fasting lipid profile	X			X	X
CBC, urea, and electrolytes	X				X
Cardiovascular effects					
QTc prolongation	X	with addition of other QT prolonging drugs			
Orthostatic hypotension	X	every assessment			
Neurologic effects					
Extrapyramidal symptoms	every assessment				
Sedation	every assessment				
Tardive dyskinesia	AIMS every 6 months				
Anticholinergic effects					
Constipation, blurred vision, dry mouth, sedation, urinary retention	every assessment				

APMs have been linked to several serious health risks, such as mortality, myocardial infarction, stroke, pneumonia, and falls. When prescribed in patients with dementia, APMs were associated with a 54% relative increase in mortality over 12 weeks.[193] We do not know whether APMs are associated with an increase in mortality for older adults without dementia..

FDA approval of APMs for augmentation in depression treatment occurred after the landmark STAR*D study. Despite several studies of APMs in depression, its role in the treatment of late life depression is not clear. For older adults, who are at high risk for adverse events from APMs, balancing the risks and benefits of APM augmentation in depression treatment is critical.

Lithium

Despite being perceived only as a treatment for bipolar disorder by many, lithium is an important option for older adults with treatment resistant depression. A systematic review and meta-analysis of nine RCTs with 237 adults with resistant depression found that lithium augmentation was significantly better than placebo in achieving a response (OR 2.89; 95% CI: 1.65-5.05).[194]

While there is less evidence as it relates to lithium augmentation in older adults specifically, one systematic review that captured 57 older patients treated with lithium augmentation found a response rate of 42% (95% CI: 21–65).[195] Additionally, patients with depression using lithium may have a lower overall risk for suicidal behavior compared with non-users; however, the absolute effect sizes are small and it is unclear if the risk reduction conferred by lithium is significantly different from that conferred by newer antidepressants.[196]

Laboratory monitoring of lithium levels is required due to risk of renal, thyroid, and parathyroid disease, and should be checked 5-7 days after a dose change or a change in health status. Patients on steady doses should have routine monitoring done at least every six months. Other laboratory measurements include baseline urine analysis, blood urea nitrogen, creatinine, thyroid stimulating hormone, and calcium levels, as well as an electrocardiogram for patients with cardiovascular risk factors. Patients with reduced kidney function are at greater risk of toxicity. Lithium should be avoided in patients with severe cardiac disease and in those prone to dehydration. Significant drug interactions can occur between lithium and thiazide diuretics, ACE inhibitors, NSAIDs, and some antibiotics.

Other medication options

Stimulants

Utilizing stimulants (e.g., methylphenidate) as stand-alone agents in depressed and apathetic patients is not supported by evidence and is not a good strategy in unipolar major depression. However, they can be used as adjunctive treatments in unipolar major depression, particularly in older adults with depression who have apathetic or neurovegetative symptoms. In one RCT of 143 older patients, combined treatment with citalopram and methylphenidate demonstrated a higher rate of remission (60.4%) compared with either drug alone (41.7% and 29.8%, respectively, p=0.01). In this trial, all treatments led to an improvement in cognitive functioning, although augmentation with methylphenidate did not show any added cognitive benefit.[197] This strategy should be avoided in patients with heart failure, arrhythmias, and coronary artery disease, as there are cardiovascular risks associated with stimulant use.[197] Methylphenidate is not recommended for treating isolated apathy symptoms in patients with dementia.[198,199]

Sedatives

The use of sedating medications such as benzodiazepines also needs to be carefully considered in older patients. Although in general the use of benzodiazepines should be minimized in treating the elderly, these agents can constitute an important treatment strategy in acute-phase treatment of patients with severe depression with anxious distress. Quickly treating anxiety and agitation may be particularly useful in preventing suicide in those at high risk, although it is less clear if the same risk/benefit profile extends to older adults.[200] Also, if anxiety is interfering with initiation of antidepressant medication (either before taking the drug or early in taking it due to the medication's activating properties), bridging an antidepressant with a benzodiazepine may be reasonable for a short time in highly selected patients.

