Diagnosis and Treatment of Depression in Late Life

Sidney Zisook, M.D., and Nancy S. Downs, M.D.

Major depression and dysthymia are common and often disabling disorders in late life. Several features of late-life depression, such as its frequent association with general medical conditions, polypharmacy, cognitive disturbances, and adverse life events, make accurate diagnosis a substantial clinical challenge. Yet, prompt diagnosis is an important component of implementing appropriate treatment strategies. An ideal treatment program integrates patient and family education, focused psychotherapy, and pharmacotherapy. Because of pharmacokinetic and pharmacodynamic changes associated with aging, lower doses of medication and more gradual dose increases than are required in younger adults are needed in the treatment of elderly depressed patients. In addition, medications should be selected that have minimal antihistaminic, anticholinergic, and antiadrenergic effects, minimal cardiovascular risk, and minimal drug-drug interactions. Since depression in late life tends to be at least as chronic and/or recurrent as depression earlier in life, treatment for acute depressive episodes should last at least 6–8 months, and long-term maintenance treatment should be considered in selected individuals.
(J Clin Psychiatry 1998;59[suppl 4]:80–91)

The graying of America challenges all psychiatric clinicians to become experts in the diagnosis and treatment of mood disorders in the elderly. Population projections show the elderly population (65 years and older) rising steadily from a 1900 level of 4.0% of the total U.S. population, through 12.6% in 1990, and an estimated 22.9% by 2050.[1] Given the high prevalence of mood disorders in adults now entering the later phases of life and the chronic and recurrent nature of those disorders, it is likely that most psychiatric clinicians soon will be seeing substantial numbers of elderly patients with mood disorders in their practices. This manuscript reviews—and emphasizes the unique aspects of—the epidemiologic considerations, diagnostic characteristics, morbidity and mortality, and treatment principles related to depression in late life.

EPIDEMIOLOGIC CONSIDERATIONS

Depression is not an inevitable consequence of aging. Indeed, most epidemiologic studies find the highest rates of mood disorders in relatively young adults, with significantly lower prevalence rates reported for individuals aged 65 years and above. Yet, depressive symptoms and syndromes cannot be ignored in late life. They are a major source of pain, disability, and dysfunction throughout the life cycle.[2] According to the Epidemiologic Catchment Area (ECA) Study,[3] the lifetime occurrence of depressive symptoms lasting at least 2 weeks and not explained by physical illness or ingestion of medications, drugs, or alcohol is substantial (Table 1).

A full major depressive episode is experienced by 2% of the elderly, dysthymia in another 2%, and bipolar disorders in 0.2%. These rates are conservative estimates of the overall burden of mood disorders in the elderly. They exclude depressive symptoms secondary to a general medical illness or medications (common in the elderly), depressive episodes of less than 1 year following the death of a loved one (also common in the elderly), atypical features (overeating and oversleeping), and psychomotor retardation. In addition, individuals who minimize or deny dysphoria and anhedonia were probably missed in this survey. Most other community samples of older adults using different diagnostic instruments than the ECA have found somewhat higher rates of major depression and dysthymia.[4]

Several studies have found depressive symptoms in older adults to be the most prevalent in the "oldest-old" (80 years and older) and in females.[5–7] While female gender is a risk factor for major depression throughout the adult life cycle, gender differences in the prevalence of major depression appear to narrow as age increases.[4] Compared with the rates of major depression in the general population, the prevalence of major depression in several special populations, such as primary care outpatient facilities,[8,9] acute care medical facilities,[10–12] and long-term facilities,[13,14] is substantially higher. Although the rate of major depression has been estimated at ap-

From the Department of Psychiatry, University of California, San Diego.
Presented at the symposium "Beyond SSRIs," held January 3–4, 1997, Buckhead, Ga., which was supported by an unrestricted educational grant from Glaxo Wellcome.
Reprint requests to: Sidney Zisook, M.D., Department of Psychiatry, 0603-R, University of California, San Diego, 9500 Gilman Drive, La Jolla, CA 92093-0603

Table 1. Lifetime Prevalence of Depressive Symptoms in Individuals Aged 65 Years and Older*

Symptom	Percentage Reporting Symptoms
Dysphoria	25
Death thoughts	22
Sleep change	19
Appetite change	16
Fatigue	11
Diminished concentration	8
Psychomotor change	7
Guilt	5
Loss of interest	2

*Data from reference 30. Symptoms lasting ≥ 2 weeks and not explained by general medical illness, drugs, alcohol, or medications are listed.

