Depression in the Elderly

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Educational Objectives

After reviewing this article, readers should be able to:
- Describe the epidemiology of geriatric depression.
- Review the diagnosis and treatment of geriatric depression.
- Describe appropriate pharmacological options in the treatment of geriatric depression.

Abstract

Geriatric depression is a common problem that is underrecognized and frequently overlooked. It is not part of the normal aging process. Depression can have serious adverse effects on the patient and family; it affects quality of life, and it may also affect length of life. Successful treatment not only is possible but also is likely with proper identification and management of the problem.

Recent studies indicate that patients’ decisions about such critical issues as whether to use aggressive therapy for chronic medical problems or resuscitation in the event of cardiac arrest are influenced by depression more than by their underlying condition or prognosis. Well-tolerated, effective treatment, including antidepressants, electroconvulsive therapy, cognitive behavioral therapy, problem-solving therapy (especially with executive dysfunction), bibliotherapy (reading self-help literature), and wellness adjuncts, all can help in overcoming geriatric depression.

This article reviews the epidemiology, diagnosis, and treatment of depression in the elderly with a particular emphasis on newer pharmacotherapeutic agents.

Introduction

A number of misconceptions lead to the underdiagnosis, misdiagnosis, and underreporting of depression in older adults. Hopelessness, “ageism,” and the lack of linkage among health care, mental health, and service professionals have created a system of care for elderly depressed patients that is fragmented, inadequate, and passive. Concurrent medical problems and lower functional expectations of patients by physicians often obscure the degree of impairment that exists.

Typically, patients might not complain of depressed mood; instead, they might complain of less specific symptoms such as insomnia, anorexia, and fatigue.

Patients may stoically view their feelings of sadness as a weakness or as something to be expected. Although there is generally agreement that treatment is required for a major depressive episode in both young and old patients, less severe depressive illness, which may be viewed as an acceptable response to life stress or a normal part of aging, is often dismissed.

With the social, physical, emotional, and financial challenges of later life, it is surprising that elderly people do not become depressed more frequently. Besides the obvious decline in quality of life, there are increased risks of suicide, social and cognitive impairment, poor compliance in treating their own physical illness, and worsening of associated physical conditions. The role of the primary care physician is paramount in the care of the depressed elderly.

Epidemiology

The percentage of elderly people continues to grow in America, with the “oldest old” now recognized as the fastest-growing segment. Nearly 7 million of the 35 million Americans (15%–25%) 65 years of age or older have depression, and 1 million of the 7 million have major depression; the overall prevalence is 1% (1.4% in women, 0.4% in men). By 2020, these figures will swell by another 60%.

The annual direct and indirect costs of depression ($43 billion) are equal to those for coronary heart disease. The prevalence rate approaches 12% to 30% in long-term-care facilities and 60% to 70% in subacute rehabilitation centers after treatment in a hospital. Depression has been identified in 17% to 37% of patients.
of patients treated in primary care settings, with 30% of these patients having major depression,\(^2\) whereas the rate drops to 3% for healthy elderly people living in the community.\(^2,13\)

Three-fourths of these patients are initially seen in the primary care setting.\(^8\) Although recurrence may be as high as 40%, the figures are lower than that reported in the younger population, partly because of the tendency to focus on somatic symptoms in the elderly and partly because of cognitive impairment that interferes with the accurate reporting of symptoms.

Subsyndromal depression is a clinically significant depressive disorder that does not fulfill the duration criteria or the number of symptoms necessary to make the diagnosis of dysthymia or major depression.\(^14\) Minor depression in the elderly is more prevalent than major depression.\(^11\) Minor depression may be the residual phase of a major depressive episode, but it simply lacks the criterion of duration, a brief episode of an underlying current major depressive disorder or, more likely, a reaction to the routine stressors prevalent in older populations. Fifteen percent to 25% of minor depressions evolve into a major depressive episode within a two-year period, and these are associated with significant disability as well as suicidal ideation.\(^4,15\)

The rate of minor depression ranges from 2.5% to 9.4%, but it increases significantly (by 47% to 53%) as individuals move into clinical settings.\(^3,16\) The rate among nursing-home residents averages about 30%. The ratio of females to males is 1.3 to 1—less than for major depression, which is a ratio of 1.4 to 0.4.\(^16\)

Untreated, the natural course of depression is one to two years, but 53% of patients have an increased likelihood of becoming disabled one year later, and 51% have more disability days than persons with major depression.\(^4,15\) Patients with minor depression are also more likely to have a concomitant anxiety disorder. The increased use of health services and costs (1.5 to two times), including physician visits (an increase of 38% to 61%), medications, and an increased length of stay in acute hospital and rehabilitation settings are common.