Long term use of benzodiazepines is ultimately discouraged in the majority of older adults due to many adverse effects, which include risk of cognitive impairment, falls and fractures, impaired driving, tolerance and dependence, and overdose mortality.[201]

Neuromodulation therapies

Clinicians may choose to refer patients with treatment resistant depression to a psychiatric specialist, who may recommend treatment with neuromodulation, such as electroconvulsive therapy (ECT) or transcranial magnetic stimulation (TMS).

Electroconvulsive therapy (ECT)

ECT can become the treatment of choice in severely depressed patients with significant safety concerns, such as suicidality, catatonia, failure to thrive, or psychotic/agitated features. ECT requires anesthesia and comprehensive monitoring while an electrical current induces a seizure lasting <1 minute. ECT is typically administered about three times a week for one to four weeks, with an average course of 10 treatments. It has been shown to improve symptoms of treatment resistant depression, with a rapid response to treatment.[202] The Consortium for Research in ECT report showed that ECT resulted in prompt improvement for the majority of patients and reported a 75% remission rate among 217 patients (aged 18-85), with 65% of patients achieving remission by the fourth week of treatment.[202] However, the risk of relapse is high without the use of other interventions to maintain remission such as maintenance treatment or a taper of ECT or the use of antidepressant medications.[202,203]

Side effects of ECT include headache, upset stomach, muscle aches, and memory loss, which generally resolves in days to weeks. For the majority of patients, cognitive side effects are transient and resolve completely in days to weeks, although a small minority have lasting difficulties (likely influenced by many other factors). Conversely, some patients have improvement in cognition as depression goes into remission.[204] ECT can be safely utilized in patients with dementia, as cognitive status is not a contraindication to treatment.[203-205] In fact, ECT is an appropriate treatment strategy for patients with treatment-resistant, severe agitation in dementia.[206]

While psychiatrists generally select the patients for whom ECT might be appropriate, primary care providers may be asked to medically evaluate patients prior to ECT. Although there are no strict contraindications, ECT does pose increased risk in those with unstable cardiac disease (ischemia, arrhythmias, or uncontrolled hypertension), recent stroke, or increased intracranial pressure. ECT can be safely used in the elderly and in persons with pacemakers and automated implantable cardioverter defibrillators, or those using blood thinners. A pre-ECT workup should include an emphasis on uncovering cardiopulmonary disease, evidence of neurological symptoms, or difficulty with anesthesia as well as serum electrolytes, kidney function tests and an ECG.[207,208]

Transcranial magnetic stimulation (TMS)

An emerging area of importance in treatment resistant depression is TMS, which involves administering magnetic impulses to activate neurons primarily in the prefrontal cortex, an area that has been implicated in depression. No anesthesia is required for the procedure, and it is generally well tolerated with side effects such as mild site discomfort, headache, and light-headedness. However, TMS requires treatments five days a week over approximately six weeks. TMS has not been well studied in older patients, and there is a trend to suggest lower efficacy in late life depression.[209] Although the impact in significant treatment resistance and speed of improvement of TMS may not be equivalent to ECT, it is recognized as a potential consideration within the approach of treatment resistant depression.[210-212] Psychiatrists generally select patients for whom TMS might be appropriate.

Ketamine

Ketamine, an N-methyl-D-aspartate antagonist, has received recent FDA approval for the treatment of depression in an intranasal form. It may have a role in the treatment of some patients who have not benefited from standard therapies. In one RCT, 297 patients who had previously had at least some response to oral antidepressants were randomized to a) esketamine nasal spray plus an oral antidepressant versus b) continuing their oral antidepressant alone for 16 weeks. Patients randomized to the esketamine + antidepressant treatment who had previously achieved stable remission on an oral antidepressant had a 51% reduced risk of relapse (HR 0.49; 95% CI: 0.29-0.84) compared with those randomized to the oral antidepressant alone.[213] However, there is still uncertainty around the best route (intranasal versus intravenous versus oral), dose, and long-term efficacy.[214] Concerning older adults in particular, the **TRANSFORM-3 trial** randomized 138 older adults with treatment-resistant depression to receive esketamine nasal spray and an oral antidepressant (esketamine/antidepressant) or only an oral antidepressant for 4 weeks. No significant benefit to the esketamine treatment was found with regard to the primary endpoint (change in the Montgomery-Asberg Depression Rating Scale).[215] Therefore, while ketamine may be an appropriate treatment adjunct for some patients, it is likely not appropriate for most older adults at the time of this publication.

