

CLINICAL PRACTICE

Late-Life Depression

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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.

A 71-year-old man, whose wife died 6 months previously, presents with foot pain from diabetic neuropathy, poor sleep, lack of energy, and increasing frustration about his inability to “keep his diabetes under control.” On examination, he also notes lack of interest in usual activities, decreased appetite, a weight loss of 4.5 kg (10 lb) over the past 3 months, and intermittent thoughts that he would be better off dead. How should his case be managed?

THE CLINICAL PROBLEM

As many as 10% of adults 65 years of age or older who are seen in primary care settings have clinically significant depression.¹ Depression is particularly common in women, in patients with chronic medical disorders² or persistent insomnia, and in patients who have experienced stressful life events (e.g., the loss of a spouse), functional decline, or social isolation.³ Criteria for the diagnosis of an episode of major depression are summarized in Table 1.

Late-life depression is often undetected or undertreated in primary care,⁴ especially in men and members of racial and ethnic minority groups.⁵ Reasons for undertreatment include stigma associated with depression⁶ and the belief that depression is a normal part of aging.⁷ Patients and providers may correctly associate depression with the loss of a loved one; however, if symptoms of major depression persist for more than 2 months after a loss, treatment for depression should be strongly considered. Coexisting problems, such as chronic medical disorders, pain, cognitive impairment (which can be associated with depression or dementia), and alcohol or substance misuse, may also complicate the diagnosis and treatment of depression.

Late-life depression that is untreated can last for years and is associated with a poor quality of life, difficulty with social and physical functioning, poor adherence to treatment, worsening of chronic medical problems,² and increased morbidity and mortality from suicide and other causes. Older men have the highest rates of completed suicide (with the use of firearms in most cases).⁸ Recognizing and treating depression^{9,10} and reducing access to firearms may be the most important things primary care providers can do to reduce the risk of suicide.

STRATEGIES AND EVIDENCE

SCREENING

The Patient Health Questionnaire 2 (PHQ-2), a two-item screening instrument that asks about depressed mood and anhedonia (loss of interest and pleasure) in the previous 2 weeks, is easily administered by an office staff member or a physician during a primary care visit. This questionnaire is useful in identifying patients at

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Table 1. Criteria for the Diagnosis of an Episode of Major Depression.*

Five or more of the following nine symptoms nearly every day during the same 2-wk period (with at least one of the symptoms being either depressed mood or diminished interest or pleasure):

Depressed mood most of the day nearly every day
 Markedly diminished interest or pleasure in all or almost all activities
 Clinically significant weight loss in the absence of dieting or weight gain (e.g., a change of more than 5% in body weight in a month) or a decrease in appetite
 Insomnia or hypersomnia
 Observable 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, recurrent suicidal ideation without a specific plan, a specific plan for committing suicide, or a suicide attempt

* These criteria are adapted from the *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition. These symptoms cause significant distress or impairment in social, occupational, or other important areas of functioning, and they are not due to the direct physiological effects of a substance or a general medical condition (e.g., hypothyroidism). These symptoms are not better accounted for by bereavement (i.e., after the loss of a loved one), and they persist for longer than 2 months or are characterized by marked functional impairment, morbid preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation. If the patient has symptoms of depression as well as a history of mania or symptoms of mania, he or she may not have a diagnosis of depression but may have bipolar disorder.

high risk for depression, and it has a sensitivity of 100%, a specificity of 77%, and a positive predictive value of 14%.¹¹ (The full questionnaire is available at www.aafp.org/afp/20040915/1101.html.) Positive results should prompt a clinical evaluation for major depression.

EVALUATION

Evaluation of the patient should include a review of the nine symptoms of major depression (Table 1), including thoughts of suicide. This evaluation can be facilitated with the use of a brief, nine-item self-rating scale called the Patient Health Questionnaire 9 (PHQ-9).¹² (The full questionnaire is available at www.depression-primarycare.org/clinicians/toolkits/materials/forms/phq9/.) Clinicians should assess the duration of the patient's current depressive episode, associated functional impairment, and history of and treatment for depression.

