

## CLINICAL PRACTICE

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## Depression in the Elderly

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*This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the author's clinical recommendations.*

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**A 74-year-old woman with hypertension that is well controlled with hydrochlorothiazide is brought by her daughter for an evaluation. The daughter states that her mother is withdrawn, often tearful, and at times appears to have memory problems but has no history of psychiatric illness. The patient is a retired teacher who is widowed and has lived independently for several years. During the last few months, she has stopped going to church and visiting friends. The patient's symptoms include irritability, anhedonia, fatigue, a 4.5-kg (10-lb) weight loss over a period of 3 months, and difficulty sleeping. She feels like a burden to her family. How should she be treated?**

## THE CLINICAL PROBLEM

Late-life depression is the occurrence of major depressive disorder in adults 60 years of age or older. Major depressive disorder occurs in up to 5% of community-dwelling older adults, and 8 to 16% of older adults have clinically significant depressive symptoms.<sup>1</sup> Rates of major depressive disorder rise with increasing medical morbidity, with reported rates of 5 to 10% in primary care<sup>2</sup> and as high as 37% after critical care hospitalizations.<sup>3</sup>

Patients with late-life depression are heterogeneous in terms of clinical history and coexisting medical conditions. As compared with older adults reporting an initial depressive episode early in life, those with late-onset depression are more likely to have neurologic abnormalities, including deficits on neuropsychological tests and age-related changes on neuroimaging that are greater than normal; they are also at higher risk for subsequent dementia.<sup>4</sup> Such observations informed the hypothesis that vascular disease may contribute to depression in some older adults.<sup>5,6</sup>

The diagnostic criteria for major depression in the *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition (DSM-5), require the presence of either sadness or anhedonia with a total of five or more symptoms over a 2-week period (Table 1). Low mood may be less common in older adults with depression than in younger adults with the disorder, whereas irritability, anxiety, and somatic symptoms may be more common. Psychosocial stressors such as the death of a loved one may trigger a depressive episode, although transient reactions to major losses can resemble depression. In DSM-5, unlike previous editions, grief after the death of a loved one is not considered to be exclusionary.

Coexisting medical illness complicates the management of depression. Persons with late-life depression have higher rates of coexisting conditions and concomitant medication use than their nondepressed counterparts. The relationship between depression and a coexisting medical illness may be bidirectional: medical problems such as chronic pain may confer a predisposition to depression, and depression is associated with worse outcomes for conditions such as cardiac disease.<sup>7</sup> Coexisting illness raises concerns about polypharmacy, including the effects of psychotropic



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## KEY CLINICAL POINTS

## DEPRESSION IN THE ELDERLY

- Late-life depression (occurring in persons 60 years of age or older) is common and is often associated with coexisting medical illness, cognitive dysfunction, or both.
- Depressed older adults are at increased risk for suicide.
- Screening for depression is important, but positive screening results should be followed by a thorough evaluation to assess patient safety and ensure that treatment is warranted.
- Either pharmacotherapy or psychotherapy may be used as first-line therapy.
- Currently available antidepressants show efficacy in depressed older populations, but older adults may be at increased risk for medication side effects. Selective serotonin-reuptake inhibitors (SSRIs) are considered first-line pharmacotherapy.
- Standardized psychotherapy techniques are also effective for depression in older adults.

drugs on medical conditions and the metabolism of other medications. Age-related declines in drug metabolism may also contribute to increased rates of medication side effects.

Coexisting cognitive impairment is common in persons with late-life depression and can involve multiple cognitive domains, including executive function, attention, and memory. Depression may be both a risk factor for and a manifestation of cognitive decline: depression is associated with an increased long-term risk of dementia.<sup>8</sup> Cognitive deficits may thus be signs of accelerated brain aging that confers a predisposition to and perpetuates depression.<sup>6</sup>

## STRATEGIES AND EVIDENCE

## EVALUATION

The U.S. Preventive Services Task Force recommends depression screening if support is in place to ensure accurate diagnosis and appropriate treatment and follow-up, and annual depression screening is now covered by Medicare Part B. However, screening without a subsequent confirmatory evaluation leads to false positive diagnoses and unnecessary treatment.<sup>9</sup> To fully evaluate depression, clinicians should use validated measures, such as the Patient Health Questionnaire 9, that reflect diagnostic criteria (Table 1). Because older adults, particularly elderly white men, have high suicide rates,<sup>10</sup> the presence of suicidal thoughts should be carefully explored.