Engel noted that the rising number of do-not-resuscitate (DNR) orders might be a manifestation of the patient’s inability to fight on—a response to illness described as the “giving-in, given-up” complex.\(^17\)

The National Institute of Mental Health states that geriatric depression is one of the most common conditions associated with completed suicide in older Americans.\(^18-20\) Older Americans make up 15% of the population, but they account for 18% of suicide deaths—almost twice that of the general population. Elderly white men are at the highest risk, whereas elderly women are less likely than younger women to complete a suicidal act. These alarming statistics may reflect the much higher suicide completion rates of older men living alone. Importantly, studies show that the majority (75%) of elderly people who have committed suicide had visited a primary care physician within the preceding month, but their symptoms were unrecognized and untreated.\(^20\)

Depression is the most common diagnosis in older individuals who commit suicide; it is more common than substance abuse or psychosis occurring alone or in combination with mood disorders in the young.\(^14\) Major depression adds to the risk of mortality regardless of health status.\(^21,22\)

### Associated Risk Factors for Depression

Risk factors for depression in the elderly include:\(^3,8,20,23,24\)

- a history of depression.
- chronic medical illness.
- female sex.
- widowed, single, or divorced status.
- brain disease.
- alcohol and occult substance abuse.
- smoking.
- certain drug therapies.
- stressful life events, especially the loss of a spouse, hospitalization, unemployment, and lack of social support.
- living alone.
- a lack of community activities or involvement.

Up to 15% of widowed individuals experience potentially serious depression for as long as one year after the loss of their spouse.

The hallmark of depressive illness in elderly patients is associated with a concurrent medical comorbidity, a factor that represents a major difference from depression in younger populations.\(^4,20,25,26\) Major depression is more likely to be found in medically ill patients who are older than 70 years of age, hospitalized (11%), or institutionalized (12%).\(^8\)

Depression often results in higher morbidity and mortality rates through a vicious circle and represents a risk factor for death that can last for many years beyond widowhood, isolation, or financial deprivation.\(^20\) Severe or chronic diseases are associated with a higher prevalence and persistence of depression, including:\(^8,26-29\)

- chronic renal or pulmonary disease (15%–30%).
- connective tissue disorders (15%–45%).
- stroke (30%–60%).
- arthritis (20%–35%).
- coronary and ischemic heart disease (8%–44%).
- cancer (1%–40%).
- endocrinopathies (30%–40%).
- Parkinson’s disease (40%).
- sleep apnea (15%–25%).
- obesity.
- Alzheimer’s disease (20%–40%).
- dementia (17%–31%).
- various autoimmune, infection-related, and inflammatory problems.

Failure to treat underlying depression in these patients may lead to suboptimal decisions and care.\(^3\)

Medications may also produce depression in the elderly. The need for older patients to take multiple medications to treat several medical problems makes polypharmacy a common phenomenon that is often difficult to identify. Dosage reductions and the outright elimination of or a change of agents may be necessary in an attempt to identify the agent responsible for depression and other adverse drug reactions.

Drugs that have frequently been reported to cause depression include steroids; histamine H\(_2\) blockers; centrally active alpha blockers; stimulants; antibiotics; sedatives; benzodi-
azepines; and anti-inflammatory, cardiovascular, chemotherapeutic, antipsychotic, antiparkinsonian, and anticonvulsant agents. Dosage reduction, when possible, is always a good place to start. A follow-up evaluation in two to three weeks should show some response, depending on the agents to be tapered and stopped.

Pathophysiology

Depression can be classified into three major types:

- **Early-onset**, with longstanding psychobiological vulnerability (i.e., positive family history and prior episodes)
- **Late-onset**, associated with stressful life events
- **Late-onset**, with underlying vascular pathology

Anatomical changes in the frontolimbic areas of the brain (e.g., the orbitofrontal cortex, anterior cingulate, and gyrus rectus) have recently been associated with depression, including white-matter hyperdensities and an increased volume of cerebrospinal fluid (CSF).33–35 The severity of the hyperdensities, especially those involving the amygdala and periventricular region, correlates with the degree of depression and cognitive problems36,37 and may also help to predict treatment-refractory or unstable depression.30,38 White-matter lesions are more significant in men with late-onset depression.39,40 Gray matter decreases in patients with early-onset depression.19,33,41

Cerebrovascular lesions in the region of the striato-pallido-thalamocortical pathways and other areas have been associated with depression, cognitive problems, apathy, and lack of insight.30,31 There is growing evidence that late-onset depression in the “oldest old” population is linked to cardiovascular and cerebrovascular burden.50,51,42 E elevated corticosteroids activate the hypothalamic-pituitary-adrenal (H-P-A) axis, deregulate the serotonergic system, and are associated with hippocampal atrophy, cognitive impairment, and depression.8,11,18,43,44 It is well recognized that depression is included in the differential diagnosis for dementia in the elderly.45