Providers should ask whether the patient has a history of bipolar disorder, or manic depression, which may be misdiagnosed as unipolar depression. Screening can be facilitated by the use of a brief questionnaire called the Mood Disorder Questionnaire, which asks about symptoms and behaviors suggestive of mania. Screening questions for symptoms of mania include questions about periods of excess energy or talkativeness, racing thoughts, being much more active than usual, needing much less sleep than usual, doing

things that others thought were excessive or risky, or spending too much money.¹³

Clinicians should also obtain a medical history and perform a physical examination and laboratory tests as clinically indicated to assess medical conditions or medications that may be contributing to depression. Measurement of thyrotropin levels is recommended in patients with symptoms of hypothyroidism (e.g., fatigue, weight gain, or cold intolerance), but the value of routine thyrotropin screening in patients with depression is not well established.¹⁴ Additional screening is recommended for patients with cognitive impairment or alcohol or substance misuse (including misuse of prescription drugs) because these conditions can complicate the management of depression.

MANAGEMENT

Effective treatment of late-life depression has been associated with improved emotional, social, and physical functioning and quality of life. It has also been associated with better self-care for chronic medical conditions and reduced mortality.^{9,10,15,16}

In primary care, antidepressant medications are the most commonly used treatments for major depression, but there are several other evidence-based treatments, including structured psychotherapies.¹⁷ A recent meta-analysis of randomized, controlled trials indicated that antidepressant medications and structured psychotherapies have

roughly equivalent efficacies in older adults.¹⁸ A combination of pharmacotherapy and psychotherapy is recommended for severe or chronic forms of depression.^{19,20} Other evidence-based treatments include electroconvulsive therapy (ECT) and physical-exercise programs. Specific therapies are discussed below.

Treatment plans for late-life depression should take into account the patient's preferences, treatment history (focusing on treatments that have been helpful in the past), and coexisting medical and psychiatric conditions. Treatment availability should also be considered. Before initiating treatment, clinicians should address common patient concerns about side effects. They should reassure patients that dependence is not a realistic concern with antidepressant medications and that medications will not inhibit normal emotional reactions such as bereavement.²¹ Careful listening, education, and reassurance can help address such concerns.

Psychotherapy

Several forms of psychotherapy have been shown in randomized, controlled trials to be effective for late-life depression, including cognitive behavioral therapy (which helps patients correct negative thoughts associated with depression), interpersonal psychotherapy (which focuses on interpersonal causes of depression), and problem-solving therapy (which helps patients learn strategies for solving everyday problems associated with depression).²² Such structured psychotherapies, which can be delivered by trained therapists in 6 to 12 sessions in mental health or primary care settings, should be strongly considered if antidepressant treatment is not preferred or not effective in a patient. The efficacy of such evidence-based psychotherapies is roughly similar to that of antidepressant medications, with 45 to 70% of patients treated with psychotherapy having substantial improvement in depression (at least a 50% reduction in symptoms of depression) as compared with 25 to 35% of controls.^{18,22}

Exercise Programs

Several randomized, controlled trials suggest that short-term (e.g., 12-week), supervised, group-based physical-exercise programs involving walking or other forms of aerobic exercise can reduce depression in older adults; 45 to 65% of program

participants have a substantial reduction in symptoms of depression as compared with 25 to 30% of controls.^{17,23} A physical-exercise program could be a first-line strategy for patients with mild-to-moderate depression who prefer this approach, but it may be difficult for patients with depression to engage in such a program, and additional treatment with antidepressants or psychotherapy may be needed.

Pharmacologic Management

More than 20 antidepressants have been approved by the Food and Drug Administration (FDA) for the treatment of depression in older adults. Selective serotonin-reuptake inhibitors (SSRIs) are most often used as first-line treatments (Table 2). The most common side effect is gastrointestinal irritation (dyspepsia or nausea), which usually resolves within 7 to 10 days. Serotonin-norepinephrine reuptake inhibitors (SNRIs) may be particularly useful for patients with coexisting pain, particularly if it is neuropathic. Side effects include nausea, agitation, insomnia, and hypertension, especially at high doses. Although head-to-head comparisons are scarce, some research suggests that SNRIs may be less well tolerated by frail older adults than SSRIs.²⁶ Mirtazapine, an antidepressant with serotonergic and noradrenergic properties, is associated with sedation, increased appetite, and weight gain; thus, it may be particularly useful for patients with insomnia or weight loss. Bupropion may cause jitteriness and insomnia, and it may be particularly useful in patients with lethargy, daytime sedation, or fatigue. Neither mirtazapine nor bupropion has sexual side effects. Trazodone is not recommended as a primary antidepressant because of sedation and orthostatic hypotension at therapeutic doses, but in low doses (e.g., 25 to 50 mg) it is useful for insomnia associated with depression.²⁷ Priapism is a rare but potentially serious side effect.²⁸