Important features of the history are summarized in Table 2. Warning signs supporting urgent

intervention include severe or worsening symptoms, suicidality, and impairment in daily functioning. 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, and low levels

**Table 1. DSM-5 Diagnostic Criteria for Major Depressive Disorder.\***

**Five or more of the following symptoms must be present nearly every day during a 2-wk period:**

Core symptoms (≥1 required for diagnosis)

Depressed mood most of the day

Anhedonia or markedly decreased interest or pleasure in almost all activities

Additional symptoms

Clinically significant weight loss or increase or decrease in appetite

Insomnia or hypersomnia

Psychomotor agitation or retardation

Fatigue or loss of energy

Feelings of worthlessness or excessive or inappropriate guilt

Diminished ability to think or concentrate, or indecisiveness

Recurrent thoughts of death or suicidal ideation

\* DSM-5 denotes *Diagnostic and Statistical Manual of Mental Disorders*, fifth edition.

**Table 2. Crucial Elements of the History.**

History Component	Rationale
Psychiatric history	
Past psychiatric diagnoses and treatment	Allows confirmation of diagnosis and can guide treatment decisions
Current suicidal thoughts and past suicide attempts	Crucial in assessing safety; past suicide attempts indicate increased risk of future attempts
Substance use	Indicates contributing factors, such as alcohol use, for which additional intervention may be needed
Problems with memory	Initial screen for cognitive problems; should address with both patient and family if possible
Medical history	
Presence of chronic pain	May exacerbate depression and indicate need for additional treatment
Polypharmacy	May complicate antidepressant treatment
Problems with medication adherence	May lead to nonresponse to antidepressant treatment
Review of current medications	To identify any medications that may confer a predisposition to depression (e.g., propranolol, prednisone)
Social history	
Recent stressors or losses	Factors contributing to depression
Available social support	Indicates extent of social engagement or isolation
Access to transportation and ability to drive	Indicates ability to engage socially and to meet basic needs such as shopping for groceries
Access to guns	Indicates increased risk that a suicide attempt would be lethal
Family history	
Dementia	Indicates increased risk of dementia for the patient
Suicide	Indicates increased risk of suicide for the patient

of vitamin B<sub>12</sub> and folate may contribute to depression. Cognitive screening (e.g., with the Mini-Mental State Examination) is warranted in persons reporting memory problems and may reveal deficits in visuospatial processing or memory even if the total score is in the normal range. Neuropsychological testing may help identify early dementia, but because acute depression negatively affects performance, testing should be postponed until depressive symptoms diminish.

## TREATMENT

### LIFESTYLE CHANGES

Depressed older adults should be encouraged to increase their physical activity to the extent that they can. In a meta-analysis of seven randomized, controlled trials, moderate-intensity exercise reduced depressive symptoms.<sup>11</sup> Other reasonable recommendations include improving nutrition and increasing engagement in pleasurable activities and social interactions. However, be-

cause depression increases the challenge of initiating lifestyle changes, these recommendations are generally insufficient in the absence of other interventions, such as pharmacotherapy, psychotherapy, or both.

### PHARMACOTHERAPY

Owing to their favorable adverse-event profiles and low cost, selective serotonin-reuptake inhibitors (SSRIs) are first-line treatments for late-life depression (Table 3). In some randomized, controlled trials,<sup>12,13,15,16</sup> but not others,<sup>17-19</sup> SSRIs such as sertraline, fluoxetine, and paroxetine have been more effective than placebo in reducing depressive symptoms and increasing rates of remission of depression. Generally, trials that showed a significant benefit in patients with late-life depression were larger than those that did not; for example, trials showing a benefit of sertraline included more than 350 participants in each study group.<sup>12,13</sup> In the largest studies,<sup>12,13,15,16</sup> rates of SSRI response (defined as ≥50% reduction in the