Diagnosis

The possibility of depression is always present in the clinical encounter. The rate at which primary health care providers recognize clinical depression varies widely: from 19% to 94%.25 Cognitive impairment and other medical comorbidities often hinder the ability to arrive at an accurate diagnosis.46 Yet elderly patients overwhelmingly prefer the care of their primary physician to that of a mental health professional. With the advent of managed care plans, this trend is expected to increase. There is little to no relationship between the rate of recognition by health care clinicians and the rate of treatment or referral.3

As with all other diseases, the fundamental approach to the diagnosis of depression consists of taking a systematic history, including its onset (gradual rather than sudden), its duration (longer than two weeks), its intensity, and the presence of confounding medical illness.2,4 In general, older adults do not recognize their own depression and thus might not admit to feeling depressed if asked directly about it. More commonly, they are preoccupied with bodily functions and report symptoms such as memory loss, falls, anxiety, or a variety of somatic complaints. Sleep disturbances, appetite or weight fluctuations, and changes in mentation are more common in the elderly.

Relevant items that might need to be tested include reminiscences and a life review.25 Stability, personality, and coherence of one’s life story are related to mood and a sense of mastery over health-related issues in the oldest old.47 Practitioners should actively look for psychotic symptoms related to violence and suicide risk. When a patient is asked, “How are you doing?”, the patient’s automatic, simple answer of “fine” should not be taken at face value, because the question is not an

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**Table 1: Definition of Depression**

1. Depressed mood most of the day nearly every day, as indicated by either subjective report (e.g., feels sad or empty) or observation made by others (e.g., appears tearful).
2. Markedly diminished interest or pleasure in all (anhedonia), or almost all activities most of the day, nearly every day (as indicated by either subjective account or observation made by others).
3. A significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly every day.
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others, not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.
10. The symptoms do not meet the criteria for a Mixed Episode.
11. The symptoms cause a clinically significant distress or impairment in social, occupational, or other important areas of functioning.
12. The symptoms are not due to the direct physiological effects of a substance (e.g., a drug of abuse, or a medication) or a general medical condition (e.g., hypothyroidism).
13. The symptoms are not better accounted for by bereavement (i.e., after loss of a loved one); the symptoms persist for longer than two months or as characterized by marked functional impairment, morbidity preoccupation with worthlessness, suicidal ideation, psychotic symptoms, or psychomotor retardation.

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*As defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV).*

Adapted from Almeida OP, Almeida SA: *Int J Geriatr Psychiatry* 1999;14:858–865.10
adequate screening tool. Patients are more likely to respond to screening when questions about sleep and appetite lead this portion of the interview.

The physical examination should be comprehensive in order to assess comorbid states. Station and gait and the risk of falls should be evaluated, because a shorter step length and a slower gait velocity are common in depressed patients. A Mini-Mental Status Examination (MMSE) should be included with the general and mental status examination. Specific questions addressing sleep changes, appetite changes, and weight loss need to be pursued. The MMSE does not diagnose executive dysfunction, which is important to identify. Executive dysfunction involves a failure in areas of leadership, decision-making, and the processes of inference and deduction. A depression screen is a valuable tool for diagnosis and tracking. Depression, as described by the Diagnostic and Statistical Manual of Mental Disorders, fourth revised edition (DSM IV), includes the features listed in Table 1.

Although this definition of depression is reliable for younger populations, its use in the elderly can be challenging. Five or more of the nine symptoms must be present most of the day during a two-week period, according to self-report or a report by others, and at least one of these symptoms must be anhedonia or depressed mood.

Whereas the Geriatric Scale-30 may be the more precise predictor of severity of depression than 9-point scores, it is somewhat more time-consuming to perform and score. The Geriatric Depression Scale-15 is both reliable and reproducible across cultures and languages. Simple to administer, sensitive, and specific, it should be used as a screening tool when needed. Score cut-offs of 5 to 6 demonstrate a specificity of 64.5% and a sensitivity of 90.9% when compared with DSM-IV criteria. Higher scores are associated with an increasing severity of depression.

The onset of depression after a new medication, atypical withdrawal suggests dementia more than depression. Severe cognitive impairment without moderate-to-severe social withdrawal suggests dementia more than depression.

### Differential Diagnosis

Numerous misconceptions abound and can lead to the underdiagnosis, misdiagnosis, and underreporting of depression. Normal aging does not include excessive fatigue, appetite changes, or increasing irritability that leads to isolation. Depression can be a prodrome of dementia, it can coexist with dementia, or it can be a risk factor for dementia. However, excessive psychomotor retardation, dysphoria, decreased concentration, and cognitive decline may be related to a reversible depression (pseudo-dementia) rather than a progressive dementia; this needs to be investigated as a reversible cause of dementia.

The differential diagnosis is broad and varied and must include alcoholism, adverse effects of medications, early dementias, infections, metabolic disorders, bipolar disorders, and malignancy. Elder abuse may be particularly difficult to identify. The extensive differential diagnosis makes it necessary to seek key clues.