BOTTOM LINE: Patients who fail to respond to two or more antidepressant trials at a therapeutic dose for an adequate duration have treatment-resistant depression. In these patients, primary care providers should assess patient safety, re-confirm the diagnosis of depression, and address barriers to medication trials – and then involve a specialist for consideration of trials of newer and/or riskier medications or neuromodulation.

Putting it all together

Depression is not a normal part of aging and should not be neglected in clinical evaluations of older adults. Screening for depression in older adults is similar to screening for depression in adults of all ages, and we recommend using the validated 2-question tool PHQ-2. If the PHQ-2 is positive (score ≥3), clinicians should confirm the diagnosis using DSM-5 criteria and determine the severity using a validated tool like PHQ-9 or GDS (which may be better for patients with cognitive impairment). Older adults have particularly high rates of suicide (especially older men), and healthcare professionals should be prepared to evaluate the risk of suicide and intervene if needed to ensure safety.

Management of depression involves offering treatment based on depression severity and incorporation of patient preferences. Psychotherapies, such as cognitive behavioral therapy, are effective treatments for depression in older adults and may be considered as first line treatments depending on symptom severity and patient preferences. Antidepressants are also used to treat depression in older adults, though their efficacy may vary based on numerous clinical factors and they may be less efficacious than they are in younger patients. Clinical evidence has shown that the particular drug used is not as important as following a rational plan that includes prescribing antidepressants in adequate doses for adequate duration, monitoring patients regularly for symptoms and side effects (e.g., repeating PHQ-9), and adjusting regimens accordingly after an adequate medication trial.

For treatment resistant depression in older patients, clinicians should follow several fundamental steps. These steps include: evaluation of safety and suicide risk, re-establishing/confirming a diagnosis, and employing augmentation/switching strategies or non-medication therapies, which includes referral to a

specialist for consideration of neuromodulation. Treatment-resistant depression should be managed in consultation with a psychiatrist when possible.

In summary, depression is treatable disorder that is under-recognized in older adults. Appropriate treatment can reduce disability and improves quality of life.

Appendix 1: Patient Health Questionnaire-2 (PHQ-2)

Patient Health Questionnaire, 2-item (PHQ-2)

For each item, check the box that describes how often you have felt this way in the last two weeks.

	Not at all	Several days	More than half of days	Nearly every day
SCORE	0	1	2	3
Over the past two weeks, how often have you been bothered by feeling down, depressed, or hopeless?	❑	❑	❑	❑
Over the past two weeks, how often have you been bothered by little interest or pleasure in doing things?	❑	❑	❑	❑
Add columns:		+		+

If score is 3 or higher, perform clinical assessment for depression and/or ask the patient to complete the PHQ-9.

Appendix 2: Patient Health Questionnaire-9 (PHQ-9)

Patient Health Questionnaire, 9-item (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half of days	Nearly every day
SCORE PER ITEM	**0**	**1**	**2**	**3**
Little interest or pleasure in doing things	❑	❑	❑	❑
Feeling down, depressed, or hopeless	❑	❑	❑	❑
Trouble falling or staying asleep, or sleeping too much	❑	❑	❑	❑
Feeling tired or having little energy	❑	❑	❑	❑
Poor appetite or overeating	❑	❑	❑	❑
Feeling bad about yourself—or that you are a failure or have let yourself or your family down	❑	❑	❑	❑
Trouble concentrating on things, such as reading the newspaper or watching television	❑	❑	❑	❑
Moving or speaking so slowly that other people could have noticed. Or the opposite—being so fidgety or restless that you have been moving around a lot more than usual	❑	❑	❑	❑
Thoughts that you would be better off dead, or of hurting yourself	❑	❑	❑	❑

For total score, add columns: _____ + _____ + _____

Assess depression severity using the total score of the PHQ-9.

