



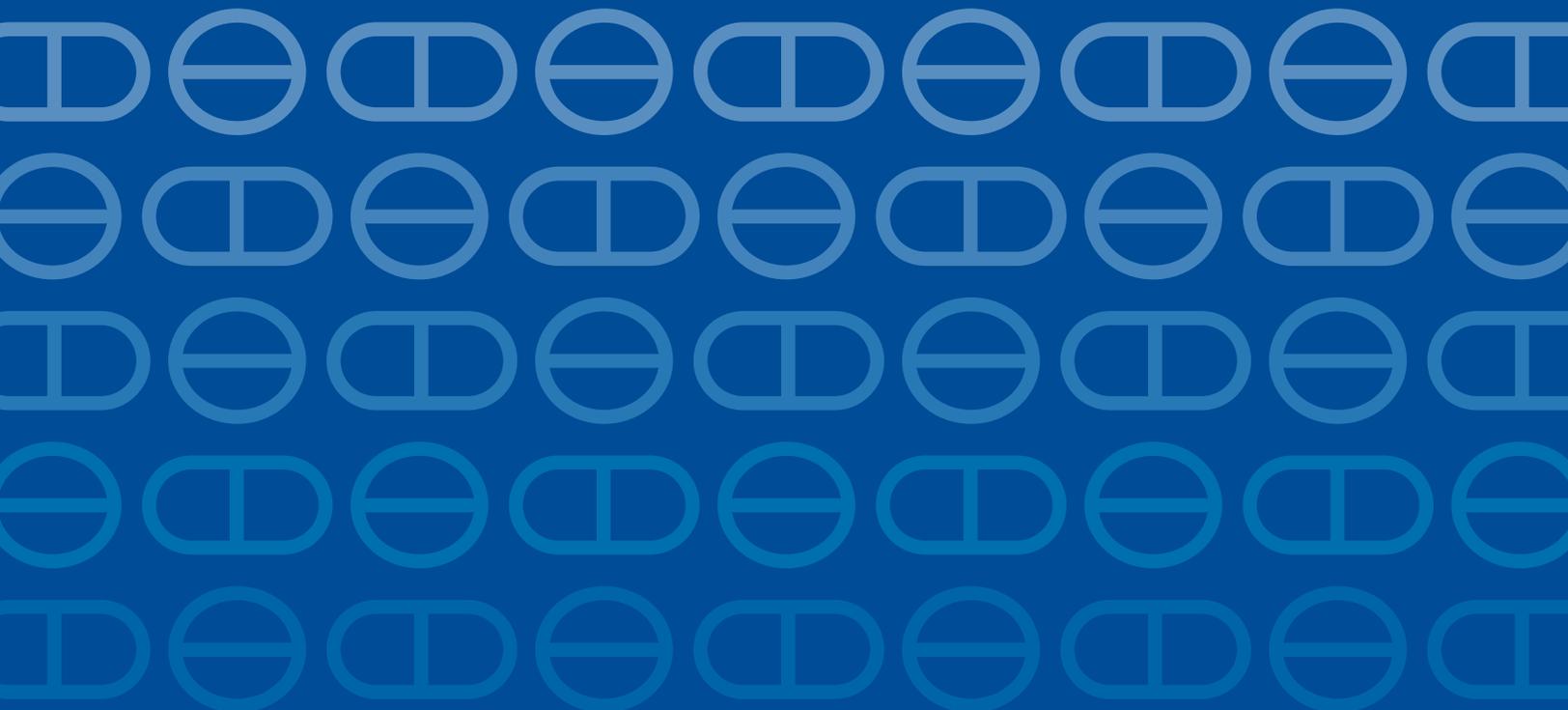
Pharmaceutical Assistance  
Contract for the Elderly



Balanced information for better care

# Managing depression in older patients

A guide to the most current evidence



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## A guide to the most current evidence

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### Managing depression in older patients

#### Accreditation:

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#### Credit Designation:

The Harvard Medical School designates this enduring material for a maximum of 1.5 *AMA PRA Category 1 Credits*<sup>™</sup>. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

#### 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 top 4-5 key messages
- “Academic detailing” educational sessions in physicians’ 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:

- Screen for depression in older adults, diagnosing with DSM-5 criteria and establishing severity using a validated tool like PHQ-9.
- Offer treatment based on depression severity and patient preference:
  - Refer to psychotherapy, such as CBT.

- Prescribe an antidepressant, such as escitalopram or sertraline.
- Monitor response to treatment, look for side effects, titrate doses as needed, or switch therapy if no or low response.
- In patients at risk, evaluate risk of suicide and develop a plan using the SAFE-T framework.
- Refer to a specialist for issues of ongoing treatment resistance or safety concerns.

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# Introduction

The word depression conveys universal feelings of frustration, intense sadness or disappointment, and in addition, also describes a serious medical illness that negatively affects how one feels, thinks, and acts. Clinical depression, often referred to as major depressive disorder, can be defined as the presence of sadness or anhedonia (a loss of interest in activities one used to enjoy) with five or more symptoms of depression, as we describe later (see page 8).<sup>1</sup> This document primarily discusses unipolar major depressive disorder and persistent depressive disorder, previously called dysthymia. The terms depression and major depressive disorder will be used interchangeably throughout this document, and depressive symptoms refer to disease manifestations.

Depression contributes to a variety of distressing emotional, cognitive, and physical problems and can decrease a person's ability to function in the way they once did. Although depression symptoms are common in persons who are aging or in poor physical health, it is not a normal part of aging.<sup>2</sup> This document summarizes the evidence for identifying, diagnosing, and managing older adults with depression, addressing the unique challenges that face this population.

## Late life depression

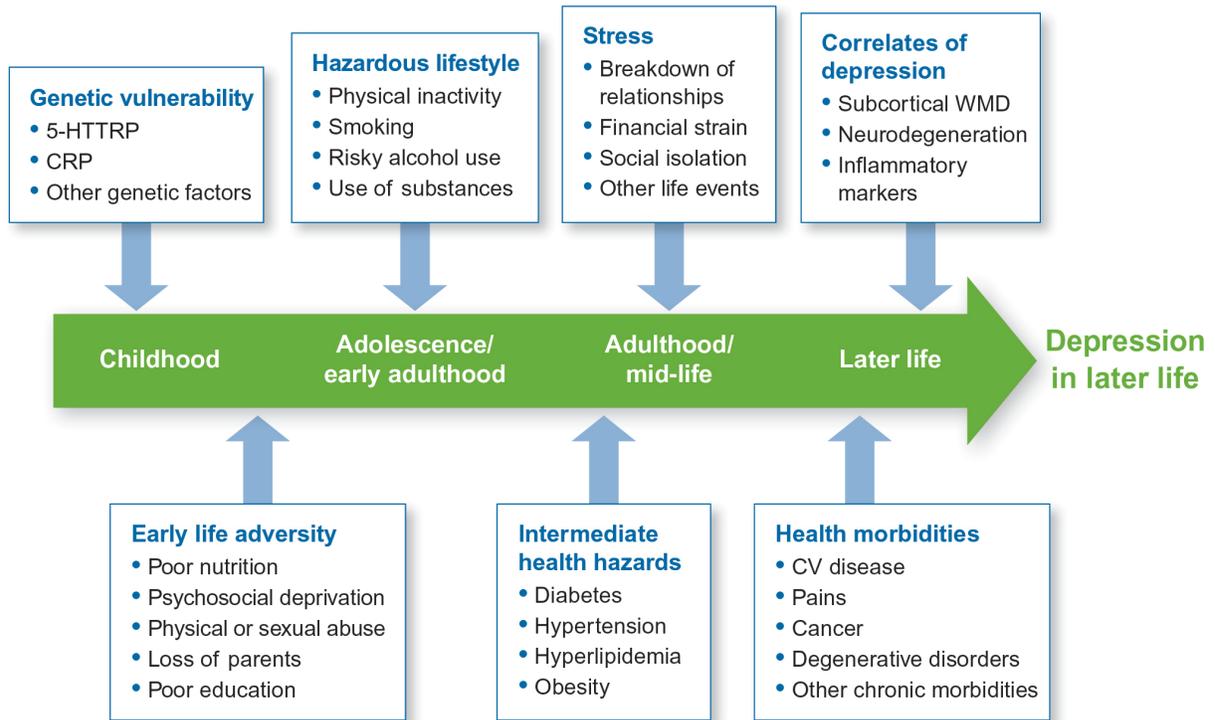
While depression can occur at any age, a depressive episode that occurs in older adults is referred to as late life depression. Major depressive disorder is common, affecting 5% of community-dwelling older adults, with 8-16% of older adults reporting clinically significant depressive symptoms.<sup>2</sup> Rates of major depression and minor depression symptoms in medical and institutional settings are dramatically higher (Table 1). Although patients with minor depression symptoms have notable symptoms, they are not sufficient to meet criteria for major depression.<sup>2-5</sup>

**Table 1: Prevalence of depression in older patients<sup>2-5</sup>**

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

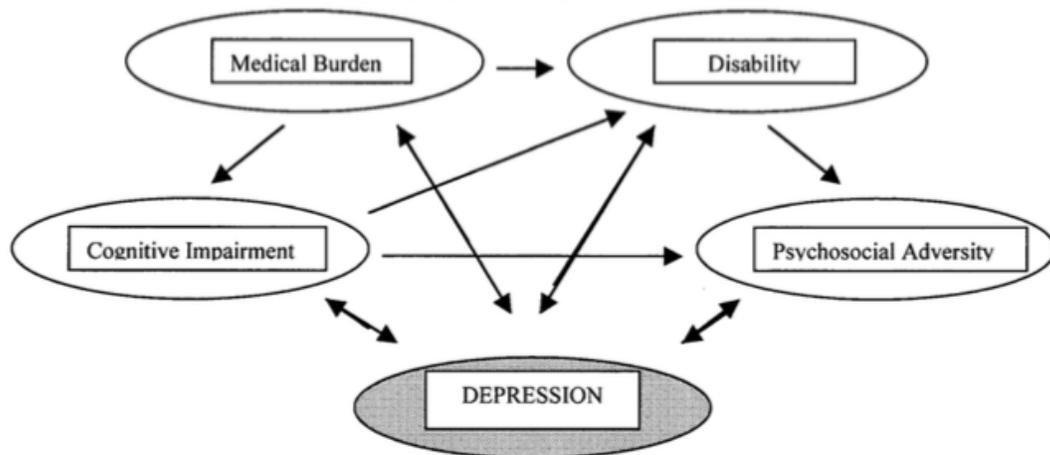
Risk factors for depression accumulate through life and encompass overall health, lifestyle, stress and adversity (Figure 1).

Figure 1: Risk factors through the life span<sup>6</sup>



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).<sup>3</sup>

Figure 2: Health factors that contribute to late life depression<sup>3</sup>



Depression increases medical costs and burden. In 2010, costs of depression in adults of all ages totaled \$210 billion due to absenteeism, medical, drug, and suicide-related costs.<sup>7</sup> Patients with significant depression had total health care costs roughly 50% higher than those without.<sup>8,9</sup> Compared to non-depressed elders, those with late life depression had nearly twice the number of doctor's appointments and spent nearly twice as many days in the hospital.<sup>10,11</sup>

## Undertreating depression

Depression in the elderly is under-recognized in the primary care setting. Comorbid medical conditions and lower functional expectations of elderly patients can obscure the degree of impairment that comes with depression in this population. Older patients do not always report depressed mood and may have less specific symptoms, such as insomnia, anorexia, fatigue, pain, irritability, anxiety, or multiple unexplained medical symptoms.<sup>2,12</sup> Elderly patients may also have more stigmatized attitudes about mental illness, which may prevent them from seeking care.<sup>8,13</sup>

Only one in three adults who screen positive for depression receive treatment. A study of the U.S. Medical Expenditure Panel Surveys analyzed 46,417 responses submitted by participants aged 18 years or older. Of adults who screened positive for depression, 28.7% received any depression treatment. When treatment was recommended antidepressants were prescribed to over 80% of patients, with psychotherapy utilized by 20-30% of patients. Older adults overwhelmingly received depression care in primary care settings and had a much lower utilization of psychotherapy than younger adults.<sup>14</sup>

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**BOTTOM LINE: Depression is common older adults, but it is not a normal part of aging. Late life depression is a heterogeneous illness that is associated with a range of associated health conditions and is undertreated in primary care.**

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## Impact of depression on health outcomes

Patients with depression in late life have worse health outcomes than patients without depression, such as increased risk of stroke, mortality in patients with comorbid coronary heart disease, and elevated risk of suicide.<sup>15-17</sup> Late life depression is associated with cerebrovascular comorbidities, neurodegenerative pathologies, and biochemical changes, which are broadly described as vascular depression (see page 11 for details). Sustained vigilance for and appropriate management of conditions comorbid with depression may delay or even prevent the patient's decline in the long run.