The onset of depression after a new medication, atypical injuries, and steady weight loss suggests other processes. Severe cognitive impairment without moderate-to-severe social withdrawal suggests dementia more than depression.

### Treatment Options

From 65% to 75% of cases of depression are treatable; depression can be fatal in 15% of cases if it remains untreated. The earlier the intervention in primary care, the earlier the remission. A “watch-and-wait” period of no more than two weeks for bereavement is acceptable. The lesser the intensity of the initial grief reaction, the better the eventual outcome.

Timing is also important in the administration of estrogen for cognitive problems in older women; later administration worsens the problems. The outcome of comorbid illness is positively correlated with treatment of the underlying depression. Poor functioning, anxiety, and hopelessness predict a poor response; referral to a mental health specialist should be considered.

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### Table 2  Modified Geriatric Depression Scale

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>Are you basically satisfied with your life?</td>
<td></td>
<td></td>
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<tr>
<td>Have you dropped many of your activities and interests?</td>
<td></td>
<td></td>
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<tr>
<td>Do you feel that your life is empty?</td>
<td></td>
<td></td>
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<tr>
<td>Do you often get bored?</td>
<td></td>
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<tr>
<td>Are you in good spirits most of the time?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are you afraid that something bad is going to happen to you?</td>
<td></td>
<td></td>
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<tr>
<td>Do you feel happy most of the time?</td>
<td></td>
<td></td>
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<tr>
<td>Do you feel helpless?</td>
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<tr>
<td>Do you prefer to stay at home rather than going out to do new things?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you feel that you have more problems with your memory than most?</td>
<td></td>
<td></td>
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<tr>
<td>Do you think it is wonderful to be alive?</td>
<td></td>
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<tr>
<td>Do you feel pretty worthless the way you are now?</td>
<td></td>
<td></td>
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<tr>
<td>Do you feel full of energy?</td>
<td></td>
<td></td>
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<tr>
<td>Do you feel that your situation is hopeless?</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you think that most people are better off than you are?</td>
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<td></td>
</tr>
</tbody>
</table>

## Table 3 Medications for Depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dosage Range (mg)*</th>
<th>Adverse Effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TCAs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amitriptyline†</td>
<td>25–150</td>
<td>Anticholinergic and cardiac effects, sedation, orthostatic hypotension, weight gain, reduced seizure threshold, increased falling risk</td>
<td>Antiarrhythmics‡, MAOIs‡, SSRIs, serotonin syndrome</td>
</tr>
<tr>
<td>Desipramine (Norpramin)</td>
<td>25–150</td>
<td>Anticholinergic and cardiac effects, sedation, orthostatic hypotension, weight gain, reduced seizure threshold, increased falling risk</td>
<td>Antiarrhythmics‡, MAOIs‡, SSRIs, serotonin syndrome</td>
</tr>
<tr>
<td>Doxepin† (Sinequan)</td>
<td>25–150</td>
<td>Anticholinergic and cardiac effects, sedation, orthostatic hypotension, weight gain, reduced seizure threshold, increased falling risk</td>
<td>Antiarrhythmics‡, MAOIs‡, SSRIs, serotonin syndrome</td>
</tr>
<tr>
<td>Imipramine (Tofranil)</td>
<td>25–150</td>
<td>Anticholinergic and cardiac effects, sedation, orthostatic hypotension, weight gain, reduced seizure threshold, increased falling risk</td>
<td>Antiarrhythmics‡, MAOIs‡, SSRIs, serotonin syndrome</td>
</tr>
<tr>
<td>Nortriptyline (Pamelor)</td>
<td>25–150</td>
<td>Anticholinergic and cardiac effects, sedation, orthostatic hypotension, weight gain, reduced seizure threshold, increased falling risk</td>
<td>Antiarrhythmics‡, MAOIs‡, SSRIs, serotonin syndrome</td>
</tr>
<tr>
<td>Protriptyline (Vivactil)</td>
<td>15–50</td>
<td>Anticholinergic and cardiac effects, sedation, orthostatic hypotension, weight gain, reduced seizure threshold, increased falling risk</td>
<td>Antiarrhythmics‡, MAOIs‡, SSRIs, serotonin syndrome</td>
</tr>
<tr>
<td>Amoxapine</td>
<td>50–400</td>
<td>Extrapyramidal movement disorders, male sexual dysfunction, endocrine dysfunction</td>
<td>MAOIs‡</td>
</tr>
<tr>
<td><strong>MAOIs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tranylcypromine sulfate (Parnate)</td>
<td>30</td>
<td>Orthostatic hypotension</td>
<td>MAOIs‡, meperidine‡, vasoconstrictors‡, narcotics‡, decongestants‡</td>
</tr>
<tr>
<td>Phenelzine sulfate (Nardil)</td>
<td>45–60</td>
<td>Orthostatic hypotension</td>
<td>MAOIs‡, meperidine‡, vasoconstrictors‡, narcotics‡, decongestants‡</td>
</tr>
<tr>
<td><strong>SSRIs</strong></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Escitalopram oxalate (Lexapro)</td>
<td>10–20</td>
<td>GI symptoms, anxiety, somnolence, sexual dysfunction</td>
<td>MAOIs‡, TCAs, neuroleptics, antihistamines, antiarrhythmics‡</td>
</tr>
<tr>
<td>Citalopram hydrobromide (Celexa)</td>
<td>20–60</td>
<td>GI symptoms, anxiety, somnolence, sexual dysfunction</td>
<td>MAOIs‡, TCAs, neuroleptics, antihistamines, antiarrhythmics‡</td>
</tr>
<tr>
<td>Fluvoxamine (Luvox)</td>
<td>25–150</td>
<td>GI symptoms, insomnia, anxiety</td>
<td>MAOIs‡, TCAs, neuroleptics, antihistamines, antiarrhythmics‡</td>
</tr>
<tr>
<td>Fluoxetine (Prozac)</td>
<td>10–40</td>
<td>Anorexia, agitation, anxiety, GI symptoms, insomnia, weight loss</td>
<td>MAOIs‡, TCAs, neuroleptics, antiarrhythmics‡</td>
</tr>
<tr>
<td>Paroxetine HCl (Paxil)</td>
<td>25–35.7</td>
<td>GI symptoms, anxiety, insomnia, fatigue, dry mouth</td>
<td>MAOIs‡, TCAs, neuroleptics, antiarrhythmics‡</td>
</tr>
<tr>
<td>Sertraline (Zoloft)</td>
<td>25–200</td>
<td>GI symptoms, sexual dysfunction, weight gain, headache</td>
<td>MAOIs‡, TCAs, neuroleptics, antiarrhythmics‡</td>
</tr>
</tbody>
</table>