**Table 3. Antidepressants Commonly Used to Treat Late-Life Depression.\***

Class and Agent	Initial Daily Dose	Therapeutic Daily Dose	Side Effects	
			Common	Serious but Rare
<b>First-line therapy</b>				
SSRIs			Nausea, diarrhea, headaches, sexual dysfunction, increased risk of falls	Abnormal bleeding (due to altered platelet function), hyponatremia
Sertraline	25–50 mg	50–100 mg, to a maximum of 200 mg		
Escitalopram	10 mg	10–20 mg		
<b>Second-line therapy</b>				
SNRIs			Nausea, diarrhea, headaches, sexual dysfunction, diaphoresis, dry mouth	Hypertension
Duloxetine	20–30 mg	60 mg, to a maximum of 120 mg†	Possible increased risk of falls	
Venlafaxine XR	37.5–75 mg	150 mg, to a maximum of 225 mg		
Antidepressants with novel mechanisms				
Bupropion XL	150 mg	300 mg, to a maximum of 450 mg	Jitteriness or agitation, headaches, tremors	Seizures (avoid in patients with risk factors for seizures)
Mirtazapine	15 mg at bedtime	30 mg, to a maximum of 45 mg	Dry mouth, sedation, weight gain	Increased serum cholesterol levels
<b>Other options to consider</b>				
Tricyclic antidepressants				
Nortriptyline	25–50 mg at bedtime	75–100 mg, to a maximum of 150 mg‡	Sedation, anticholinergic effects (dry mouth, constipation), weight gain, sexual dysfunction, increased risk of falls	Cardiac arrhythmias; overdose can be fatal
Second-generation antipsychotic agents§				
Aripiprazole	2–5 mg	5 mg, to a maximum of 15 mg	Sedation, nausea, headache, weight gain, increased cholesterol levels	Tardive dyskinesia, the neuroleptic malignant syndrome, increased stroke risk among patients with dementia-related psychosis¶

\* This table does not provide a comprehensive list of antidepressant drugs (rather, one to two examples per class) or of side effects. Selective serotonin-reuptake inhibitors (SSRIs) are typically used as first-line therapy. Use of sertraline is supported by data from large randomized, controlled trials<sup>12,13</sup>; such data are lacking for escitalopram, but it is commonly used owing to a generally favorable adverse-event profile. Serotonin–norepinephrine reuptake inhibitors (SNRIs) and agents with novel pharmacologic mechanisms are often used as second-line therapy. Duloxetine use is supported by a large randomized, controlled trial<sup>14</sup>; data supporting venlafaxine, bupropion, and mirtazapine are from smaller controlled trials or open-label trials. Owing to their side-effect profiles, tricyclic antidepressants and second-generation antipsychotic agents should be used only for persons who do not have a response to other treatment options. These guidelines are concordant with recommendations in the American Psychiatric Association *Practice Guideline for the Treatment of Patients with Major Depressive Disorder*, third edition.

† According to the package insert, there is no evidence that doses higher than 60 mg per day confer an additional benefit.

‡ Dosing should target plasma steady-state levels of 80 to 120 ng per milliliter.

§ Second-generation antipsychotic agents should be used for antidepressant augmentation, not as the sole therapy for depression.

¶ An increased risk of stroke is specifically reported for older patients with dementia-related psychosis. Whether the same risk extends to other older patients is not known.

severity of depression) ranged from 35 to 60%, as compared with placebo response rates of 26 to 40%. Although not reported for all studies,<sup>12,13</sup> remission rates (defined as a minimal level of depressive symptoms) were 32 to 44% with SSRIs versus 19 to 26% with placebo.<sup>15,16</sup> SSRIs may also effectively treat severe depression: although a randomized trial did not show a significant difference in remission rates between citalopram and placebo, a post hoc analysis suggested that severely depressed patients were more likely to have a remission with citalopram (35% vs. 19%).<sup>19</sup>

Common adverse effects of SSRIs, which are typically mild, include nausea and headache (Table 3). Of concern are reports noting a higher risk of stroke among persons taking SSRIs than among nonusers of antidepressants (annualized stroke rate of approximately 4 vs. 3 per 1000 person-years in one report<sup>20</sup>). However, a similar increase in the risk of stroke has been noted with other antidepressant classes, and it is unclear to what extent the increased risk may be explained by the underlying depression or other associated factors.

Serotonin–norepinephrine reuptake inhibitors (SNRIs) are commonly used as second-line agents when remission is not obtained with SSRIs. In small studies, venlafaxine did not show greater efficacy than placebo,<sup>21,22</sup> but a larger, placebo-controlled trial of duloxetine showed significant improvements in late-life depression (response rate, 37% vs. 19%; remission rate, 27% vs. 15%).<sup>14</sup> As observed in trials involving younger adults, randomized trials involving older adults have not shown significant differences between the benefits of SSRIs and those of SNRIs, although adverse effects may be more frequent with SNRIs.<sup>21,22</sup>

Tricyclic antidepressants have efficacy similar to that of SSRIs in the treatment of late-life depression<sup>23</sup> but are less commonly used owing to their greater side effects (Table 3). If SSRIs or SNRIs are ineffective, tricyclic antidepressants may be considered (either as monotherapy or as augmentation). However, tricyclic antidepressants are included in the Beers Criteria list of potentially inappropriate medications associated with high rates of adverse drug events among older adults.<sup>24</sup>