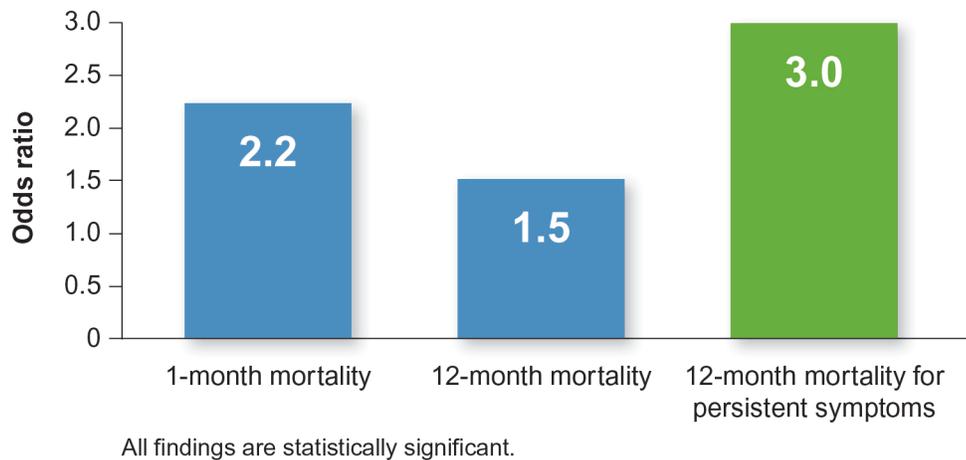
## Risk of cardiovascular disease and mortality

The link between depression in older individuals and increased risk of adverse outcomes in cardiovascular disease is well established.<sup>18-21</sup> In a meta-analysis of 21 studies with 47,625 older people (mean age of 74 years) over a median 8.8 years, participants with depressive symptoms had a higher risk of stroke (Hazard Ratio [HR] 1.36; 95% confidence interval [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), than those without depressive symptoms. Patients with apathy 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).<sup>22</sup>

Depression has been associated with an increased risk of mortality. 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-5), whereas only 8.6% had a recorded diagnosis of depression. After adjusting for confounders, baseline depression was associated with all-cause mortality one month (odds ratio [OR], 2.2; 95% CI: 1.18-4.10) and 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 the highest risk of mortality and were associated with a three-fold increase in mortality at 12 months (95% CI: 1.08-8.20) (Figure 3).<sup>23</sup>

**Figure 3: Depression and all-cause mortality after cardiac surgery<sup>23</sup>**



## Interaction of cognition and depression in late life

Late life depression is associated with cognitive deficits and increased risk for cognitive decline. Symptoms can involve loss of executive function, attention, verbal learning, motor speed, and processing speed.<sup>24</sup> In addition, the diminished ability to think or concentrate is a core criterion in the Diagnostic and Statistical Manual of Mental Disorders, 5<sup>th</sup> Edition (DSM-5) for major depressive disorder. Cognitive impairment complicates the identification and treatment of late life depression and has been detected in 40–60% of non-demented individuals with late life depression.<sup>25</sup> The correlation between depression and cognitive decline is complex and multifactorial. Late life depression may be potentially both a risk factor and early symptom of dementia.<sup>24,26</sup>

A prospective cohort examined trajectories of depressive symptoms and risk of new diagnosis of dementia 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 increasing 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. 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 the consistently minimal symptoms. No difference in dementia risk between

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moderate and high and increasing depression symptoms was observed.<sup>27</sup> Tracking the depressive symptoms of older individuals over time may help identify those at greatest risk for dementia.

Remission of depression in older adults does not eliminate the risk of cognitive decline. 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 assessing for cognitive decline. Older adults with depression had more cognitive decline, especially for episodic and working memory, than never depressed older adults, regardless of whether depression remitted.<sup>26</sup>

## Suicide in the elderly

Older adults have the highest rate of suicide with depression being a major risk factor.<sup>28</sup> 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.<sup>29</sup> Older Caucasian men in particular have the highest suicide rate of all demographics.<sup>17,30</sup> 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 to commit suicide. Men are more likely to utilize a firearm, while women are more likely to attempt overdose by pills.<sup>31</sup>

Among patients with major depressive disorder, 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 (HR 7.74; 95% CI: 3.40-17.6) was the major risk factor determining overall long-term risk.<sup>32</sup>

Access to a firearm is a modifiable suicide risk factor. Suicide attempts by firearms were more effective than any other means of suicide, with 80%-90% of attempts being successful.<sup>33,34</sup> Access to firearms increases the risk for completed suicide three-fold (OR 3.24; 95% CI: 2.41-4.40).<sup>33</sup> More than 50% of completed suicides utilize a fire arm with other common means, suffocation and poisoning, accounting for 26% and 15% of completed suicides, respectively.<sup>35</sup>

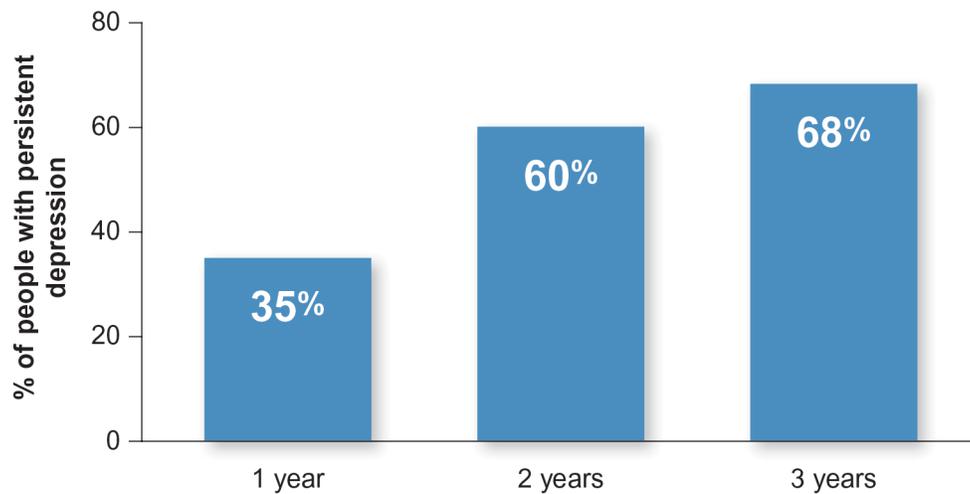
It is common for older individuals who attempt suicide to contact their primary care providers in the time leading up to suicide compared to younger adults. A review of 40 studies examining the rates of contact between suicide victims and their care providers revealed that while 3 in 4 individuals who 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 1 in 5 suicide victims had contact with mental health services within a month before their suicide. Lifetime mental health service rates of contact for women tended to be higher than for men.<sup>36</sup> Healthcare providers must be receptive to the warning signs of instability and suicidality in their patients.

## Prognosis for depression in older adults

Many patients with depression remain symptomatic or have delayed recovery, despite availability of pharmacologic and psychosocial treatment.<sup>37</sup> About two-thirds of older patients recover from depression in three years. A longitudinal 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 in a primary care cohort. 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 4).<sup>37,38</sup>

**Figure 4: Proportion of primary care patients age 55 and over remitting from a major depressive episode<sup>38</sup>**



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, comorbid anxiety symptoms, and executive dysfunction.<sup>37,38</sup> Factors predicting the chronicity of a depressive episode include comorbid medical illness, duration of depressive episode, persistent depressive disorder, and “double depression” (persistent depressive disorder in addition to major depression), personality disorder and neuroimaging abnormality.<sup>37,39</sup>

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**BOTTOM LINE: Patients with depression in late life have increased risk of stroke and mortality. Sustained vigilance for the presence of conditions comorbid with depression may delay or even prevent the patient’s decline in the long run. Suicide rates are high in older adults.**

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## Screening for depression in the elderly

The U.S. Preventive Services Task Force (USPSTF) recommends screening all adults for depression. Screening should be implemented with support systems in place to ensure accurate diagnosis, effective treatment, and appropriate follow-up. The harms of screening for depression in adults is small to none while integrated programs could improve clinical outcomes through the reduction or remission of depression symptoms and decrease clinical morbidity.<sup>40</sup> However, screening without a follow-up confirmatory evaluation can lead to false positive diagnoses and unnecessary treatment.<sup>2,41</sup>

## 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.<sup>40</sup>

The PHQ-2 is a quick, initial screen that has been shown to be efficacious in predicting depression in older adults. It is a validated set of two questions:

1. During the past two weeks, have you often been bothered by feeling down, depressed, or hopeless?
2. During the past two weeks, have you often 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.<sup>41</sup>

**Table 2: Comparison of screening tools for depression<sup>41</sup>**

	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 examples of longer self-rating scales in response to which patients have to rate the presence or frequency of a range of depression symptoms. These tools are used to establish depression severity and may be repeated periodically to monitor treatment response.<sup>42</sup> See Appendices 1-3 for examples of these questionnaires. Once a patient screens positive for possible depression, a formal diagnosis and assessment 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.<sup>1</sup> However, the term “depression” largely refers to major depressive disorder as defined by the DSM-5.<sup>1,43</sup> These diagnostic criteria are the same for all adults, as the DSM does not distinguish depression based on age.<sup>1</sup>

### 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 defines depression as the presence of sadness or anhedonia with five or more symptoms (Table 3).<sup>1</sup>

**Table 3: Diagnostic criteria for major depressive episode according to DSM-5 criteria<sup>1</sup>**

Major Depressive Episode (DSM-5)
<p><b>Either one or two of the following must be present:</b></p> <ul style="list-style-type: none"><li>• depressed mood</li><li>• markedly diminished interest or pleasure in (almost) all activities</li></ul> <p><b>Plus other symptoms to make a total of five:</b></p> <ul style="list-style-type: none"><li>• significant weight gain or loss (when not dieting) or decrease or increase in appetite</li><li>• insomnia or hypersomnia</li><li>• psychomotor agitation or retardation</li><li>• fatigue or loss of energy</li><li>• feelings of worthlessness or excessive or inappropriate guilt</li><li>• diminished ability to think or concentrate or indecisiveness</li><li>• recurrent thoughts of death, suicidal ideation, or a suicide attempt or a specific plan for committing suicide</li></ul>
<p><b>In addition,</b></p> <ul style="list-style-type: none"><li>• symptoms should cause clinically significant distress or impairment in social, occupational, or other important areas of functioning</li><li>• the episode is not attributable to<ul style="list-style-type: none"><li>— the direct physiological effects of a substance (e.g., a drug of abuse, a medication)</li><li>— a general medical condition (e.g., hypothyroidism)</li></ul></li><li>• symptoms are not better described by schizophrenia, delusional disorder, or other psychotic disorders there has never been a manic or hypomanic episode</li></ul>

Depressive episodes with insufficient number of symptoms or too short in duration to meet the criteria for major depression can still impact affected individuals. Minor or subsyndromal depression has comparable disease burden to major depression, such as poor health and social outcomes, functional impairment, and higher healthcare utilization.<sup>5</sup>

In addition, it is important to differentiate bipolar disorder from unipolar depression and other manifestations of depression. Bipolar disorder requires a manic episode, defined by persistently elevated, expansive, or irritable mood with increased activity or energy, lasting at least one week or hypomanic episode, which differs from a manic episode only in duration, generally four days. Additional criteria of which at least three are required include:

- 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

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- 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 disorder experience severe depression and may need to be adequately diagnosed to receive proper treatment. Conversely, many patients with depression may fall within the spectrum of bipolar disorder, which would influence choice of medication.

Although late life subsyndromal depression is more prevalent than major depression, a review of published studies found a median 27% of older adults achieve remission after  $\geq 1$  year. Additionally, the disease can evolve, with approximately 8–10% of older persons with subsyndromal depression developing major depression every year. Efforts to address subsyndromal depression symptoms could lead to prevention of considerable morbidity for the growing number of older adults.<sup>5</sup>

## New in the DSM-5

### Bereavement and significant loss

Many older individuals experience the loss of loved ones, but significant loss also encompasses the decline of physical ability, social status, mobility, independence, ambitions, and financial income. These changes are associated with a range of feelings, such as denial, disbelief, sadness, anger, despair, guilt, yearning. However, although significant loss may induce great suffering, it does not typically induce major depression, according to clinical DSM-5 definitions. Bereavement-related depression tends to occur in persons who are vulnerable to depressive disorders. 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. Moreover, symptoms may be the catalyst of a clinically significant major depressive episode.<sup>1</sup>

As an update from the DSM-IV definition, the DSM-5 removed the bereavement exclusion for the 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 major depression diagnosis simply based on bereavement may leave the person untreated for major depression, which is associated with high suicide risk.<sup>1</sup> Therefore, it is important to distinguish major depression from bereavement (Table 4).