* Dosages in the elderly should be lower and dictated by clinical judgment.
† Not recommended in the elderly.
‡ May cause potentially fatal interaction.
GI = gastrointestinal; MAOI = monoamine oxidase inhibitor; SSRIs = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
Watchful waiting in patients with subsyndromal depressive states is not indicated if social support is inadequate or if there is significant impairment of activities of daily living (ADL). Ethical concerns have been raised about the use of placebo in the treatment of depression in the elderly because of the heterogeneity of causes and responses. Most treatment errors are the result of the non-use or misuse of medications, not overmedication. The most recent study of maintenance treatment of depression in the elderly available at this writing demonstrated the superiority of treatment for two years with paroxetine (Paxil) to psychotherapy alone or placebo in lowering relapse rates significantly.

Many medications are available for the treatment of depression in the elderly (Table 3). Some of these agents are preferred for certain comorbid conditions (Table 4). These drugs may protect against a decrease in gray matter in the elderly, provide neuroprotection, and enhance brain-derived neurotrophic factor.

Start low and go slow. Clinicians should use the lowest dosage range, as shown in Table 3, and should maintain this level for several weeks before increasing the dosage if there is no improvement. Adverse drug effects are quite common in older people because of polypharmacy and multiple physical changes, particularly decreased drug-binding proteins; muscle mass; and renal, hepatic, and cardiac function. Care should be taken in selecting an antidepressant medica-

### Table 3 Medications for Depression (continued)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dosage Range (mg)*</th>
<th>Adverse Effects</th>
<th>Interactions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Miscellaneous Agents</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Venlafaxine (Effexor)</td>
<td>75–150</td>
<td>Anxiety, sexual dysfunction, elevated blood pressure, sedation, nausea, visual symptoms</td>
<td>MAOIs, SSRIs, antihistamines, benzodiazepines, neuroleptics</td>
</tr>
<tr>
<td>Nefazodone</td>
<td>200–400</td>
<td>Anxiety, sexual dysfunction, elevated blood pressure, sedation, nausea, visual symptoms</td>
<td>MAOIs, SSRIs, antihistamines, benzodiazepines, neuroleptics</td>
</tr>
<tr>
<td>Mirtazapine (Remeron)</td>
<td>15–45 at night</td>
<td>Sedation, asthenia, constipation, weight gain</td>
<td>MAOIs, SSRIs, antihistamines, benzodiazepines, neuroleptics</td>
</tr>
<tr>
<td>Trazodone (Desyrel)</td>
<td>50–600</td>
<td>Sedation, orthostatic hypotension, priapism</td>
<td>MAOIs†</td>
</tr>
<tr>
<td>Bupropion (Wellbutrin)</td>
<td>300</td>
<td>Lower seizure threshold</td>
<td>MAOIs†</td>
</tr>
<tr>
<td>Maprotiline (Deprilept, Ludiomil, Psyromin)†</td>
<td>50–150</td>
<td>Lower seizure threshold</td>
<td>MAOIs</td>
</tr>
<tr>
<td></td>
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</tbody>
</table>