Open-label and small, controlled trials support the use of bupropion (response rate, 71%)<sup>25</sup> and mirtazapine (response rate, 47%)<sup>26</sup> in patients with late-life depression; however, data from rigorous placebo-controlled trials are lacking. De-

spite occasional clinical use, there have been no large, robust, controlled trials of stimulants in depressed older adults.<sup>27</sup>

Since their approval for adjunctive use in treatment-resistant depression, the second-generation antipsychotic agents olanzapine and aripiprazole have been increasingly used in the treatment of nonpsychotic depression.<sup>28</sup> In open-label studies, 50% of depressed older adults who did not have a full response to an antidepressant were reported to have a remission with aripiprazole augmentation.<sup>29,30</sup> However, these trials are limited by the lack of blinding and the lack of a control group. A pooled subgroup analysis incorporating data from three placebo-controlled trials involving mostly younger adults showed that among adults 50 to 67 years of age, remission rates with 6 weeks of aripiprazole augmentation were higher than with placebo augmentation (32.5% vs. 17.1%).<sup>31</sup> These remission rates did not differ significantly from rates among younger adults. Akathisia was the most common side effect in this population, occurring in 17% of older patients. Longer-term safety and efficacy data in older patients are needed.

#### PSYCHOTHERAPY

Psychotherapies are effective treatments for late-life depression and may be considered as first-line therapy, depending on availability and patient preference. Standardized psychotherapeutic approaches include a short-term treatment phase, consisting of weekly visits over a period of 8 to 12 weeks. Some persons may require a longer period of treatment or may require less frequent sessions after short-term treatment. Although other therapies may also be effective, the evidence base for short-term treatment is strongest for cognitive behavioral therapy and problem-solving therapy. However, generalizability is a concern because most studies of psychotherapy for late-life depression have involved cognitively intact, well-educated, white, and relatively young geriatric populations.<sup>32</sup>

Cognitive behavioral therapy focuses on identifying and reframing negative, dysfunctional thoughts while increasing participation in pleasurable and social activities. A meta-analysis of 23 randomized, controlled trials showed that cognitive behavioral therapy was significantly more effective in reducing depressive symptoms than treatment as usual or placement on a wait

list for treatment but was not more effective than other psychotherapies.<sup>33</sup> However, it may have a weaker effect in physically ill or cognitively impaired persons.<sup>34</sup> More recent trials assessing Internet-based approaches to cognitive behavioral therapy also show efficacy for depression; however, older adults are poorly represented in these studies and may require help navigating the website or using the computer.<sup>35</sup>

Problem-solving therapy focuses on the development of skills to improve the ability to cope with life problems. Randomized trials involving older adults have shown that problem-solving therapy results in greater improvements in depression than usual care or reminiscence therapy,<sup>36</sup> a psychotherapy focusing on the evaluation and reframing of past life events. Problem-solving therapy effectively treats depressive symptoms in older adults with cognitive deficits (specifically, coexisting executive dysfunction),<sup>37</sup> a group that often has a poor response to antidepressant medications.<sup>38,39</sup> In a trial involving a cognitively impaired population, problem-solving therapy resulted in higher remission rates than supportive therapy (46% vs. 28% at 12 weeks).<sup>37</sup> Problem-solving therapy also results in greater improvement in disability than does supportive therapy, with benefits maintained for at least 24 weeks.<sup>40</sup>

Interpersonal therapy for older adults with depression focuses on role transitions, grief, and interpersonal issues. In randomized trials, interpersonal therapy resulted in significantly greater reductions in depressive symptoms than usual treatment.<sup>41</sup> As with cognitive behavioral therapy, persons with coexisting medical conditions or cognitive deficits may not have a good response to interpersonal therapy.<sup>42</sup>

#### MAINTENANCE THERAPY

Longitudinal studies have shown a significant benefit of continued treatment after remission. One study involved older adults with recurrent depression who had a short-term remission with nortriptyline and interpersonal therapy over a period of 16 weeks. Study participants were randomly assigned to maintenance therapy with nortriptyline or placebo and to monthly maintenance psychotherapy (interpersonal therapy) or no psychotherapy. After 3 years, relapse rates were significantly lower among persons assigned to continued treatment with nortriptyline alone (43%), nortriptyline and interpersonal therapy

(20%), or interpersonal therapy alone (64%) than among persons receiving placebo and no interpersonal therapy (90%)<sup>43</sup>; the combination of nortriptyline and interpersonal therapy was significantly more effective than interpersonal therapy alone. However, in a similarly designed study involving mostly patients with a first episode of depression, maintenance treatment with paroxetine (alone or with interpersonal therapy), but not with interpersonal therapy alone, reduced the risk of relapse at 2 years, as compared with no active maintenance therapy.<sup>42</sup> Data from long-term randomized, controlled trials are lacking to assess the efficacy of maintenance treatment with either cognitive behavioral therapy or problem-solving therapy for late-life depression.