Table 2. Age-Related Chronic Medical Conditions*

	Frequency per 1000 persons in USA		
Medical Condition	Age ≤ 45 y	Age 46–64 y	Age ≥ 65 y
Arthritis	30	241	484
Hypertension	129	244	372
Hearing impairment	37	141	321
Heart disease	31	134	295
Diabetes	9	57	99
Visual impairment	19	48	79
Cerebrovascular disease	1	16	63
Constipation	11	19	60

*Data from reference 19.

Table 3. General Medical Conditions and Major Depression*

Condition	Percentage With Major Depression
Stroke	5–34
Cancer	0–50
Myocardial infarct	15–19
Rheumatoid arthritis	3–42
Parkinson's disease	17–29
Diabetes	5–11

*Data from reference 20.

Table 4. Guidelines for Diagnosing Major Depression With Coexisting General Medical Disorders in Late Life

- Major depression is NOT a "normal" response to aging or medical illness
  - Rule out major depression due to general medical condition
  - Rule out substance-induced mood disorder
  - Rule out adjustment disorder
  - Otherwise, diagnose mood disorder as a separate disorder
- When etiology of specific symptoms is unclear, do one of the following:
  - Emphasize psychological symptoms (eg, dysphoria, anhedonia, feelings of worthlessness)[25,26]
  - Substitute behavioral or cognitive symptoms (eg, withdrawal, brooding, pessimism)[27] for questionable somatic symptoms
- Use additional resources—family, caregivers, medical records, and frequent reassessments
- Loss of interest is more helpful than sadness as a screening symptom
- Recent social withdrawal, irritability, somatization, and hypochondriasis are clues to an undiagnosed depression

proximately 12% for nursing home residents, lesser, but clinically important depressive symptomatology occurs in an additional 30% to 35%.[4] Perhaps more alarming is the 14% incidence of new cases of depression over a 6-month period.[15] Those at highest risk in nursing homes are cognitively intact patients who are the sickest, most disabled, and most dependent.[15]

Despite the high prevalence of depression in nursing homes and in patients receiving general medical care, depression and dysthymia remain largely unrecognized and untreated among the elderly.[16] As in other stages of the life cycle, depression in late life tends to be a chronic and recurrent disorder.[17] For example, during the first year of follow-up in a study of 124 subjects with late-life depression, only 35% achieved full remission of symptoms without evidence of relapse, 22% got well but relapsed, 29% remained continuously ill, and 14% died.[18] Risk factors for poor outcome include lack of appropriate acute and maintenance treatment, severe initial symptoms, cognitive impairment, and physical illness.[18]

DIAGNOSTIC ISSUES

The diagnostic criteria for major depression and dysthymia are the same in the elderly as they are in other age groups. However, in clinical practice, the diagnosis is complicated by at least three factors commonly seen in late-life: comorbid general medical conditions, cognitive deterioration and disorders, and multiple adverse life events. Each of these factors obfuscates recognition of major depression and may lead to misdiagnosis.

Comorbid General Medical Condition

The longer one lives, the greater the likelihood that systemic medical conditions will develop (Table 2). Consequently, depressive symptoms in the elderly often will occur in the context of one or more general medical conditions. To compound the problems of comorbidity, however, many of the general medical conditions common in the elderly are associated with especially high rates of depression (Table 3).[20] Thus, it is no surprise that elderly inpatients with major depression have been reported to have an average of five comorbid Axis III disorders, with circulatory and digestive system disorders being the most prevalent.[21]

Late-life individuals with depression are particularly prone to somatic complaints—in part due to their propensity toward general medical illness, as well as the aches, pains, and concerns that are part of aging. Several studies have documented the tendency of elderly persons with depression to focus their attention and complaints on somatic rather than psychological symptoms[22,23]; however, others have found minimal to no differences in the symptomatic presentations of depression in old versus young adults.[24]

Distinguishing the symptoms of depression from those of other conditions in medically ill elderly patients is by

no means simple. Consequently, the diagnosis of major depression or dysthymia is easy to miss in the elderly. Table 4 summarizes guidelines for diagnosing depression in the face of general medical disorders.