### Table 4 Treatment Recommendations for Depressed Patients with Comorbid Medical Conditions

<table>
<thead>
<tr>
<th>Medication of Choice</th>
<th>Drugs to Avoid</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Neurologic disease</strong></td>
<td></td>
</tr>
<tr>
<td>Alzheimer’s dementia</td>
<td>SSRIs, nefazodone, venlafaxine</td>
</tr>
<tr>
<td>Parkinson’s disease</td>
<td>Bupropion, venlafaxine</td>
</tr>
<tr>
<td>Stroke</td>
<td>SSRIs, possibly secondary amines</td>
</tr>
<tr>
<td>Cancer</td>
<td>TCAs, duloxetine</td>
</tr>
<tr>
<td>Cachexia</td>
<td>Sertraline, paroxetine, trazodone, nefazodone, TCAs, venlafaxine</td>
</tr>
<tr>
<td>Nausea</td>
<td>Bupropion, SSRIs, venlafaxine</td>
</tr>
<tr>
<td>Pain (severe with cancer)</td>
<td>TCAs, duloxetine</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>SSRIs, bupropion, nefazodone</td>
</tr>
</tbody>
</table>

MAOI = monoamine oxidase inhibitor; SSRI = selective serotonin reuptake inhibitor; TCA = tricyclic antidepressant.
tion and determining the dosing guidelines and the length of therapeutic trials. Prudence dictates avoiding drugs with significant anticholinergic side effects, such as tricyclic antidepressants (TCAs) as well as sedating antidepressants, which may increase the risk of falling. Agents like sertraline (Zoloft, Pfizer), sustained-release bupropion (Wellbutrin SR, Glaxo-SmithKline), and citalopram hydrobromide (Celexa, Forest) are recommended by expert consensus primarily because these agents help avoid many of the common problematic drug interactions.55

TCAs are no longer considered first-line therapy for older patients, although they are thought to be equally effective in comparisons with younger populations.56 Significant anticholinergic side effects and problems with adhering to dosage recommendations are the major reasons for the reduced use of TCAs.

Selective serotonin reuptake inhibitors (SSRIs) are the usual first-line drugs, and selective serotonin–norepinephrine reuptake inhibitors (SNRIs) are usually the first drugs that are substituted when initial monotherapy fails.57 Although fluoxetine (Prozac, Eli Lilly) was the first SSRI to be approved for geriatric depression, it would be hard to argue with the use of the short-half-life SSRIs as a first-line treatment in this population. Better tolerated than monoamine oxidase inhibitors (MAOs) and TCAs, SSRIs have a therapeutic response rate approaching 75%.54 Dropout rates are 50% to 70% for TCAs, and the cost of SSRIs is offset by the need for less intensive inpatient and outpatient care.54

Common side effects include agitation, insomnia, fatigue, dry mouth, weight loss, headache, anxiety, nausea, diarrhea, and constipation.54 Transitory gastrointestinal distress may be reduced by slow titration and by taking the medication with meals. Sexual dysfunction occurs in 15% to 30% of patients taking SSRIs.54 Because the incidence of dysfunction is much lower.54

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Sertraline, citalopram, and escitalopram (Lexapro, Forest) are associated with a low rate of drug–drug interactions; they are available in a wide range of dosages and are well tolerated.55 Duloxetine (Cymbalta, Eli Lilly) significantly improves arthritis pain in depressed elderly patients and may be useful for depressed patients with associated pain caused by cancer.57

Executive dysfunction, anhedonia, and decreased noradrenergic tone, characteristic of late-onset depression, may be associated with a poor response to antidepressant therapy, particularly SSRIs.58 Recently, the syndrome of inappropriate antidiuretic hormone secretion (SIADH) has been identified in 12% to 25% of elderly patients taking SSRIs.59 Because the integrity of the receptor sites for these agents appears to be a function of serum cholesterol, excessive swings or reductions may affect therapeutic efficacy.60

Alternative drugs such as mirtazapine (Remeron, Organon) and venlafaxine (Effexor, Wyeth) have been shown to be equal in efficacy to sertraline.54 Venlafaxine appears to be useful in elderly patients with treatment-resistant depression, but careful blood pressure monitoring is important in patients with pre-existing cardiovascular disease. Bupropion, in its extended-release and SR forms, promotes compliance, and its efficacy appears to be equivalent to that of the TCAs and SSRIs. Although bupropion has been removed from the Canadian and European markets because of associated liver failure, there are no recommended guidelines for the monitoring of liver functions. Sexual dysfunction is less common with mirtazapine, nefazodone, and bupropion.