#### BRAIN STIMULATION

Electroconvulsive therapy (ECT) is the most effective treatment for severely depressed patients, including elderly patients. Although antidepressant medication is first-line therapy, ECT should be considered in patients if they are suicidal, have not had a response to antidepressant pharmacotherapy, have a deteriorating physical condition, or have depression-related disability that threatens their ability to live independently. Available data from open-label trials, typically involving persons who had not had a response to antidepressants, suggest remission rates of 70 to 90% with ECT, although remission rates in community samples may be lower (30 to 50%).<sup>44</sup> Data from high-quality blinded, sham-controlled studies using modern ECT techniques are lacking. In addition, randomized trials show high subsequent relapse rates (40 to 50% in the 6 months after treatment).<sup>45</sup> Current ECT protocols are safe, with few contraindications. Common side effects include postictal confusion with both anterograde and retrograde amnesia; current administration techniques, such as unilateral electrode placement with a brief pulse, substantially reduce this risk, and cognitive symptoms typically resolve after the completion of ECT. Persons with cardiovascular or neurologic disease are at increased risk for ECT-related memory problems.

Transcranial magnetic stimulation is a newer treatment for depression that uses a focal electromagnetic field generated by a coil held over the scalp, most commonly positioned over the left prefrontal cortex. Sessions are scheduled five times a week over a period of 4 to 6 weeks. In a

trial involving mostly younger depressed adults, transcranial magnetic stimulation was superior to sham treatment (remission rate, 14% vs. 5%).<sup>46</sup> This treatment does not require anesthesia and does not have cognitive side effects. However, a meta-analysis of six trials comparing transcranial magnetic stimulation with ECT showed that ECT has higher remission rates.<sup>47</sup> Although a large multisite trial did not show that age was a significant predictor of response,<sup>48</sup> other studies have suggested that depressed older adults may not have as robust a response as younger adults.<sup>49</sup>

#### AREAS OF UNCERTAINTY

Randomized trials are needed to evaluate the efficacy and risks of many treatments currently used for late-life depression. For many antidepressants, data on efficacy and safety in older populations are scarce or absent, so treatment decisions are often guided by data from younger adults. However, there may be increased risks specific to older populations.<sup>20</sup> Data on long-term pharmacotherapy and psychotherapy maintenance strategies in older populations are also limited.

It is unclear how best to address cognitive deficits in patients with late-life depression. Cognitive impairment is predictive of a poor response to antidepressants<sup>38,39</sup>; even with remission of depression, deficits may persist and signal a high risk of dementia. In a blinded, placebo-controlled trial of donepezil as an adjunct to antidepressant therapy for the maintenance treatment of depression, the donepezil group had, at best, modest and transient improvement in cognitive measures over a 2-year period and a significantly higher risk of depression recurrence<sup>50</sup>; post hoc analyses suggested that these effects were limited to patients with concomitant mild cognitive impairment. Neither memantine, a drug approved for the treatment of Alzheimer's disease, nor stimulants such as methylphenidate have been shown to have cognitive benefits in patients with late-life depression.

#### GUIDELINES

The recommendations provided here are consistent with American Psychiatric Association practice guidelines for the treatment of major depressive disorder, which include recommendations for the treatment of older adults.<sup>51</sup> These guidelines highlight the need for careful evaluation of suicide risk and coexisting medical conditions in this population.

#### CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette is having a first episode of depression and also has some memory problems. It is crucial to ask about suicidal thoughts, alcohol use, and coexisting medical illnesses. First-line treatment could involve either pharmacotherapy or psychotherapy (in particular, problem-solving therapy, because it has been shown to benefit depressed patients who also have cognitive impairment); the choice would depend on the patient's preference and the availability of psychotherapy. If medication were used, the recommended initial therapy would be administration of an SSRI, starting at a low dose (e.g., sertraline at a daily dose of 25 mg) in order to assess the patient for side effects and then increasing to a minimum therapeutic dose (50 mg daily in the case of sertraline). Higher doses may be needed for maximal efficacy (e.g., 100 mg or more of sertraline daily), with close attention to side effects. If the depressive symptoms are not sufficiently reduced, I would consider a change to an SNRI, such as venlafaxine. Screening for cognitive deficits should be performed and formal neuropsychological testing should be considered if cognitive symptoms persist or worsen despite antidepressant therapy.

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