Tricyclic antidepressants are effective but are no longer considered to be first-line treatments because of their side effects (Table 2) and because of cardiotoxic effects in patients who take an overdose. They should be considered in patients who have previously had a good response to tricyclic antidepressants or who have depression that does not improve with other antidepressants. Tricyclic antidepressants are contraindicated in patients with a recent history (e.g., within

Table 2. Commonly Used Antidepressants for Major Depression.*

Medication	Starting Dose	Therapeutic Dose	Half-Life†	Side Effects	Comments
SSRIs					
Fluoxetine (Prozac)¶	10 mg once daily	10–60 mg once daily	Long	Nausea, dyspepsia, anorexia, tremors, anxiety, sexual dysfunction, jitteriness, insomnia, hyponatremia‡	Risk of serotonin syndrome if combined with certain drugs§
Sertraline (Zoloft)¶	25 mg once daily	50–200 mg once daily	Short	Loose stools, diarrhea	Relatively few drug–drug interactions
Citalopram (Celexa)¶	10 mg once daily	20–60 mg once daily	Short		Relatively few drug–drug interactions
Escitalopram (Lexapro)	10 mg once daily	10–30 mg once daily	Short		
Paroxetine (Paxil)¶	10 mg once daily	20–50 mg once daily	Short	Dry mouth, drowsiness, fatigue, weight gain, hyponatremia‡	
SNRIs					
Venlafaxine (Effexor)¶	25 mg once daily	25–150 mg twice daily	Ultrashort	Nausea, sweating, dry mouth, dizziness, agitation, insomnia, somnolence, sexual dysfunction	Relatively few drug–drug interactions, risk of serotonin syndrome if combined with certain drugs§
Venlafaxine XR (Effexor XR)	37.5 mg once daily	75–300 mg once daily	Short	Hypertension	
Duloxetine (Cymbalta)	30 mg once daily	20–60 mg once daily	Short	Hypertension	Should not be broken (enteric coated)
Other newer antidepressants					
Mirtazapine (Remeron)¶	15 mg every night	15–45 mg every night	Short	Sedation, weight gain, no sexual side effects	Relatively few drug–drug interactions
Bupropion (Wellbutrin)¶	75 mg once daily	75–150 mg twice or thrice daily	Ultrashort	Insomnia, agitation, jitteriness; no sexual side effects or weight gain	Contraindicated in patients at increased risk for seizures
Bupropion SR (Wellbutrin SR)	100 mg once daily	100–150 mg twice daily	Short	Insomnia, agitation, jitteriness; no sexual side effects or weight gain	Contraindicated in patients at increased risk for seizures
Tricyclic antidepressants					
Nortriptyline (Pamelor)¶	10 mg every night	75–125 mg every night	Short	Fatigue	
Desipramine (Norpramin)¶	25 mg once daily	100–200 mg once daily	Short	Insomnia, agitation	

* The list of medications is not comprehensive. SSRIs denotes selective serotonin-reuptake inhibitors, and SNRIs serotonin-norepinephrine reuptake inhibitors.

† Short-acting antidepressants (particularly paroxetine) have been associated with an influenza-like discontinuation syndrome with symptoms such as insomnia, nausea, imbalance, sensory disturbances, and hyperarousal when the drug is discontinued abruptly or tapered too rapidly. The symptoms are usually mild and last 1 to 2 weeks, and they can be minimized by slowly tapering the antidepressant (e.g., over a 2-to-4-week period).

‡ In a trial reported by Fabian et al.,²⁴ hyponatremia developed in 9% of older adults in whom paroxetine treatment was initiated. Hyponatremia appeared to be particularly problematic for patients with a lower body-mass index and a baseline plasma sodium level of less than 138 mmol/liter.

§ The serotonin syndrome is a potentially lethal complication manifested as altered mental status, myoclonus, tremors, hyperreflexia, fever, and autonomic changes. This syndrome is associated with combinations of serotonergic antidepressants (SSRIs or SNRIs) with certain drugs (e.g., meperidine, tricyclic antidepressants, sumatriptan, tramadol, linezolid, and monoamine oxidase inhibitors). Data are from Boyer and Shannon.²⁵

¶ Generic preparations of this medication are available.

|| Secondary amine tricyclic antidepressants (e.g., nortriptyline and desipramine) are preferred in older adults because of a lower side-effect burden than that of tertiary amine tricyclic antidepressants (e.g., amitriptyline, doxepin, and imipramine). Tricyclic antidepressants are contraindicated in patients with a recent history (e.g., within 2 weeks) of myocardial infarction, cardiac conduction defects, orthostatic hypotension, urinary retention, prostatic hypertrophy, cognitive impairment, or narrow-angle glaucoma. Measurement of serum levels of tricyclic antidepressants may be useful to evaluate patients for persistent depression or excessive side effects. The best evidence for a therapeutic blood level exists for nortriptyline, which has been reported to have a therapeutic window of 50 to 150 ng per milliliter. An electrocardiogram should be obtained before initiation of treatment and after dose increases with tricyclic antidepressants.