Modafinil (Provigil, Cephalon) is a wakefulness-promoting agent that can increase noradrenergic tone as an augmentation strategy with fewer side effects (e.g., tachycardia, anxiety, insomnia). As a result, it might be useful in late-onset or resistant depression that does not respond to SSRIs alone.61,62

Despite a generally negative perception of MAOIs among clinicians, these agents are safe and effective in older patients.54 A period of at least five to seven weeks is required to attain full therapeutic efficacy. Patients may need at least a two-week washout period before starting an MAOI if another psychotherapeutic medication (or another drug that may have an adverse interaction with an MAOI) is to be prescribed.

If the patient is being switched from an MAOI to another antidepressant, the two-week washout period is also necessary before the patient begins taking the new antidepressant.53 The serotonin withdrawal syndrome (e.g., tremor, diarrhea, fever, incoordination, myoclonus, agitation, shivering, mental status changes, hyperreflexia, and diaphoresis) can follow the use of MAOIs with TCAs and SSRIs. A tyramine-free diet is required for patients taking an MAOI.

For the “vascular” type of depression, drugs that improve adrenergic tone (e.g., desipramine [Norpramin, Sanofi-Aventis]) or dopaminergic tone (bromocriptine), or both (amphetamine) are required. Alpha-antagonists such as trazodone (Desyrel, Apothecon), amitriptyline, the benzodiazepines, and dopamine antagonists should be avoided because they impede recovery from ischemic lesions.9

Traditional stepwise monotherapy is yielding to augmentation (the addition of a non–FDA-approved or an “off-label” agent with counterdepressive qualities) and combination (the addition of a second FDA-approved antidepressant) strategies (polypharmacy) in the specialty of psychiatry. The use of multiple agents with different variations inherent to individual psychiatric practice has led to polypharmacy as the perceived and probable standard of care.50,54 The most commonly used augmentation strategy is the addition of lithium, and the most common combination strategy is the addition of bupropion.

A cholinesterase inhibitor may be useful if it is added to an antidepressant in cases of mild cognitive impairment and late depression, because the latter may precede the development of Alzheimer’s disease by five years.9 Low-dose antipsychotic agents and a referral to a specialist are indicated for patients with concomitant psychotic symptoms as well as resistant depression. The medication should be continued for six months after remission.20 Controversial therapies include the use of mifepristone (Mifiprex, Danco), metyrapone (Metopiron, Novartis), and ketoconazole (Nizoral, PriCara); also controversial is the role of stress and glucocorticoids with involvement of the amygdala, the H-P-A axis, and related cardiovascular conditions.8,13,18,28,65–67

After the decision to initiate drug therapy is made, close follow-up is essential. Goals of treatment in depression should include improvement in social and family function, reduced discomfort, and a significant improvement in satisfaction with life
in general.23 One can look to improvement in appetite, sleep patterns, energy, and attitude to determine when treatment responses are adequate.23 Some patients early in their treatment do, in fact, deteriorate and become progressively agitated. This possibility should be discussed with the patients before therapy has begun and at their follow-up visits.

A partial treatment effect should be evident in three to four weeks, but a full therapeutic response takes months.23,55 Six to 12 months is typical for recovery from a severe episode of depression. The first follow-up visits should be scheduled within two weeks. For patients at increased risk (e.g., men living alone), a telephone follow-up can be made after a week of therapy.55

Early visits are intended to assess titration and tolerance of medications. The one-month and six-week follow-up visits would be appropriate intervals to access early positive (or negative) responses. Upward dosage adjustments should probably not be made more often than every four to six weeks.

Decisions about continuing treatment should be made in conjunction with the patient after an evaluation of the response to and tolerance of the regimen prescribed. Medication should be continued for at least six months after remission. Medications should probably not be tapered or stopped in the winter because of the high correlation between Seasonal Affective Disorder (SAD) and depression.

Some patients who have done particularly well with treatment may be resistant to tapering or stopping their medications. Exploration of this issue sometimes reveals that they are feeling well for the first time in many years, and the medications should probably be continued indefinitely in this subset of patients. Improved quality-of-life factors (e.g., positive affect, better health status, and a reduction in somatic complaints) predict increased compliance with antidepressant use and a decrease in do-not-resuscitate (DNR) decisions.47,56

Electroconvulsive therapy (ECT) should be considered if depression is severe (i.e., if the patient has suicidal ideation or psychosis or will not eat).20,68 After ECT, the patient should be kept on antidepressant medication and mood stabilizers, because relapse approaches 100%.69 Maintenance ECT may be more cost-effective than maintenance pharmacotherapy in depressed elderly patients who have responded to ECT.70

Wellness advice should be offered. Adjunctive therapies like exercise (physical and mental), low-calorie intake, and specific nutrients have all been associated with improved mental and physical health and should be encouraged.43 Neutraceuticals such as folate may be helpful in increasing the responsiveness to SSRIs in the elderly.71