**Table 4: Distinguishing bereavement from major depression<sup>1,44</sup>**

	Bereavement	Major Depression
<b>Predominant affect</b>	<ul style="list-style-type: none"> <li>feeling of emptiness or loss</li> </ul>	<ul style="list-style-type: none"> <li>persistently depressed mood; inability to anticipate happiness or pleasure</li> </ul>
<b>Timing/Intensity</b>	<ul style="list-style-type: none"> <li>decrease in intensity with time; occurs in waves (“pangs of grief”)</li> </ul>	<ul style="list-style-type: none"> <li>persistent, unremitting</li> </ul>
<b>Associated Factors</b>	<ul style="list-style-type: none"> <li>symptoms connected to thoughts/ reminders of deceased.</li> <li>can be accompanied by positive emotions and humor</li> </ul>	<ul style="list-style-type: none"> <li>symptoms connected to pervasive unhappiness</li> </ul>
<b>Thought Content</b>	<ul style="list-style-type: none"> <li>preoccupation with memories of deceased</li> <li>self-esteem preserved</li> <li>may have a passive desire to “join” the deceased, but not suicidal thoughts</li> </ul>	<ul style="list-style-type: none"> <li>self-critical or pessimistic</li> <li>self-loathing or feelings of worthlessness</li> <li>thoughts of one’s own death, focused on worthlessness, undeserving of life, or unable to cope with the pain of depression</li> </ul>

## 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. The criteria for major depressive disorder may be continuously present during that time. This diagnosis is a new designation in the DSM-5 and includes both the diagnostic categories of chronic major depression and dysthymia from the DSM-IV (Table 5).<sup>1</sup>

**Table 5: Clinical features of persistent depressive disorder<sup>1</sup>**

<b>Persistent Depressive Disorder (DSM-5)</b>
<b>Depressed mood for most of the day, more days than not, for two years</b>
<b>Plus two or more of the following:</b> <ul style="list-style-type: none"><li>• poor appetite or overeating</li><li>• insomnia or hypersomnia</li><li>• low energy or fatigue</li><li>• low self-esteem</li><li>• poor concentration or difficulty making decisions</li><li>• feelings of hopelessness</li></ul>
<b>In addition,</b> <ul style="list-style-type: none"><li>• During a 2-year period, person has not been without above symptoms for more than 2 months.</li><li>• There has never been a manic or hypomanic episode; criteria not met for cyclothymic disorder.</li><li>• Symptoms are not better explained by schizophrenia or other psychotic disorder.</li><li>• Symptoms are not attributable to substance abuse or another condition.</li></ul>

### **Vascular depression**

Vascular depression is a unique subtype of late life depression, although it is not a formal DSM-5 diagnosis.<sup>45</sup> Patients with vascular depression have a distinct clinical and neuropsychological profile and a positive association with hypertension. Vascular depression is characterized by increased cognitive impairment (especially executive dysfunction), more prominent apathy, psychomotor retardation, impaired insight into illness, limited feelings of guilt, and higher risk of relapse/recurrence.<sup>45,46</sup>

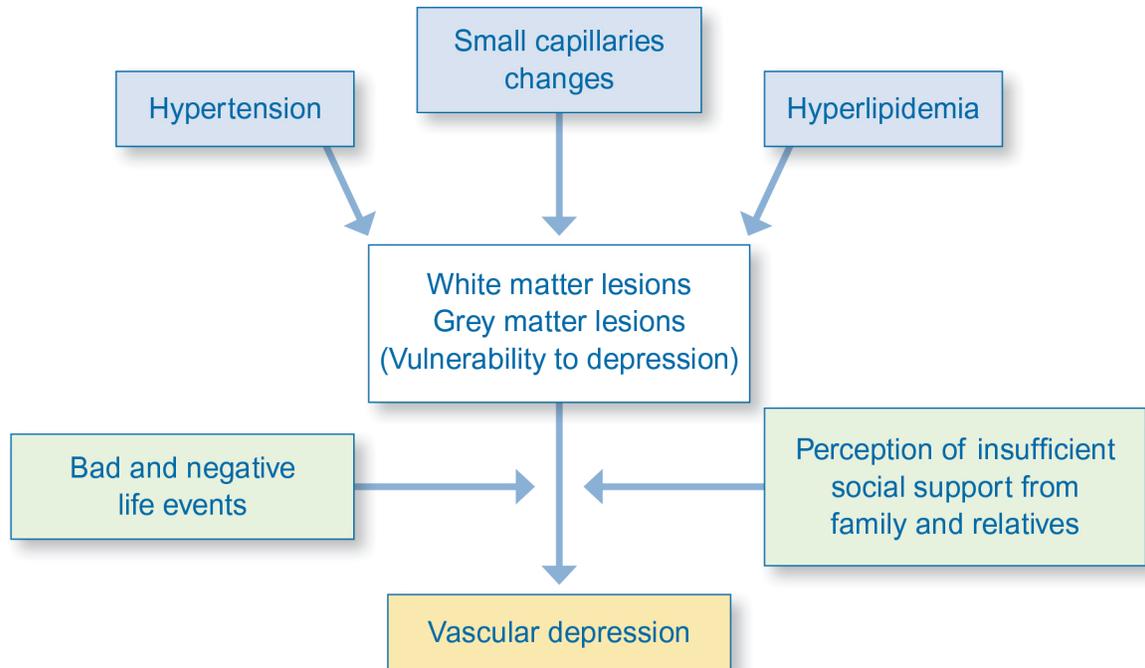
Clinical features of vascular depression include:<sup>45</sup>

- depression occurring at age 65 years or later
- absence of family history
- executive dysfunctions, loss of energy, subjective feeling of sadness, anhedonia, psychomotor retardation, motivational problems, reduced processing speed and visuospatial skills, deficits in self-initiation, lack of insight
  - depressive symptomatology may not meet criteria for any mood disorder in DSM-5
- high cardiac illness burden, increased rates of vascular risk factors (e.g., hypertension) than patients with non-vascular depression<sup>47,48</sup>
- high risk for cognitive decline and progression to dementia than patients with non-vascular depression<sup>47,48</sup>
- fluctuating course of cognitive impairment due to progression of white matter hyperintensities
- treatment resistance and poor outcome, including increased mortality
- gait abnormalities<sup>47,48</sup>

Vascular depression is linked to abnormalities such as microvascular lesions as well as changes to the frontal and temporal gray matter. Cerebrovascular disease consisting of small vessel ischemic changes

may predispose or perpetuate depressive symptoms as a consequence of structural damage to frontal-subcortical circuits. (Figure 5).<sup>45,46</sup>

**Figure 5: Possible mechanisms of vascular depression<sup>45</sup>**



Although diagnosis of this form of depression is evolving, it highlights the importance of addressing the conditions such as hyperlipidemia and hypertension that contribute to the development of vascular depression. For more about these topics see [AlosaHealth.org/Depression](https://AlosaHealth.org/Depression).

### **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.<sup>49</sup> Symptoms of apathy can occur in both the context of depression, neurocognitive disorders, or independently as an isolated syndrome of disturbed motivation (Table 6).<sup>22</sup>

**Table 6: Differential diagnosis of apathy and depression by exclusive and overlapping symptoms<sup>49</sup>**

Apathetic symptoms	Overlapping symptoms	Emotional symptoms of depression
<ul style="list-style-type: none"> <li>• reduced initiative</li> <li>• decreased participation in external activities unless engaged by another person</li> <li>• loss of interest in social events or everyday activities</li> <li>• decreased interest in starting new activities</li> <li>• decreased interest in the world around him or her</li> <li>• emotional indifference</li> <li>• diminished emotional reactivity</li> <li>• less affection than usual</li> <li>• lack of concern for others' feelings or interests</li> </ul>	<ul style="list-style-type: none"> <li>• psychomotor retardation</li> <li>• anhedonia</li> <li>• anergia</li> <li>• less physical activity than usual</li> <li>• decreased enthusiasm about usual interests</li> </ul>	<ul style="list-style-type: none"> <li>• sadness</li> <li>• feelings of guilt</li> <li>• negative thoughts and feelings</li> <li>• helplessness</li> <li>• hopelessness</li> <li>• pessimism</li> <li>• self-criticism</li> <li>• anxiety</li> <li>• suicidal ideation</li> </ul>

### Psychotic depression

Psychotic major depression in individuals older than 60 years is highly prevalent in inpatient settings and is a difficult-to-treat condition that causes great suffering and disability.<sup>50</sup> It is characterized by unipolar major depression with psychotic features such as delusions, fixed false beliefs, and/or hallucinations, false sensory perceptions, being more common. Psychotic depression can represent a psychiatric emergency due to the elevated suicide risk or impacted ability to care for oneself. Timely referral to a psychiatrist is important to mitigate safety risks and to distinguish psychotic depression from other etiologies of psychosis, with dementia being a common cause.<sup>50</sup>

### Assessment of 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 abuse, and the presence of cognitive dysfunction and psychotic symptoms. Because older adults under report symptoms of depression and symptoms of depression can co-occur with memory problems, additional information from a family member or caregiver is important.<sup>42</sup>

### Patient history

In older adults, a patient's medical history should be carefully reviewed, as somatic illnesses can induce or worsen depressive symptoms.<sup>42</sup> Critical elements of psychiatric history include presence of factors such as psychosis, bipolar disorder, mania, suicidality (ideation/plan/intent), and problems with memory and functional ability. Social factors such as support (emotional and practical) influence daily routine, as well as 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.<sup>2</sup>

As suicide rates are more common in older adults, the presence of suicidal thoughts should be carefully investigated when evaluating depression in these individuals.<sup>2</sup> In particular, 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.<sup>17</sup> Inquiries include whether they have thoughts of death, wish to be dead, or even have a specific suicide plan.<sup>42</sup> See more about assessing for suicide on page 16.

### Cognitive testing

Cognitive assessment should always be part of routine evaluation of older adults because depression is often associated with cognitive impairment.<sup>42,43</sup> 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 is needed in older persons who report memory problems and may reveal deficits in visuospatial processing or memory even if the total score is normal in range.<sup>2</sup>

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 are effective in improving survival and function in older persons.<sup>42</sup>

### 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.<sup>43</sup>

**Table 7: Differential diagnosis of late-life depression<sup>43</sup>**

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, H <sub>2</sub> -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.<sup>42</sup> Recommended laboratory tests include blood counts to test for anemia and measurement of the glucose level, as well as measurement of thyrotropin, since hypothyroidism can mimic depressive symptoms. Measurement of serum levels of vitamin B<sub>12</sub> and folate is also commonly recommended, because the prevalence of vitamin B<sub>12</sub> deficiency increases with age.<sup>2</sup>

## Establish severity

Once the diagnosis of depression is made using the DSM-5 criteria, establish the baseline severity. The DSM-5 bases severity on the number of criterion symptoms and the degree of functional disability. This translates to severity by number of symptoms:

- minor (or subsyndromal): <5 symptoms
- mild: 5 symptoms
- moderate: 6-7 symptoms
- severe: 8-9 symptoms

Another approach is to utilize PHQ-9 scores to map to severity and help guide treatment selection.

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

The PHQ-9 can also be used to objectively track and monitor response to treatment.

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**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 use DSM-5 criteria to make the diagnosis. A more comprehensive screening tool (e.g., PHQ-9) can establish depression severity and monitor response to treatment.**

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# Assessing safety of patients with depression

While there is a large range of risk considerations in the care of older vulnerable patients with multiple comorbidities, such as the risks associated with dependency, driving, and falling, the risk of suicide is particularly prominent in patients with depression. In patient care, providers should maintain an awareness of whether patients are safe in relation to the treatment given and in the setting in which they are being treated, and if not, the treatment plan requires modification.

## Evaluating safety of the patient

Conducting clinical evaluations and assessing suicide risk is one of the most complicated roles a psychiatrist can play. However, most older patients, who are at highest risk of suicide, are not seeing psychiatrists, but rather primary care physicians. Thus, all providers should be able to assess and manage suicide risk in their patients and to effectively flag patients who should be referred to mental health providers or patients whom are needed to be to the hospital for emergency evaluation and/or care.

All patients with a mental health disorder require an assessment of suicide risk, especially those who indicate signs of suicidality upon depression screening. Through questioning and observation, the clinician obtains information about the patient's mental state, psychiatric history, medical history, and suicidal thinking and behavior. This information enables the clinician to identify factors that may affect the risk for suicide, address the patient's safety needs, and determine the most appropriate treatment.

Although routine screening for suicidality is not common practice, clinicians will frequently encounter patients reporting thoughts of death or self-harm. The frequency of depression symptoms on the PHQ-9 in primary care settings has been linked to risk of suicide attempts. An analysis of 207,265 PHQ-9 responses from 84,418 patients with depression (aged  $\geq 13$  years) over three years found that responses to item 9 ("How often have you been bothered by thoughts that you would be better off dead, or of hurting yourself?") of the PHQ-9 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 thoughts of death or self-harm "not at all" to 4% among those reporting thoughts of death or self-harm "nearly every day." Similarly, cumulative risk of suicide death over one year increased from 0.03% among those reporting thoughts of death or self-harm ideation "not at all" 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.<sup>51</sup>

## 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 screening tool to identify those at greatest risk of suicide. Several screening tools have been developed and are used in research.

- 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).<sup>52</sup>
- 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.