2 weeks) of myocardial infarction, cardiac conduction defects, orthostatic hypotension, narrow-angle glaucoma, urinary retention, prostatic hypertrophy, or cognitive impairment. Monoamine oxidase inhibitors have a narrow therapeutic index and require special dietary and medication restrictions. Their use, which is generally limited to patients in whom other antidepressants have failed or in patients who have had a previous response to this class of drugs, should involve consultation with a physician who is experienced in prescribing them.

There have been few head-to-head comparison studies of various antidepressants in older adults, but data from randomized, placebo-controlled trials of various agents in older adults suggest similar efficacies.²⁹ However, as compared with SSRIs, tricyclic antidepressants may be associated with higher dropout rates due to side effects.³⁰ In addition to side-effect profiles, other considerations in the selection of antidepressants include the patient's response to previous treatment, the potential for drug interactions, the frequency of dosing, the safety of the drug in overdose, and cost. The consideration of responses to treatment in close relatives with depression may also be helpful predicting a patient's responsiveness, although this correlation has not been well studied. One commonly used approach involves initial treatment with an SSRI, with a switch to a different class according to the patient's symptoms and the side-effect profile of the drug if the SSRI is not effective or is poorly tolerated.³¹

Up to 12 weeks of treatment with antidepressant medications may be needed to elicit a full response. However, a recent study suggests that a full response is expected in two thirds of patients who have partial improvement after 4 weeks of treatment, as compared with about one third of patients without a response at 4 weeks.³² Even under the best of circumstances, only 40 to 65% of patients have an adequate response to any given antidepressant, and trials of alternative antidepressants or combinations of antidepressants, with or without psychotherapy, are required in a substantial number of patients.³³⁻³⁵

Antidepressant monotherapy is preferred in order to minimize side effects and drug interactions, reduce out-of-pocket costs, and enhance the likelihood of treatment adherence. To minimize side effects, starting doses for older adults may be lower than those for younger adults, but

older adults often require full adult doses for an adequate response (Table 2).

Recent FDA analyses suggest that antidepressant use may increase the risk of suicidal thoughts in youths and adults younger than 25 years of age. However, these drugs have a neutral or protective effect against suicidal ideation or behavior in older adults.³⁶

Antidepressant treatment should be continued at full doses for at least 6 to 12 months after patients are in remission because recurrence rates after earlier discontinuation are as high as 70%. In controlled trials involving older adults with depression who had a response to antidepressant treatment, patients who were randomly assigned to receive such continuation treatment had a 60% reduction in the risk of recurrence as compared with patients who received placebo after discontinuation of antidepressant therapy.^{37,38}

Electroconvulsive Therapy

Several randomized, controlled trials have established the efficacy of ECT for severe late-life depression, with efficacy rates ranging from 60 to 80%.³⁹⁻⁴² ECT is particularly indicated for patients with depression that is resistant to other treatments and for patients at risk for serious harm because of psychotic depression, suicidal ideation, or severe malnutrition. ECT is usually administered as a series of 6 to 12 treatments in an inpatient psychiatric setting over a period of 2 to 4 weeks. Common side effects include headache that usually responds to analgesics and temporary confusion or memory impairment. Less common side effects include memory loss for events during the period surrounding treatment and falls immediately after treatment sessions. The mortality associated with ECT is less than 1 death in 10,000 patients. A successful course of ECT should be followed by maintenance pharmacologic treatment because of high rates of relapse. In a randomized trial involving patients with depression that had improved after ECT, 6-month relapse rates were 84% among patients receiving placebo, 60% among patients receiving nortriptyline, and 39% among patients receiving lithium plus nortriptyline.⁴³

TREATMENT FOLLOW-UP

During the initial 8 to 10 weeks of pharmacologic or nonpharmacologic treatments for depression, patients should be followed closely (e.g.,

weekly or every other week, either in person or by telephone) for side effects, drug interactions, and worsening of depression (e.g., psychotic or manic symptoms or suicidal ideation) and in order to adjust treatment as needed. Such close follow-up during this initial treatment phase may reduce the rates of premature discontinuation of antidepressant medication; such discontinuation has been reported in up to 50% of patients within 4 weeks after initiating treatment. The use of rating scales such as the PHQ-9⁴⁴ can facilitate monitoring, with the goal of treatment being a complete remission of depression (e.g., a PHQ-9 score of <5 on a scale of 0 to 27, with higher scores indicating more depression).