A variety of effective psychotherapies are also available for the management of depression.72 Primary care physicians can facilitate optimal adherence to treatment by offering continued patient education and by using cognitive behavioral techniques.52,53 Other considerations include psychoneuroimmunological and spiritual factors.17,72 Regular organized religious or spiritual practices are associated with a lower incidence of depression.74

There is little evidence to support transcranial magnetic stimulation, dialectical behavior therapy, light therapy, interpersonal therapy, or St. John’s wort as therapy for depression.23 Successful treatment is measured in terms of improved quality of life, enhanced functional capacity, enhanced health status (in some cases), and increased longevity.23

Experts recommend that patients be referred for specialized geropsychiatric care if they:

- exhibit psychosis, bipolar disorder, or suicidal ideation.
- have a complex or uncertain diagnosis.
- are unresponsive.
- are intolerant of an adequate trial of first-line treatment.
- require more than one drug.
- are candidates for ECT.
- are severely ill.

Conclusion

Although depression is common, it is not a normal process of aging. It can cause significant morbidity and mortality, and it is both diagnosable and treatable by the primary care physician. Outcomes in the elderly are comparable to those of younger populations, although remission may take longer to achieve. Because the incidence and severity of adverse effects is significant in older adults, careful follow-up is essential.

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**Bibliography and Additional Readings**


**Conflict of Interest (COI) Statement**

Dr. Birrer, Dr. DeLisi, and Dr. Dadoyan have no relationships to disclose. The content of this article has been reviewed under Jefferson’s Continuing Medical Education COI policy.
Continuing Education Questions for Physicians and Pharmacists

P&T® 2007;32(3):168–177
ACPE Program # 079-999-07-015-H04
Expiration Date: March 31, 2008

TOPIC: Depression in the Elderly

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**Topic: Depression in the Elderly**

APCE Program # 079-999-07-015-H04

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**Multiple Choice**

*Select the one correct answer.*

1. The most common diagnosis in the geriatric population of those who commit suicide is:
   a. dementia.
   b. insomnia.
   c. depression.
   d. bipolar disorder.

2. Which of the following are risk factors for depression?
   a. female sex and widowed, single, or divorced status
   b. alcohol and occult substance abuse
   c. stressful events (i.e., loss of spouse, hospitalization, unemployment)
   d. all of the above

3. What is the hallmark of depression in the elderly that is different from depression in the younger population?
   a. concurrent medical comorbid conditions
   b. age
   c. social status
   d. memory loss

4. Which of the following drugs are not frequently reported to cause depression?
   a. histamine blockers and sedatives
   b. centrally active alpha blockers and stimulants
   c. antipsychotic and antiparkinsonian agents
   d. none of the above

5. Which criteria comprise a tool for diagnosis and tracking of depression in the elderly?
   a. *Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)*
   b. Mini-Mental Status Examination (MMSE)
   c. Beers Criteria
   d. none of the above

6. Pharmacotherapy management to treat depression in elderly patients should:
   a. “start high and go immediately”
   b. “start low and go slow”
   c. “start high and go slow”
   d. “start low and go immediately”

7. Which of the following class of drugs is not recommended treatment for depression in the elderly?
   a. SSRIs
   b. SNRIs
   c. TCAs
   d. MAOIs

8. What is the first line of therapy for depression in the elderly?
   a. SSRIs
   b. SNRIs
   c. TCAs
   d. MAOIs

9. A patient recently started taking escitalopram. What is the common side effect you should counsel the patient to expect?
   a. agitation
   b. insomnia
   c. weight loss
   d. all of the above

10. For a full therapeutic response of medication to be seen, it may take:
    a. less than one week.
    b. one week.
    c. two to four weeks.
    d. up to 12 weeks.
CE Registration and Evaluation Form

Date of publication: March 2007
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Authors: Richard B. Birrer, MD, Michael DeLisi, MD, and Talin Arsen Dadoyan, MD
Submission deadline: March 31, 2008
ACPE Program # 079-999-07-015-H04

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Signature (required) Date _______________

Answer Sheet

Please fill in the box next to the letter corresponding to the correct answer

1. a □ b □ c □ d □ 6. a □ b □ c □ d □
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Evaluation

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☐ This program will not change my behavior because my current practice is consistent with what was taught.
☐ This activity will not change my behavior because I do not agree with the information presented.
☐ I need more information before I can change my practice behavior.
☐ I will immediately implement the information into my practice.

10. Will you take any of the following actions as a result of participating in this educational activity (check all that apply)

☐ Discuss new information with other professionals  ☐ Consult the literature
☐ Discuss with industry representative(s)  ☐ Participate in another educational activity
☐ Other ___________________________________  ☐ None

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