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.<sup>52,53</sup>

### SAFE-T Step 1: Risk factors

Enhancing protective factors and reducing risk factors is the core of treating patients at risk for suicide. Multiple factors can increase one’s risk for suicide, and there is not one set of factors that are predictive of suicide. Risk factors include demographics, psychiatric symptomatology, psychiatric illness and comorbidity, family history, personality disorder/traits, substance use/abuse, severe medical illness, life stressors, suicidal behavior, psychological vulnerability, and access to weapons or potentially lethal doses of unused prescription medications (e.g., encouraging disposal of unused opioids). Identifying modifiable risk factors are key to risk reduction (Table 8).<sup>53</sup>

**Table 8: Risk factors for suicide<sup>52,53</sup>**

Risk factor	Description
Current/past psychiatric disorders	mood disorders, psychotic disorders, alcohol/substance abuse, 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 of a family member or past suicide attempt
Change in treatment	e.g., discharge from a psychiatric hospital or in providers
Access to lethal methods	understand access to firearms and other means (e.g., medications, razor blades)
Precipitants/ stressors/ interpersonal	<ul style="list-style-type: none"> <li>• triggering events leading to humiliation, shame or despair</li> <li>• ongoing medical illness (e.g., central nervous system disorders, pain)</li> <li>• intoxication</li> <li>• family turmoil/chaos</li> <li>• history of physical or sexual abuse</li> <li>• social isolation</li> </ul>
Key Symptoms	anhedonia, hopelessness, anxiety/panic, insomnia, command hallucinations, impulsivity, executive dysfunction

### SAFE-T Step 2: 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 relationship. One of the most critical protective factors is the status of connection to significant others, such as loved ones, friends, and/or family. Unfortunately, a patient's support system can be paradoxical and may also be the cause of stress.

### **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 individuals will report having suicidal ideas even when such thoughts are present.<sup>54</sup>

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?"<sup>54</sup>

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?"<sup>54</sup>

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, asking about the specific plans for suicide and whether any steps have been taken can help determine the severity of intentions. 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.<sup>54</sup>

For individuals who have thoughts of self-harm or suicide. It is not typical for a patient rapidly to progress from ideation to attempt (Table 9), it is often a process of escalating risk starting with ideation than progressing to plan, behaviors, intent and then finally, attempt.<sup>55</sup>

**Table 9: Assessment of suicidality<sup>55</sup>**

Stage	Description
<b>Ideation</b>	<ul style="list-style-type: none"> <li>• Have you ever felt that life was not worth living?</li> <li>• Have you ever wanted to go to sleep and not wake up?</li> <li>• Have things ever reached the point where you have had thoughts about harming yourself or committing suicide?</li> </ul>
<b>Plan</b>	<ul style="list-style-type: none"> <li>• Have you made a specific plan to harm or kill yourself? (If so, what does the plan include?)</li> <li>• What do you envision happening if you actually killed yourself? (e.g., escape, reunion with significant other, rebirth, reactions of others)</li> </ul>
<b>Behaviors</b>	<ul style="list-style-type: none"> <li>• Have you made any particular preparations?</li> <li>• Have you ever started to harm (or kill) yourself but stopped before doing something?</li> </ul>
<b>Intent</b>	<ul style="list-style-type: none"> <li>• What is the extent the patient intends on carrying out the plan?</li> <li>• What extent does patient see the plan as lethal?</li> <li>• How impulsive is the patient?</li> </ul>
<b>Attempt</b>	<ul style="list-style-type: none"> <li>• Have you ever had a suicide attempt?</li> <li>• When? Triggers? What was the act? Was help sought?</li> </ul>

If depressive symptoms (especially anhedonia, anxiety, and insomnia) are severe, or if clinical presentation seems inconsistent with an initial denial of suicidal thoughts, then additional questioning can be indicated. Asking additional questions can be useful to elucidate the underlying processes within initially reticent patients.<sup>54,55</sup>

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

Once a clinician has understood the context surrounding a particular patient case, considering risk factors, protective factors, and suicidality of the patient, risk level can be determined (Table 10). The more intense and specific the answers in the suicide inquiry and the more desperate, hopeless, agitated and impulsive the patient, the more emergent treatment is needed. Patients who also refuse to answer questions or who present as guarded in the suicidal inquiry may be the most concerning of all and would warrant additional, immediate evaluation.<sup>54</sup>

**Table 10: Levels of risk**

Risk level	Suicidality	Intervention
<b>High</b>	suicide attempt or persistent ideation with strong intent or suicide rehearsal	<ul style="list-style-type: none"> <li>• hospitalization likely indicated; suicide precautions</li> </ul>
<b>Moderate</b>	suicidal ideation with plan, but no intent or behavior	<ul style="list-style-type: none"> <li>• hospitalization, depending on risk factors.</li> <li>• develop a crisis plan and provide crisis resources</li> </ul>
<b>Low</b>	thoughts of death; no plan, intent or behavior	<ul style="list-style-type: none"> <li>• outpatient referral, symptom reduction</li> <li>• provide crisis resources</li> </ul>

Patients at high risk for suicide may be those who have made a potentially lethal suicide attempt or have strong intent, psychiatric disorders with severe symptoms or had experienced an acute precipitating event. Emergency treatment is required in patients who are highly symptomatic and have persistent thoughts of suicide, with 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.<sup>54,55</sup>

In patients where there is any concern about suicide risk, even lower risk patients, involving loved ones in obtaining additional information/perspective and partnering with them in treatment planning becomes 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.<sup>54,55</sup>

Resources include:

- **National Suicide Prevention Lifeline 1-800-273-8255 or 1-800-799-4889** (deaf/hard of hearing)
- Online support at: [suicidepreventionlifeline.org](https://suicidepreventionlifeline.org)
- **Senior Suicide Prevention** at [suicideinfo.ca/resource/seniors-suicide/](https://suicideinfo.ca/resource/seniors-suicide/)

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

The final step in a suicide assessment is follow-up with documentation that includes the assessed immediate risk level, rationale for the assigned risk level, chosen interventions to reduce suicide risk, as well as 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, psychosis, anxiety
- how protective factors have been enhanced
- how available means of harm are now less accessible
- access to firearms or medications, if patient is at risk for overdose

Even experienced providers cannot always accurately judge something as complex as suicide, and patients may attempt or even complete suicide while under the care of a primary care provider. 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.

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**BOTTOM LINE: Suicide and self-harm are serious risks in patients with depression, particularly those of advanced age. Clinicians should take all the necessary steps to evaluate and ascertain the safety of their patients before determining a treatment plan and refer to a specialist if necessary.**

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# Treatment options for depression

A simple diagnosis of depression does not give information about the cause, nor about the best interventions. Physicians should think about the four “P’s” to guide them to understand the presenting mood concern and develop an individual-specific treatment plan.<sup>56</sup>

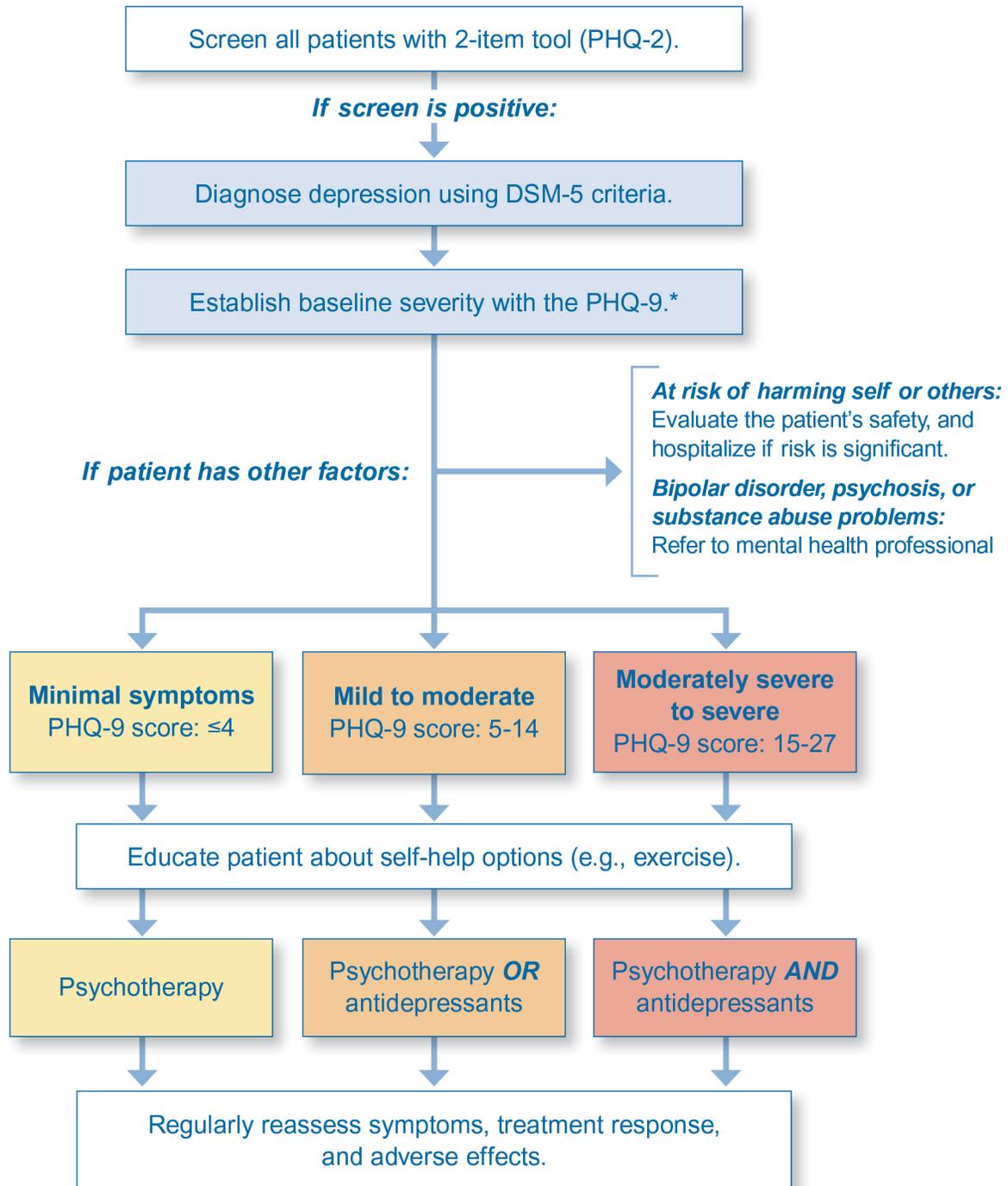
- **Predisposing:** Why is the patient vulnerable to developing the problem? Identify possible biological contributors, genetic vulnerabilities, environmental factors and psychological or personality factors which may increase the risk of developing depression.
- **Precipitating:** What triggered or exacerbated the problem? Look for 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.<sup>3</sup> The choice of treatment will depend on severity of depression, contraindications, access to care, and patient preference.<sup>3,57</sup> Combining screening information, medical and psychological histories, diagnostic criteria, severity, and the four “P’s” creates a framework for managing patients with depression and recommend evidence-based treatment options (Figure 6).

In general, depression in older patients is approached in the same way as it is for younger patients.<sup>42</sup> Various treatment approaches can be used to manage depression, such as psychotherapy, exercise, and pharmacotherapy, alone, or in combination with each other.<sup>40,58</sup> Effectively treating depression can reduce disability and improves quality of life.

Response to treatment (typically defined as a 50% reduction in measured severity) can be quantified using tools such as the PHQ-9 or the Hamilton Depression Rating Scale (HAM-D), which is primarily used in research settings. Remission from depression is difficult to define consistently and may mean different things for different patients. 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 asymptomatic remission, they have a lower risk of relapse than patients who are considered to be in remission but have residual symptoms.<sup>59</sup> Clinical studies may often allow patients to have some residual symptoms and still be considered to be in remission. However, in older adults who are burdened by many age-related symptoms (e.g. fatigue or insomnia), asymptomatic remission may not always be possible.

Figure 6. Algorithm to screen for, evaluate, and manage depression symptoms<sup>60,61</sup>



**PHQ:** Patient Health Questionnaire, 2- and 9-item versions

**DSM-5:** Diagnostic and Statistical Manual, 5<sup>th</sup> edition

\*The Geriatric Depression Scale (GDS), developed specifically for older adults, is another validated option. See [AlosaHealth.org/Depression](http://AlosaHealth.org/Depression) for more information about these tools and criteria.

Older adults view and discuss depression in different terms than younger adults.<sup>62</sup> One of the most important tenants regarding successful treatment is first addressing 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.<sup>57</sup>

Addressing preconceived notions, providing education, and setting the expectations regarding the time frame and impact of medications can be quite helpful in developing therapeutic alliance, but also assist in the patient taking 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 are effective first line treatments for depression. 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 interventions with evidence to support their use in patients with depression include problem-solving therapy, interpersonal therapy, supportive therapy, psychodynamic psychotherapy, dialectal behavioral therapy, motivational interviewing, reminiscence/life review therapy, family therapy, and exercise.