TOTAL SCORE	DEPRESSION SEVERITY
1-4	no clinical depression
5-9	mild depression
10-27	moderate to severe depression

Appendix 3: Geriatric Depression Scale-15

	Yes	No
1. Are you basically satisfied with your life?		✓
2. Have you dropped many of your activities and interests?	✓	
3. Do you feel that your life is empty?	✓	
4. Do you often get bored?	✓	
5. Are you in good spirits most of the time?		✓
6. Are you afraid that something bad is going to happen to you?	✓	
7. Do you feel happy most of the time?		✓
8. Do you often feel helpless?	✓	
9. Do you prefer to stay home, rather than going out and doing new things?	✓	
10. Do you feel you have more problems with memory than most?	✓	
11. Do you think it is wonderful to be alive now?		✓
12. Do you feel pretty worthless the way you are now?	✓	
13. Do you feel full of energy?		✓
14. Do you feel that your situation is hopeless?	✓	
15. Do you think that most people are better off than you are?	✓	

Score 1 point for each answer with a check mark.

Score >5: suggests depression; score ≥10 indicative of depression

Appendix 4: Abnormal Involuntary Movement Scale (AIMS)

Patient Name _____ Date of Visit _____

Code: 0 = None 1 = Minimal 2 = Mild 3 = Moderate 4 = Severe

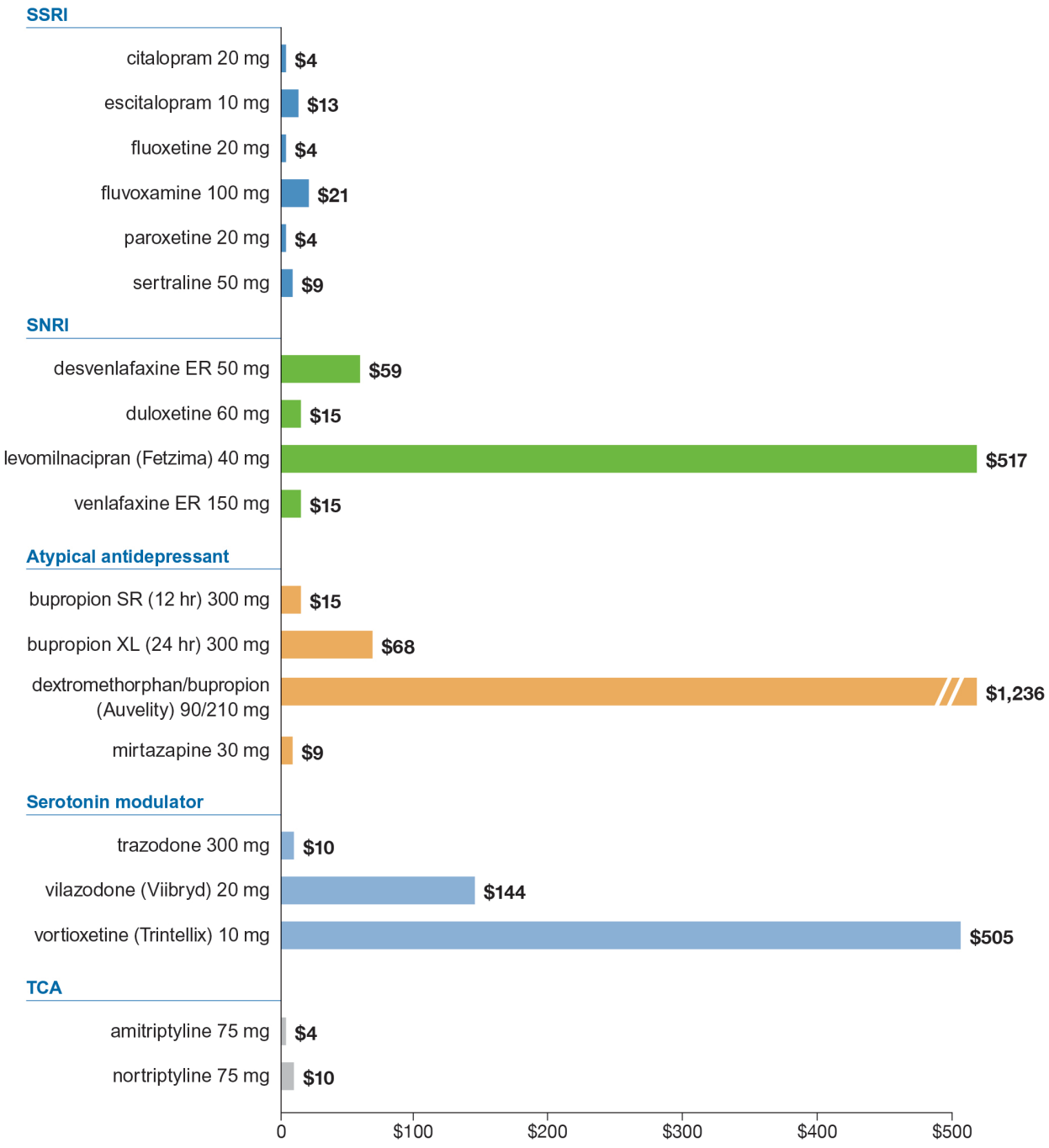
Movement Ratings:
- Rate highest severity observed in category I, II, III.
- Rate movements that occur upon activation one point less than those observed spontaneously.
- Circle movements as well as code number that applies.