Consultation with a mental health specialist is recommended for patients who prefer nonpharmacologic treatments such as psychotherapy or who have persistent depression after one or more trials of antidepressants. Other reasons for referral include psychosis, a history of mania or the emergence of manic symptoms during treatment for depression, and concern about suicide.

Several randomized trials have shown that, as compared with usual care, systematic programs of care management for depression can significantly increase patient and provider satisfaction and the effectiveness of treatment.^{9,10,15,45} In these programs, a care manager (usually a nurse or social worker) supports the treating physician by providing the patient with information about depression, proactively tracking depression with the use of a scale such as the PHQ-9, monitoring treatment adherence and side effects, providing brief evidence-based psychotherapy, and facilitating consultation with a psychiatrist.

AREAS OF UNCERTAINTY

There is controversy about the effectiveness of psychotherapies and antidepressant medications in patients with depression that does not meet the full diagnostic criteria for major depression.^{46,47} Watchful waiting may be appropriate for such patients as long as the depression is carefully tracked and treatment is initiated if symptoms worsen.

The optimal care of patients with depression that is resistant to one or more antidepressants remains uncertain. Studies involving younger adults^{33,34} suggest that several trials of antidepressant medications, alone or in combination

with other medications or psychotherapy, are indicated. A recent trial involving older adults with depression showed that 50% of patients with an incomplete response to the SSRI paroxetine had a full response when a second antidepressant was added.³⁵ ECT has been shown to be efficacious in patients in whom other treatments have failed, but its use is frequently not considered in primary care. More research comparing ECT with other active treatments is needed. Other strategies that may improve depression include aggressively treating coexisting conditions such as pain⁴⁸ and addressing psychosocial stressors that contribute to depression. However, such strategies have not been carefully studied.

More research is needed to guide the treatment of older patients with depression and associated cognitive impairment or dementia. In the absence of definitive evidence, many clinicians prefer a stepwise treatment approach that starts with a trial of an antidepressant before considering the addition of an antimental agent such as a cholinesterase inhibitor or memantine.⁴⁹ More research is also needed regarding improved access to treatment for older adults who are at high risk for undertreatment; these patients include elderly men and members of minority groups.

GUIDELINES

Although they were not specifically developed for older adults, the Agency for Health Care Policy and Research guidelines for the treatment of depression in primary care, which were first published in 1993⁵⁰ and were updated in 1998,⁵¹ are largely applicable to the treatment of late-life depression. A recent British practice guideline⁵² and several consensus statements⁵³⁻⁵⁵ focus on the treatment of depression in older adults. The recommendations in this article are generally concordant with those guidelines.

CONCLUSIONS AND RECOMMENDATIONS

The patient described in the vignette has symptoms that are typical of major depression, although other causes of his depressive symptoms (e.g., colon cancer as a potential cause of weight loss) should also be investigated. Untreated, he would be at substantial risk for poor functioning, poor

self-care, worsening of his chronic medical problems,² and suicide.

Initial treatment may involve either a trial of an antidepressant or psychotherapy (e.g., interpersonal therapy); the choice should be guided by the patient's preferences, his treatment history, and the costs and availability of treatments. If medication is used, I would generally start with a low dose of an SSRI and increase the dose gradually over the next 2 to 4 weeks to a therapeutic dose, as tolerated (Table 2). The patient should be closely monitored for adherence to and the effectiveness and adverse effects of treatment, and the medication should be adjusted if the depression does not show improvement after 2 to 4 weeks of treatment.

Patients with depression that persists after one or more trials of medication, each lasting 8 to 12

weeks, and those who are at high risk for suicide, who have had previous mania or manic symptoms while receiving antidepressant medications, or who have psychotic symptoms should be referred for psychiatric consultation. For patients with depression that has improved, maintenance treatment for at least 6 to 12 months should be considered in order to reduce the risk of relapse.

Educational information about late-life depression is available from the National Institute of Mental Health (www.nimh.nih.gov/HealthInformation/Depressionmenu.cfm), the American Association for Geriatric Psychiatry (www.aagppa.org), and the IMPACT Program for Late-Life Depression (<http://impact-uw.org>).

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