Many therapists integrate elements of the various evidence-based therapy options into their practice. Referral to an accessible therapist, even if they are not providing a structured course of CBT, is beneficial in the treatment of major depression. Healthcare providers should not discount referral to available social worker/therapist even if they are not specialized.

### Lifestyle changes

Depressed older adults should be encouraged to increase their physical activity to the extent that they can. Reasonable lifestyle changes recommendations include improving nutrition, increasing engagement in pleasurable activities and social interactions, sleep hygiene, and exercise. However, because depression increases the challenge of initiating lifestyle changes, these recommendations are generally accompanied by other interventions, such as pharmacotherapy or psychotherapy.<sup>2</sup>

A systematic review and meta-analysis of seven randomized controlled trials (RCTs) of exercise for depression in older people found that exercise significantly reduced depression severity. Most exercise interventions included both strength and endurance training and involved exercising three to five times per week for 30 to 45 minutes, over 10 weeks to six months. It was concluded that in older people with depression, structured exercise tailored to individual ability was able to reduce depression severity after three to 12 months of follow-up.<sup>63</sup>

Aerobic exercise is important lifestyle advice in older patients with 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. After 16 weeks the groups did not differ statistically on HAM-D or Beck Depression Inventory (BDI) scores ( $p=0.67$ ); all groups experienced statistically and clinically significant reductions in both 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 had a greater improvement in aerobic capacity.<sup>64</sup>

## Effectiveness of psychotherapy

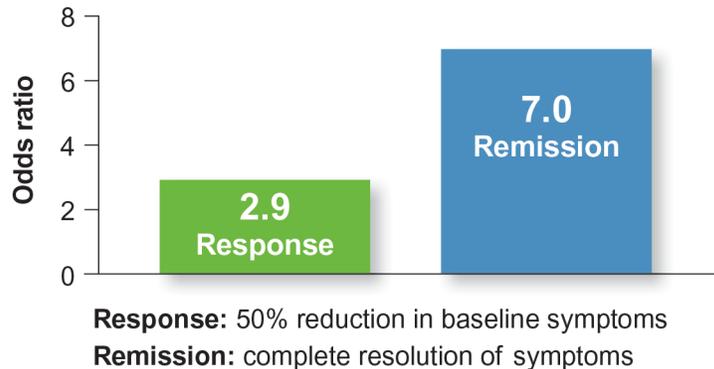
Psychotherapy interventions effectively treat older patients with depression. A systematic review and meta-analysis of 27 RCTs in 2,245 patients aged 55 years or older with acute-phase depressive disorder found a moderate- to large-effect, a standardized mean difference of 0.73 (95% CI: 0.51-0.95) for psychotherapy. Interventions in the analysis included CBT, problem-solving therapy, interpersonal therapy, brief dynamic therapy, bibliotherapy, and reminiscence therapy. When limiting the sample to trials that only included major depression, the effect size was 0.64 (95% CI: 0.42-0.87).<sup>65</sup>

For older adults, psychotherapy may be as effective as antidepressant therapy. A meta-analysis of 44 studies in 4,409 patients compared psychotherapy to drug therapy, finding no benefit in one over the other (Hedges'  $g$  -0.11; 95% CI: -0.54 to 0.33). In a few studies that looked at psychotherapy plus antidepressant therapy versus antidepressant therapy alone, there was a statistically non-significant trend toward benefit in the combined group (Hedges'  $g$  0.41; 95% CI: -0.05 to 0.88). Looking at all studies, the number of patients with depression needed to be treated with psychotherapy for one patient to benefit was three.<sup>66</sup>

## Cognitive Behavioral Therapy

CBT helps patients understand how thoughts, moods, and behaviors interact in a way that can result in depression. Patients are taught how to replace dysfunctional thoughts and behaviors with adaptive ones.<sup>67</sup> In older adults CBT improved treatment response and was more likely to achieve remission of depressive symptoms. A meta-analysis of 23 RCTs in 1,803 older patients (age  $\geq 50$  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 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 7). However, 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).<sup>68</sup>

**Figure 7. Improved response and remission to treatment with CBT vs. control**



The American College of Physicians' analysis of CBT literature found it equivalent to antidepressant medication. In younger patients with moderate depression, there was moderate-strength evidence that CBT and antidepressants led to similar response rates (risk ratio [RR] 0.90; 95% CI: 0.76–1.07) and remission rates (RR 0.98; CI: 0.73–1.32), although antidepressants were associated with more adverse events. It is important to note that comparative data in older adults are not available.<sup>69</sup>

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.<sup>70,71</sup> However access to computerized CBT options may be limited in the U.S., as many of the studied tools are available in the U.K. and Australia. Future developments include computerized online programs and applications that can assist in providing mental health services with known efficacy compared to face-to-face services.<sup>70,72,73</sup>

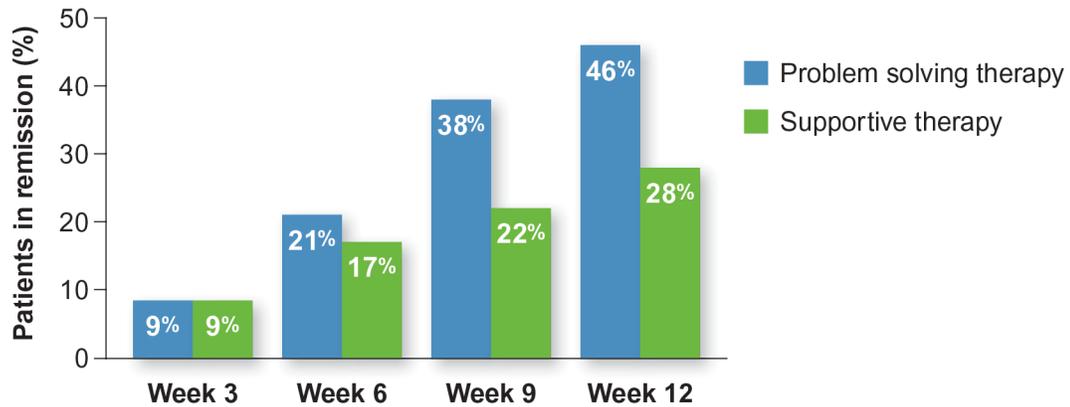
### Problem-solving therapy

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 may be a treatment alternative in an older patient population that is likely to be resistant to pharmacotherapy and has been shown to be effective in older adults with executive dysfunction or those receiving home health care.<sup>74</sup>

A two-site RCT examined whether problem-solving therapy is an effective treatment in 221 adults age 60 and older (mean age 73) with major depression and executive dysfunction. In this RCT, participants were randomly assigned to 12 weekly sessions of problem-solving therapy versus supportive therapy and 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 8).<sup>74</sup> However, like most studies of

psychotherapy, these results are only generalizable to patients who have sufficient interest, motivation, and ability to remain engaged in the weekly therapy.<sup>74</sup>

**Figure 8: Rates of remission of depression among older adults treated with problem-solving therapy<sup>74</sup>**



Problem-solving therapy also reduces suicidal ideation in depressed older adults with executive dysfunction. A secondary analysis of the RCT of problem-solving therapy versus supportive therapy described above, 61% of participants reported suicidal ideation at baseline. The supportive therapy group had a lower rate of improvement in suicide ideation (44.6%) than did the problem-solving therapy group (60.4%,  $p=0.031$ ) at 12 weeks. The reduction in suicidal ideation for the problem-solving therapy group versus supportive therapy group was sustained at 36 weeks.<sup>75</sup>

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**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. Many therapists integrate elements of the various evidence-based options into their practice, so referral to a psychotherapist can benefit older patients with depression.**

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# 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, but psychotherapy may be effective without the risk of side effects in patients with mild depression.

## Mechanism of action of antidepressants

The classic action of antidepressants is to block one or more of the transporters for serotonin, norepinephrine, and/or dopamine, which is consistent with the hypothesis that these neurotransmitters are depleted in patients with depression. Different classes of antidepressants work by different variations on this general principle (Table 11). Changes in neurotransmitter levels induced by antidepressant medications impact downstream effects in protein and gene expression, which explains why it takes antidepressants several weeks to reach their full effect and why the side effect burden tends to be highest in the first 1-2 weeks.

**Table 11: Classes of antidepressant drugs**

Class	Examples	Mechanism of action
Selective serotonin reuptake inhibitors (SSRIs)	citalopram (Celexa) escitalopram (Lexapro) fluoxetine (Prozac) paroxetine (Paxil) sertraline (Zoloft) fluvoxamine (Luvox)	selectively inhibit 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 various degrees of inhibition of the norepinephrine transporter
Atypical antidepressants	bupropion (Wellbutrin) mirtazapine (Remeron)	bupropion – structure related to amphetamine, inhibits presynaptic reuptake of dopamine and norepinephrine  mirtazapine - block presynaptic central alpha <sub>2</sub> -adrenergic autoreceptors, resulting in increased neurotransmission of noradrenaline and serotonin; also block post-synaptic 5-HT <sub>2</sub> and 5-HT <sub>3</sub> receptors
Serotonin modulator	trazodone (Desyrel, Olepto) vilazodone (Viibryd) vortioxetine (Trintillex)	act as antagonists and agonists at postsynaptic serotonin receptors and inhibit reuptake of presynaptic serotonin to varying degrees

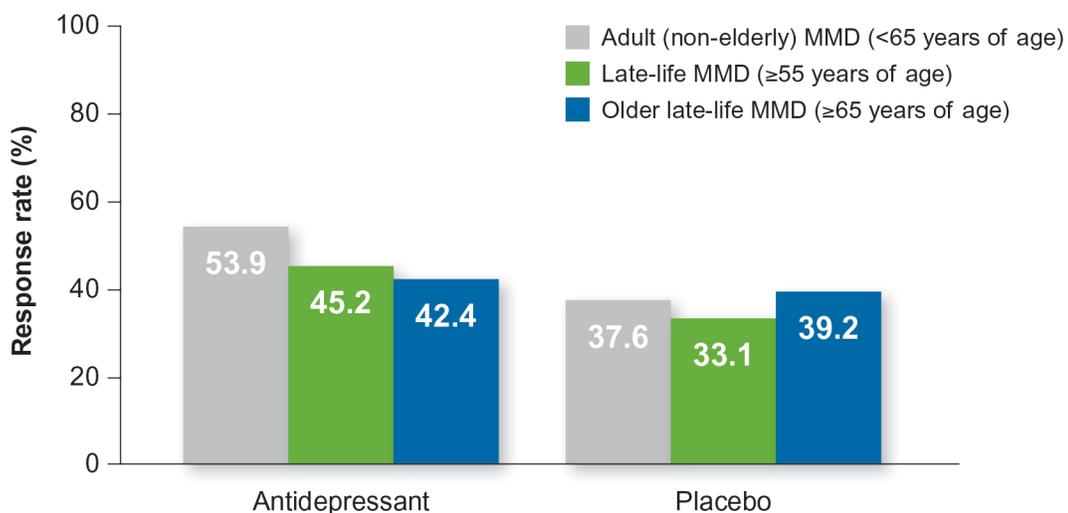
First-generation antidepressants (tricyclic antidepressants [TCAs] and monoamine oxidase inhibitors [MAOIs]) are very rarely used because second-generation antidepressants like SSRIs, SNRIs, and serotonin modulators have fewer adverse events and potential for toxicity, with similar efficacy.<sup>58</sup>

## Efficacy

Antidepressants are more effective than placebo at achieving remission of depression symptoms or a response to therapy, loosely defined as a 50% reduction in symptoms. A recent systematic review and network meta-analysis analyzed 522 double-blind RCTs trials of 21 antidepressants vs. placebo for the acute treatment of 116,477 adults ( $\geq 18$  years old, mean age of 44 years) with moderate to severe major depressive disorder. Standardized mean differences for all antidepressants (the summary effect size) was 0.3 for remission, defined as the absence of depression. All antidepressants were found to be more effective than placebo, with odds ratios for response ranging between 2.13 and 1.37.<sup>76</sup>

Response to antidepressant therapy in older adults is not as robust as 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 as age increased antidepressant response rates dipped (Figure 9). Compared to adults  $< 65$  years of age late life depression in adults age 55 and older and the subset of age 65 and older were less responsive to antidepressants. However, response to placebo was similar across the age groups.<sup>77</sup>

**Figure 9: Comparison of antidepressant and placebo response rates in younger adult and older adult patients<sup>77</sup>**



Older adults were more likely to respond to a longer treatment with antidepressants. In a meta-analysis of patients 60 years and older with nonpsychotic, unipolar major depression found antidepressants were 40% more likely to result in treatment response (95% CI: 1.24-1.57) and 27% more likely to achieve remission vs. placebo (95% CI: 1.12-1.44), respectively. Mean pooled response rates for antidepressant and placebo were 44.4% and 34.7%, respectively. When the results were analyzed by the duration of trials, 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 also seen in the clinical settings, where patients (especially with comorbid anxiety) may require more time to respond to antidepressants than their younger counterparts.<sup>78</sup>

## Safety

The frequency and severity of side effects limit tolerability of these medications (Table 12). More than 60% of patients have at least one adverse event during treatment with a second-generation antidepressant.<sup>79</sup> Although most adverse events are minor, they frequently lead to discontinuation of treatment.