		RATER / DATE	RATER / DATE	RATER / DATE	RATER / DATE
I FACIAL & ORAL MOVEMENTS	**1. Muscles of Facial Expression** e.g. movements of forehead, eyebrows, periorbital area, cheeks, including frowning, blinking, smiling, grimacing	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	2. Lips and Perioral Area e.g. puckering, pouting, smacking	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	3. Jaw Biting, clenching, chewing, mouth opening , lateral movement	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	4. Tongue Rate only increases in movement both in and out of mouth. NOT inability to sustain movement. Darting in and out of mouth	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
II EXTREMITY MOVEMENTS	**5. Upper (arms, wrists, hands, fingers)** Include choreic movements (i.e. rapid objectively purposeless, irregular, spontaneous) athetoid movements. DO NOT INCLUDE TREMOR (i.e. repetitive, regular, rhythmic)	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	6. Lower (legs, knees, ankles, toes) Lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion of foot	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
III TRUNK MOVEMENTS	**7. Neck, shoulders and hips** Rocking, twisting, squirming, pelvic gyrations	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
IV GLOBAL JUDGEMENT	**8. Severity of abnormal movements overall**	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	9. Incapacitation due to abnormal movements	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	10. Patient's awareness of abnormal movements. Rate only patients report: No Awareness = 0 Aware, no distress = 1 Aware, mild distress = 2 Aware, moderate distress = 3 Aware, severe distress = 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
V DENTAL STATUS	**11. Current problems with teeth and/or dentures**	YES NO	YES NO	YES NO	YES NO
	12. Are dentures usually worn	YES NO	YES NO	YES NO	YES NO
	13. Endentia?	YES NO	YES NO	YES NO	YES NO
	14. Do movements disappear with sleep?	YES NO	YES NO	YES NO	YES NO

Available for use in the public domain.

Appendix 5: Costs of select antidepressants

Figure 13: Price of a 30-day supply of antidepressant medications



Pharmacy prices from goodrx.com, January 2023. Listed doses are based on Defined Daily Doses by the World Health Organization. All doses shown are generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives. These doses should not be used as a guide for treatment.

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About this publication

These are general recommendations only; specific clinical decisions should be made by the treating clinician based on an individual patient's clinical condition.

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