**Table 12: Adverse events of antidepressant drugs**

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

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 short term in duration, the risk of adverse events in this group is not precisely estimated.<sup>80</sup>

## Summary of antidepressant factors

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**

DRUG	STARTING DOSE	THERAPEUTIC DOSE <sup>g</sup>	Anticholinergic effects	Drowsiness	Agitation	GI distress	QTc prolongation
<b>SSRIs</b>							
citalopram (Celexa) <sup>a</sup>	10 mg	20 mg	●	●	●	●	●
escitalopram (Lexapro)	5-10 mg	10-20 mg	●	●	●	●	●
fluoxetine (Prozac) <sup>b</sup>	10 mg	40-60 mg	●	●	●	●	●
fluvoxamine (Luvox)	50 mg	100-200 mg	●	●	●	●	●
paroxetine (Paxil; Paxil CR) <sup>c</sup>	10 mg; 12.5 mg	50 mg; 62.5 mg	●	●	●	●	●
sertraline (Zoloft)	25-50 mg	50-200 mg	●	●	●	●	●
<b>SNRIs</b>							
duloxetine (Cymbalta)	20-30 mg	60 mg	●	●	●	●	●
levomilnacipran (Fetzima) <sup>d</sup>	20 mg	40-120 mg	●	●	●	●	●
venlafaxine (Effexor) <sup>d</sup>	37.5-75 mg	150 mg-225 mg	●	●	●	●	●
desvenlafaxine (Pristiq) <sup>d</sup>	25-50 mg	50-100 mg	●	●	●	●	●
<b>ATYPICAL ANTIDEPRESSANTS</b>							
bupropion XL (Wellbutrin XL) <sup>e</sup>	150 mg	300 mg	●	●	●	●	●
mirtazapine (Remeron)	7.5 mg	30 mg	●	●	●	●	●
<b>SEROTONIN MODULATORS</b>							
vilazodone (Viibryd)	10 mg	20 mg	●	●	●	●	●
vortioxetine (Trintellix)	5 mg	5-20 mg	●	●	●	●	●
<b>TCA</b> s							
amitriptyline (Elavil)	25 mg	100-300 mg	●	●	●	●	●
nortriptyline (Pamelor)	25-50 mg	75-100 mg	●	●	●	●	●
<b>OTHER</b>							
bupirone (Buspar) <sup>f</sup>	15-20 mg	10-60 mg	●	●	●	●	●

● = infrequent; ● = frequent; ● = very frequent or treatment limiting

<sup>a</sup> Black box warning caps dose at 20 mg per day

<sup>b</sup> Long half life may lead to accumulation

<sup>c</sup> Anticholinergic effects limit use in older patients

<sup>d</sup> Monitor for increases in blood pressure

<sup>e</sup> Avoid in patients with seizure risk

<sup>f</sup> Used for augmentation

<sup>g</sup> FDA-approved doses may exceed therapeutic dose

In addition to the factors above, some antidepressants have significant drug interactions. Especially in patients with multiple medications, ensure the antidepressant selected will not affect management of other comorbid 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, causing confusion, restlessness, gait abnormality, lethargy, seizures, and coma. Hyponatremia tends to occur within first few weeks of treatment.<sup>81</sup> Older patients taking SSRIs have a 52% increased risk of hyponatremia compared to those who are not taking antidepressants.<sup>80</sup>

There are common risk factors in patients which contribute to the emergence of hyponatremia. The risk of hyponatremia is the highest with SSRIs but not confined to these antidepressant agents.<sup>82,83</sup> Older age is a major risk factor, as well as concomitant use of other hyponatremia-eliciting drugs such as thiazide diuretics, angiotensin-converting enzyme inhibitors (ACEIs), or laxatives (Table 14).<sup>81</sup>

**Table 14: Risk factors for hyponatremia<sup>81</sup>**

Type	Factor
Demographic	elderly age female sex
Comedication	diuretics (thiazides) ACEIs laxatives antiepileptics anticancer agents
Comorbidity	heart failure kidney failure cirrhosis low body weight hypothyroidism

Clinician awareness of the risk for hyponatremia is important and sodium levels should be checked in all elderly patients with abrupt/unexplained serum changes when being treated with antidepressants. Obtaining a sodium level within the first few weeks of treatment is prudent in high risk individuals, particularly individuals with a history of hyponatremia. In very sensitive 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 more attenuated risk profiles for hyponatremia.<sup>81</sup>

## Increased bleeding

Antidepressants, particularly SSRIs, may increase the risk for abnormal bleeding, particularly gastrointestinal (GI) bleeding and intracranial hemorrhage.<sup>84,85</sup> Bleeding is thought to be due to SSRIs blocking serotonin reuptake by platelets, leading to impairment of the platelet hemostatic response.<sup>80</sup>

Evidence supporting increased risk of bleeding associated with the use of SSRIs may be dependent on patient susceptibility and risk factors. The risk of upper GI bleeding is greater in older patients (the older the patient, the greater the risk), in those with a past history of upper GI bleeding or peptic ulcer, and in those who take 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.<sup>86</sup>

Many observational studies have found an association of SSRI with increased GI bleeding when compared with not taking an antidepressant. In a large observational cohort study of 60,746 people 65 years and over with late-onset depression, significantly increased risk of upper GI bleeding was observed for both SSRIs and other antidepressants:<sup>80</sup>

- 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 and 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.<sup>86</sup>

SSRI exposure has been associated with increased risk of the brain hemorrhage, largely due to intracerebral bleeding.<sup>84</sup> Current SSRI use was associated with a 17% increased risk for intracranial hemorrhage (RR 1.17; 95% CI: 1.02-1.35) relative to TCAs, and was highest during the first 30 days of use. It was also found that concomitant use of anticoagulants may increase the risk substantially (RR 1.73; 95% CI: 0.89-3.39).<sup>85</sup> The risk of intracranial hemorrhage is rare, with roughly one additional event for every 10,000 treated per year.<sup>84</sup>

## Falls and fractures

Older patients on antidepressants had an increased risk of falls and fractures versus no antidepressant use. Observational studies have found an association between SSRIs and falls and fractures (HR 1.66; 95% CI: 1.58-1.73). Risk appears to be greater in SSRI-treated patients than tricyclic antidepressants (HR 1.30; 95% CI: 1.23-1.38).<sup>80</sup>

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.<sup>87</sup>

## QTc prolongation

It is estimated that up to 3% of all prescriptions are for medications that may prolong QTc interval. Many antipsychotic medications, including intravenous haloperidol and ziprasidone, have been linked in varying degrees to QTc prolongation, torsades de pointes, and sudden cardiac death. Older antidepressants, such as TCAs have also been linked to prolongation of the QTc interval.<sup>88</sup> Systematic evaluations have suggested that some SSRIs, particularly citalopram, may have a predictable QTc-prolonging effect.<sup>88</sup> A meta-analysis of 16 prospective studies in 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). TCAs were associated with a significantly greater QTc increase than SSRIs (+7.05 milliseconds; 95% CI: 3.84–10.27). With respect to specific SSRI agents, high dose citalopram was associated with significantly greater QTc prolongation than sertraline, paroxetine, and fluvoxamine.<sup>88</sup>

Despite mounting evidence about the impact of QTc prolongation in antidepressant use, no clear guidance exists regarding how risk of QTc prolongation should be handled. The clinical significance of potential QTc prolongation properties of antidepressants is unclear. Several risk factors for QTc prolongation have been suggested, including 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 dosing and specific electrolyte disturbances (hypomagnesemia, hypokalemia, or hypocalcemia). However, in patients with risk factors for QTc prolongation, it may be reasonable to choose an SSRI other than citalopram as first-line treatment for depression.<sup>88</sup> ECG screening and monitoring should be considered 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.<sup>51</sup>

## 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.<sup>89</sup> 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, 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).<sup>90</sup>

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 allows participants to choose their own treatment and limits the randomization of each participant only to their individual range of acceptable treatment strategies.<sup>90</sup>

Overall in STAR\*D, 48.6% of patients responded to citalopram at six weeks with 36.8% remitting. The average duration required to achieve remission was seven weeks. Only 16% of patients reported intolerance to treatment.<sup>89</sup>

## Switching therapy

In patients who did not respond to treatment with an SSRI, approximately one in four patients had a remission of symptoms after switching to another antidepressant. Note that bupropion should be avoided in those patients with seizure risk. Response and remission rates were similar among the three switching options (Table 15).<sup>89</sup> Overall, 27% of patients who switched antidepressant remitted in Step 2.

**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, those failing to remit with citalopram went on to remit on sertraline. SSRIs also differ considerably in chemical structure and responses may vary on individual level. After trying another SSRI, the next course of action will 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. When switching, the first drug should be withdrawn gradually over a few weeks as second drug is gradually titrated.

### Augmentation

For patients 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 agonist at serotonin 1A receptor that is generally a well-tolerated strategy for 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.<sup>89</sup>

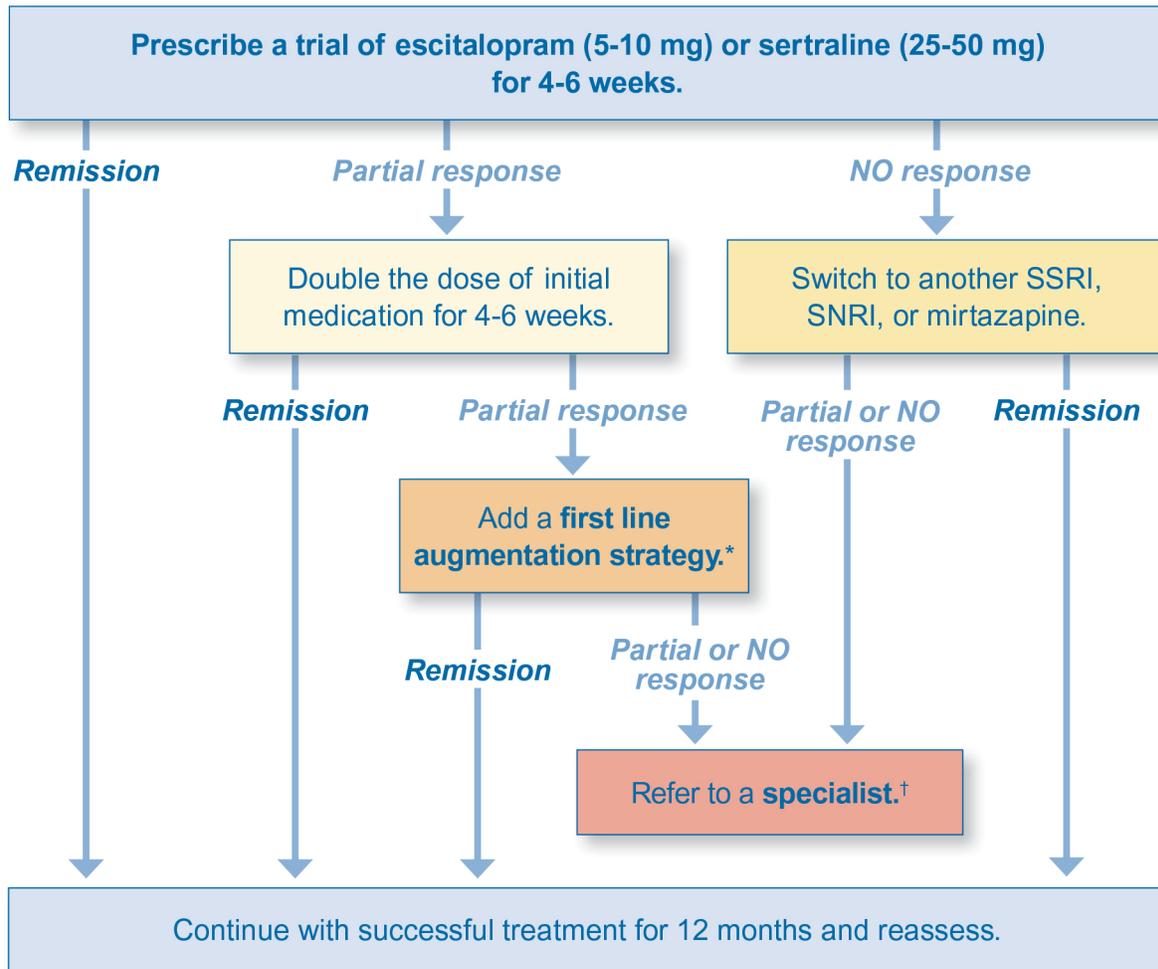
**Table 16: Remission and response rates of augmentation options in STAR\*D (Step 2)**

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, the majority of patients entered remission in the study. After step 4, two out of every three patients were in full remission (absence of depression), with the remaining third comprising of patients with no response and partial responders.<sup>89,90</sup>

Based on the strategies from the first two steps of the STAR\*D trial, Figure 10 outlines an approach regarding how to first start medication for depression and how to proceed if initial treatment fails.

Figure 10: Evidence-based approach to initiating antidepressants and modifying therapy



**SSRI:** selective serotonin reuptake inhibitor; **SNRI:** serotonin norepinephrine reuptake inhibitor

\* **First line augmentation strategy:** bupropion (avoid in seizure risk); buspirone; psychotherapy

† **Specialist referral is indicated if:** treatment resistance; psychotic features; substance abuse; suicidal risk

### STAR\*D and relevance to older adults

Although no clear superior treatment choice was revealed, results from STAR\*D suggested the importance of following a rational plan, which 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 new drug are both reasonable and equally effective options. For many, remission will require repeated trials of sufficiently dosed antidepressants for a sufficient period of time. However, after  $\geq 2$  adequate medication trials, the likelihood of remission substantially decreases. These patients should be referred to a psychiatrist for consultation.

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  $\geq 65$  years old and 24% were  $\geq 50$  years old. An 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) were associated with 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. Although they were less likely to hold negative views of themselves and report previous suicide attempts, they were also less likely to endorse symptoms consistent with generalized anxiety disorder, social phobia, panic disorder, and drug abuse.<sup>62</sup>

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;  $p=0.001$ ). This study was conducted prior to the FDA dose limit imposed on citalopram of 20mg and doses of citalopram in STAR\*D could be increased up to 60mg.<sup>91</sup>

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 compliance with medication, and minimize side effects. They 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 patients need to reach same therapeutic dose range as younger patients to achieve remission.

Assess response and tolerability 2-4 weeks after treatment initiation and consider further dose adjustment based on tolerability, improvement, and dose limit. Some response is typically seen within the first two weeks, but full response may not be seen for more than four to eight weeks or longer, as older patients may need a longer time to respond to antidepressants. However, patients with no response at six weeks are generally unlikely to show remission by 12 weeks.

In summary, general principles for treating older adults with depression are outlined below.

- **Start low, go slow, don’t stall.** Remember to titrate dose upward if partial response.
- 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 treatment for other coexisting conditions may be affected by antidepressants.

## Beyond STAR\*D

Since the results of STAR\*D, 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, which is considered the least potent inhibitor of the norepinephrine transporter. Since then, more SNRI options have become available, such as duloxetine, desvenlafaxine, and levomilnacipran, which may have different effects on patients from venlafaxine. In addition, two new serotonin modulators (vortioxetine and vilazodone) have become available, which 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 other SNRIs like duloxetine and newer antidepressants, like vortioxetine, specifically for late life depression. However, the extent to which they compare to each other or SSRIs has not been established. As patients may respond differently to different medications, there is a need for an RCT to compare medication effects of both monotherapy and combination therapy of these new agents. With these new tools, providers may pursue different mechanistic strategies in patients who do not respond to their current medication.

The strategy of augmentation of antidepressants with atypical antipsychotic medications has been explored in patients with unipolar, treatment resistant depression (see page 41 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 an important treatment modality, it is important to note that this phenomenon may be influenced by pharmaceutical bias.

## Maintenance of depression remission

Treatment of depression may evolve through different phases of response, which can be classified as acute, continuation, and maintenance.<sup>58</sup> 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.<sup>58</sup>

Once remission is achieved, continuation and maintenance are needed to sustain the response to treatment and is important for managing relapse risk. The more episodes of depression a patient has, the more vulnerable they are to relapse. Relapse is defined as the return of depressive symptoms during the acute or continuation phases and is therefore considered part of the same depressive episode, whereas recurrence is defined as the return of depressive symptoms during the maintenance phase and is considered a new, distinct episode.<sup>58</sup>

The plan for antidepressant therapy depends on the number of episodes. 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 the patient has had three or more episodes of depression, he/she should have at least three years of antidepressant therapy or could possibly receive it indefinitely.<sup>42</sup> Continue the same medications at the same doses to maintain remission.

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**BOTTOM LINE: Antidepressants 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. In older adults, start low, go slow, but don't stall with 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. Treatment approaches should be tailored to patient response.**

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# Treatment resistant depression

While many patients respond to treatment, one in three adults do not achieve remission.<sup>89</sup> 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.<sup>92</sup>

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.<sup>92</sup> 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).<sup>89,92</sup>

For patients with treatment-resistant depression, primary care provider can follow a few basic steps:

1. Evaluate safety of the patient
2. (Re)establish the correct diagnosis
3. Consider barriers to adequate dose/duration of medication trials

## 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 16.

## Re-establishing the correct diagnosis

Depression that is treatment resistant 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, underlying medical conditions, cognitive disorders, trauma, or personality disorders are suspected.<sup>93</sup> This process assists with clarifying contributing causes and identifying comorbid conditions. Inadequate treatment of comorbid conditions may be associated with treatment resistant depression.

Referral to a psychiatrist can assist in ruling out other psychiatric disorders. Misdiagnosis of bipolar disorder as unipolar depression is common, and antidepressants can be either ineffective or lead to increased agitation and anxiety. Personality disorders contribute to treatment resistance and are often not adequately addressed. Personality disorders involve a poorly integrated or disruptive sense of self which can lead to symptoms such as low self-esteem, excessive feelings of shame or inadequacy, preoccupation with criticism or rejection, feelings of emptiness, and mood instability. Even in the absence of a formal disorder, elements of personality are often driving forces in treatment resistance. Thus referral to psychotherapy can be a critical component of the treatment plan.<sup>93</sup> Psychiatrists can assist in managing these complex psychiatric disorders

## Barriers to medication trials

Barriers to adequate dose or duration of medication should be reviewed and may include factors related to both the patient and physician. The effectiveness of a medication can only be achieved if patient is adherent to the treatment plan. Patient factors interfering with treatment may include side effects or

practical issues such as the ability to recall and organize one's own medications or obtaining them from the pharmacy. Concerns, fears, beliefs, preconceived notions from the patient or their families about the medication may play a role in lack of adherence, as well as a patient's beliefs about their control over their own health.

In the same vein, medication can only be effective if the physician has provided a viable road to adequate treatment. Provider factors that influence treatment resistant depression include misconceptions regarding depression and aging, such as therapeutic nihilism (the belief that it is impossible to cure older people of their conditions through treatment). The physician-patient therapeutic alliance also appears to be strongly associated with patient adherence to and satisfaction with treatment.<sup>94</sup> The limited ability to address the depression management due to other competing health issues 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 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.

## 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 as such these medications are recommended to be used by specialists.

### Switching

Although evidence from STAR\*D forms a foundation for how to proceed with treatment in patients who do not respond to 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.

**Table 17: Remission and response rates in STAR\*D after augmentation therapy in treatment resistant depression (step 3)<sup>89</sup>**

	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
	Tranlycypromine**	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 <sub>3</sub>	3	70	25.7	24.3	10

\* Nortriptyline (Pamelor) is a TCA.

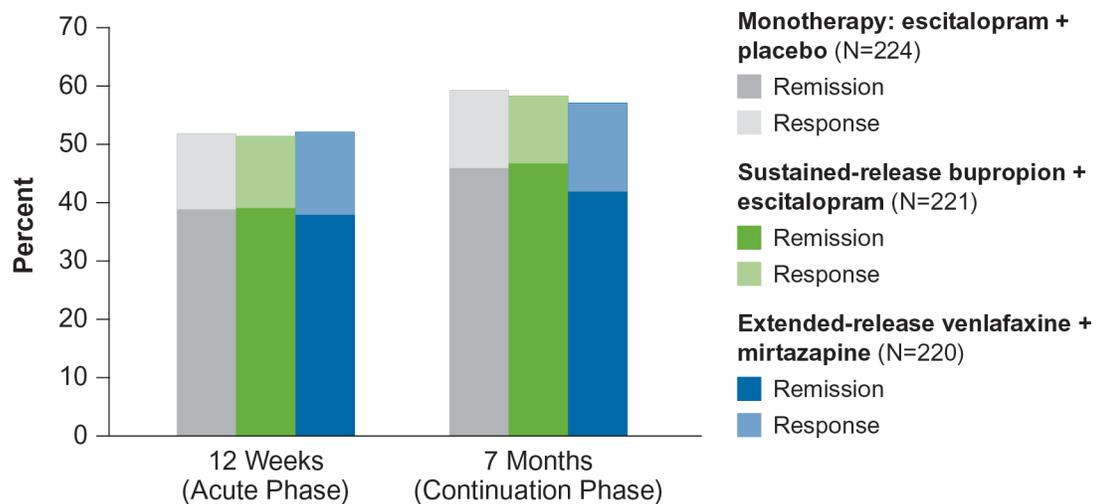
\*\* Tranlycypromine (Parnate) is an MAOI.

### Augmentation

Adding lithium or thyroid hormone, also called T<sub>3</sub> or liothyronine, was not statistically different at achieving remission (Table 17). T<sub>3</sub> treatment was better tolerated than other strategies for treatment resistance. However, the long-term effect and safety 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.<sup>89</sup>

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, with greater side effects. In a follow-up trial to STAR\*D, the CO-MED trial randomized 665 patients that compared SSRI monotherapy plus placebo, SSRI plus bupropion sustained release, and venlafaxine ER plus mirtazapine. Remission and response rates were not different among treatment groups both at 12 weeks and 7 months (Figure 11). 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.<sup>95</sup>

**Figure 11: Remission and response rates in STAR\*D after progression to combination therapy (step 4)<sup>95</sup>**



### Atypical antipsychotic medications

Several atypical antipsychotic medications (APMs) are approved for augmentation in depression treatment, and include aripiprazole (Abilify), brexpiprazole (Rexulti), quetiapine XR (Seroquel XR), and olanzapine with fluoxetine (Symbyax). As a class they are much more vastly different from one another and less selective in their action compared to antidepressants. These agents 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 in order 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 in adults found that adjunctive APMs were significantly more effective than placebo in 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.<sup>96</sup> One RCT of adults age 60 and over found a greater proportion of participants in the aripiprazole group (44%) achieved remission than did those in the placebo group (29%) when added to venlafaxine ER. Further, the resolution of baseline suicidal ideation was more marked with aripiprazole over placebo (73% vs 44%).<sup>97</sup> Another study of 1,522 older adults who did not remit on one prior antidepressant compared three groups: switching to bupropion alone, augment current antidepressant with bupropion, or augment current antidepressant with aripiprazole. Remission rates at 12 weeks were 22% for switch to bupropion, 27% for augment with bupropion, and 29% for augment with aripiprazole. Response rates were slightly higher in the aripiprazole augmentation group than both of the bupropion arms. However, relapse rates were similar between all groups.<sup>98</sup>

### 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).<sup>96</sup> One RCT highlighted the increased risk of extrapyramidal symptoms, such as akathisia, which was reported in 26% of participants on aripiprazole vs 12% of those on placebo and parkinsonism (17%) compared to placebo (2%).<sup>97</sup>

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

- **Dystonia:** an acute, involuntary contraction of major muscle group (i.e., torticollis, retrocollis, oculogyric crisis, laryngospasm)
- **Akathisia:** Motor restlessness with a compelling urge to move and difficulty sitting still/pacing. Milder form is 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, cognitive disturbance, diabetes, and treatment with antiparkinsonian agents – all of which are more likely in older people.<sup>99,100</sup> While lower with atypical antipsychotic medications, rates of tardive dyskinesia increase with duration of APM use.<sup>100</sup>

The Abnormal Involuntary Movement Scale (AIMS) is a commonly used screening and is a method of 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**

What to assess	baseline	4 weeks	8 weeks	12 weeks	annually
<b>Metabolic effects</b>					
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
<b>Cardiovascular effects</b>					
QTc prolongation	X	with addition of other QT prolonging drugs			
Orthostatic hypotension	X	every assessment			
<b>Neurologic effects</b>					
Extrapyramidal symptoms	every assessment				
Sedation	every assessment				
Tardive dyskinesia	AIMS every 6 months				
<b>Anticholinergic effects</b>					
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.<sup>101</sup> Despite the dramatic increase in mortality, similar data for older adults without dementia on APMs for depression is lacking.

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 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 as a treatment for bipolar disorder by many, lithium plays an important role for older adults with treatment resistant depression. A systematic review and meta-analysis of nine RCTs (n=237) in adults found lithium augmentation was significantly better than placebo in achieving a response (OR 2.89; 95% CI: 1.65-5.05).<sup>102</sup>

Another systematic review found a response rate of 42% (95% CI: 21–65) for lithium.<sup>103</sup> Additionally, patients on lithium had a 33% lower overall risk for suicidal behavior (0.21% per year) than the general population (0.32% per year).<sup>104</sup>

Laboratory monitoring of lithium levels is required due to risk of renal, thyroid and parathyroid disease with ongoing use 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, or those prone to dehydration. Significant drug interactions can occur between lithium and thiazide diuretics, ACEIs, NSAIDs, and some antibiotics.

### Other medication options

Utilizing stimulants (e.g., methylphenidate) as stand-alone agents in depressed and apathetic patients is not supported by the 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 neuovegetative symptoms. This strategy should be avoided in patients with heart failure, arrhythmias, coronary artery disease, and recent myocardial infarction, as there are cardiovascular risks associated with stimulant use.<sup>105</sup> In one trial, combined treatment with citalopram and methylphenidate demonstrated an enhanced clinical response in mood and well-being, as well as a higher rate of remission, compared with either drug alone. All treatments led to an improvement in cognitive functioning, although augmentation with methylphenidate did not show any added cognitive benefit.<sup>105</sup> Methylphenidate is not recommended for treating apathy in dementia.<sup>106,107</sup>

The use of sedating medications such as benzodiazepines also needs to be carefully evaluated in older patients. Quickly treating anxiety and agitation is an important modifiable risk factor in suicidality in patients who are at elevated risk. While the mainstay treatment for anxiety disorders are antidepressants and psychotherapy, especially CBT, benzodiazepines may also be used. Although in general the use of benzodiazepines should be minimized in treating the elderly, these agents can constitute an important treatment strategy in the acute phase treatment in patients with severe depression with anxious distress. In particular, in patients with severe symptoms of anxiety leading to agitation and insomnia, benzodiazepines may be helpful. Very anxious patients have difficulty initiating antidepressant medications and may experience worsened anxiety symptoms due to the activating properties of the drug. In these patients, bridging an antidepressant with a benzodiazepine may be reasonable.

However, long term use of benzodiazepines is ultimately discouraged in the majority of elders due to many adverse effects, which include risk of impaired driving, tolerance and dependence, overdose mortality, falls and fractures, and cognitive impairment. Overall, it is important to recognize the importance of recognizing and addressing comorbid anxiety in patients with depression.

### ECT and 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 becomes treatment of choice in severely depressed patients with safety concerns, such as suicidality, catatonia, failure to thrive, or psychotic/agitated features. During ECT, electrodes cause seizure lasting <1 minute, and has been shown to improve symptoms of treatment resistant depression.<sup>108</sup> ECT comes with rapid treatment response and decades of clinical experience. However, the procedure requires anesthesia, and the risk of relapse is high without the use of other interventions, such as a taper of ECT or use of antidepressant medications, to maintain remission. ECT is administered about three times a week for one to four weeks, with an average course of 10 treatments. After acute course of ECT patients require maintenance treatment with ECT or medication.<sup>108,109</sup>

ECT has been shown to be effective in clinical studies, showing robust and rapid responses in the majority of patients. The Consortium for Research in ECT report shows that ECT results in prompt improvement for the majority of patients and reports a 75% remission rate among 217 patients (aged 18-85), with 65% of patients achieving remission by week four of treatment.<sup>108</sup>

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, although this is likely influenced by many other factors. Conversely, some patients have some improvement in cognition as depression goes into remission.<sup>110</sup> ECT can be safely utilized in patients with dementia, as cognitive status is not a contraindication to treatment.<sup>109-111</sup> In fact, ECT is a treatment strategy for patients with treatment resistant, severe agitation in dementia.<sup>112</sup>

Primary care providers may be asked to medically clear patients for 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, and increased intracranial pressure. ECT can be safely used in elderly and in persons with pacemakers and automated implantable cardioverter defibrillators, or those using blood thinners. Components of pre-ECT workup include a patient history and physical examination, with emphasis on uncovering cardiopulmonary disease, evidence of neurological symptoms, or difficulty with anesthesia. Laboratory studies include serum electrolytes and kidney function, and an ECG may be performed.<sup>113,114</sup>

## 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 individuals, and there is a trend to suggest lower efficacy in late life depression.<sup>115</sup> Although the impact in significant treatment resistance and speed of improvement of TMS may not be equivalent to ECT, it is an important consideration within the approach of treatment resistant depression.<sup>116-118</sup>

## Ketamine

Ketamine, an N-methyl-D-aspartate antagonist, is an emerging off-label option for treatment resistant depression. Although initial small pilot studies have shown robust treatment effects almost immediately after treatment, there remains uncertainty regarding the routine use of ketamine for treatment resistant depression. This is because the optimal dose and frequency of treatment for depression is not

established. Additionally, the durability of treatment effect is short (e.g. days), increasing the risk of relapse, abuse/diversion, and necessity for repeated treatments. The longer-term safety and efficacy have yet to be clarified, and off-label use of ketamine for depression has not been evaluated nor sanctioned by regulatory bodies such as the FDA.

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**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. Primary care providers should ensure patient safety, re-confirm the diagnosis of depression, and address barriers to medication trials. Referral to psychiatrists is recommended for additional medication options and referral to neuromodulation.**

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## Putting it all together

Depression is not a normal part of aging and should not be disregarded in clinical evaluations of older individuals. Screening for depression in older adults involves screening for depression in all patients with a validated 2-question tool (PHQ-2). If the screen is positive, confirm the diagnosis with DSM-5 criteria and establish severity using a validated tool like PHQ-9. Like in younger adults, depression is defined and diagnosed using the DSM-5 criteria, but additional considerations may be needed in older adults, due to reduced medication response and higher associated risks and comorbidities. In patients at risk of suicide, healthcare providers should evaluate the risk and develop a plan for intervention to ensure safety.

Management of depression involves offering treatment based on depression severity and patient preference. Psychotherapies, such as cognitive behavioral therapy, are effective treatments for late life depression and may be considered as first line treatments. Antidepressants are efficacious for late life depression, but the impact may be less robust in some older 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 the patients regularly (e.g., repeating PHQ-9) for symptoms and side effects, and adjusting the regimen accordingly after an adequate medication trial.

For depression that persists despite treatment, clinicians should follow the fundamental steps to address treatment resistant depression in older patients, starting with evaluating the safety of patients, re-establishing a diagnosis, and employing various augmentation/switching strategies or alternative therapies, such as neuromodulation, to improve symptoms. In patients at suicide risk, evaluation of risk of suicide and development of a plan using the SAFE-T framework is recommended. Treatment-resistant depression should be managed in consultation with a psychiatrist.

In summary, depression is an under-recognized yet treatable condition, and appropriate treatment of depression reduces disability and improves quality of life in older adults.

# 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
<i>During the past two weeks, have you often been bothered by feeling down, depressed, or hopeless?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<i>During the past two weeks, have you often been bothered by little interest or pleasure in doing things?</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Add columns:  +  +

If score is 3 or higher, review DSM-5 criteria for depression below and 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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling down, depressed, or hopeless	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Trouble falling or staying asleep, or sleeping too much	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling tired or having little energy	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Poor appetite or overeating	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Feeling bad about yourself—or that you are a failure or have let yourself or your family down	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Trouble concentrating on things, such as reading the newspaper or watching television	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
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	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Thoughts that you would be better off dead, or of hurting yourself	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

*For total score, add columns:*

+  +

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

TOTAL SCORE	DEPRESSION SEVERITY
1-4	Minimal depression
5-9	Mild depression
10-14	Moderate depression
15-19	Moderately severe depression
20-27	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  $\geq 10$  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:**

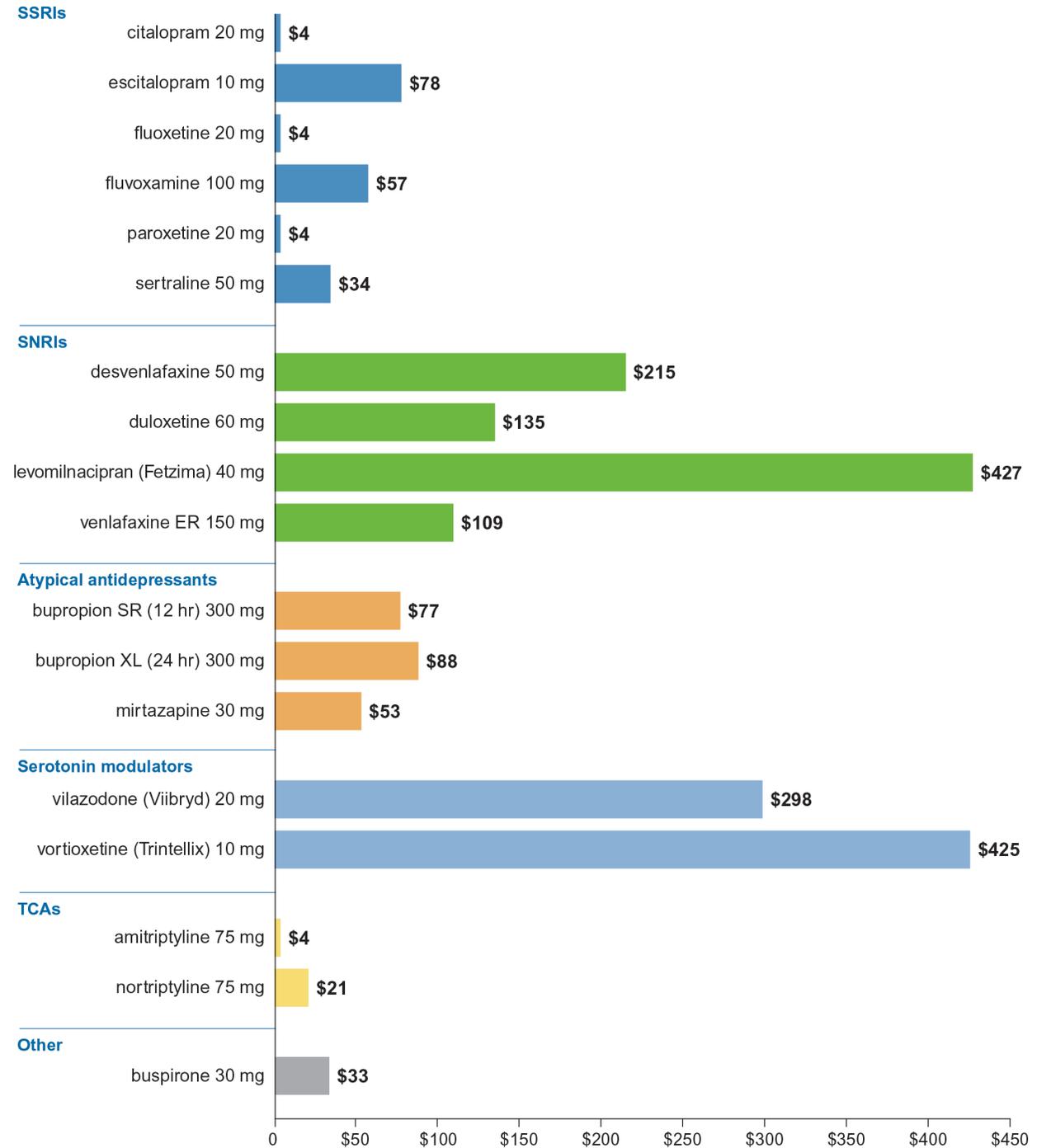
- Rate highest severity observed in category I, II, III.
- Rate movements that occur upon activation one point less than those observed spontaneously.
- Circle movements as well as code number that applies.

		RATER	RATER	RATER	RATER
		DATE	DATE	DATE	DATE
<b>I FACIAL &amp; ORAL MOVEMENTS</b>	<b>1. Muscles of Facial Expression</b> 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
	<b>2. Lips and Perioral Area</b> 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
	<b>3. Jaw</b> 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
	<b>4. Tongue</b> 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
<b>II EXTREMITY MOVEMENTS</b>	<b>5. Upper (arms, wrists, hands, fingers)</b> 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
	<b>6. Lower (legs, knees, ankles, toes)</b> 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
<b>III TRUNK MOVEMENTS</b>	<b>7. Neck, shoulders and hips</b> 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
<b>IV GLOBAL JUDGEMENT</b>	<b>8. Severity of abnormal movements overall</b>	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	<b>9. Incapacitation due to abnormal movements</b>	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4	0 1 2 3 4
	<b>10. Patient's awareness of abnormal movements. Rate only patients report:</b> 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
<b>V DENTAL STATUS</b>	<b>11. Current problems with teeth and/or dentures</b>	YES NO	YES NO	YES NO	YES NO
	<b>12. Are dentures usually worn</b>	YES NO	YES NO	YES NO	YES NO
	<b>13. Endentia?</b>	YES NO	YES NO	YES NO	YES NO
	<b>14. Do movements disappear with sleep?</b>	YES NO	YES NO	YES NO	YES NO

Available for use in the public domain.

# Appendix 5: Costs of common antidepressants

Figure 12: Price of a 30-day supply of antidepressant medications



Prices from goodrx.com, October 2018. Listed doses are based on Defined Daily Doses by the World Health Organization and should not be used for dosing in all patients. All prices shown are for generics when available, unless otherwise noted. These prices are a guide; patient costs will be subject to copays, rebates, and other incentives.

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## About this publication

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

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