First, never assume major depression is a normal response to aging or medical illness. While demoralization or fear may be expected responses to severe medical illness or disability, major depression is not. Many individuals endure even the most painful and severe medical conditions without developing a major depressive episode. When the full syndrome of a major depressive episode does present with another medical illness, it should be diagnosed as a separate, comorbid disorder and managed accordingly. The relationship between depression and concomitant general medical illness is complex. Sometimes, a depressive syndrome appears as part of a physiologic reaction to an illness, such as depression accompanying severe myxedema (i.e., mood disorder due to a general medical condition); sometimes it is precipitated by a medication used to treat another medical disorder, such as alpha-methyldopa-induced depression (i.e., substance-induced mood disorder); and sometimes depression is part of a psychological reaction to being seriously ill, such as a depressive episode following a myocardial infarct. Often, the depressive syndrome is not neatly wrapped in a single etiologic package, and the likeliest explanation for the depression comprises various combinations of the above three possibilities. Usually, it makes sense to treat the comorbid medical condition or change the offending medication before more aggressively treating the depression. However, if the major depression episode persists, it is likely to require separate treatment.

Second, when an individual symptom generally used to make the diagnosis of a depressive disorder is better understood as the direct result of a general medical condition (e.g., fatigue in influenza, thoughts of death in lung cancer, or weight loss in hyperthyroidism) it should not be counted as a symptom of depression. If enough such symptoms cast doubt on the diagnosis, psychological manifestations (e.g., persistently depressed mood, anhedonia, feelings of helplessness and worthlessness, loss of self-esteem, or suicidal ideation) should be heavily weighted.[25] Some investigators suggest substituting behavioral or cognitive symptoms (e.g., fearful or depressed appearance, social withdrawal, decreased talkativeness, brooding, self pity, or pessimism) for the standard DSM-IV somatic symptoms.[27] Others find loss of social interest, a sense of failure or being punished, and suicidal ideation most helpful in identifying major depression in medically ill patients.[26]

Third, when in doubt, interviews with family members, caretakers, or other resource people, review of medical records, and frequent reassessments often are helpful. Such ancillary information can provide valuable data about past personal and family history of mood disorders and may help provide diagnostic information not available in brief interview situations. This may be particularly important in the oldest-old (80 years and older) who are prone to deny not only DSM-IV mood symptoms of depression, but also many of the standard symptoms such as poor sleep or appetite. More often identified by family or caretakers than by the individuals themselves or even by their physicians, these low-grade but clinically debilitating syndromes consist of loss of interest in usual activities, social withdrawal, irritability, and somatization.[28]

Cognitive Deterioration and Disorders

The prevalence of mild-to-severe cognitive impairment increases with age. Based on a cutoff of 6 or more errors on the Mini-Mental Status Examination (MMSE)[29] to indicate cognitive impairment, 4% to 5% of the population aged 35 to 54 years, 6% to 9% among those aged 55 to 64 years, 12% to 15% of those aged 65 to 74 years, 22% to 26% of those aged 75 to 84 years, and 36% to 45% of those aged 85 years and older have cognitive impairment.[3] This means that a substantial number of older persons may be unable to give an accurate history, understand questions posed by their clinicians, or recall symptoms of depression.

When depressed elderly patients complain of poor concentration or thinking in lieu of other depressive symptoms, the clinician should consider the possibility of a comorbid dementing disorder or subclinical cognitive dysfunction that is amplified by the depression.[30,31] Both cortical (e.g., Alzheimer's disease) and subcortical (e.g., Parkinson's disease) dementing disorders are quite prevalent in late life and are associated with markedly elevated rates of major depression.[32,33]

When moderate-to-severe symptoms of both depressive and dementing disorders are present, the coexistence of two separate disorders is much more likely than "pseudodementia" (i.e., cognitive disturbance secondary to depression). This may even be true when the cognitive deficits clear with antidepressant treatment. Long-term follow-up studies of older patients who were initially diagnosed with pseudodementia show that many of these patients eventually manifest primary dementia without depressive features.[34] Thus, depressive symptoms may be one of the earliest manifestations of primary degenerative dementia in late life.

It is often difficult to distinguish between a depressive disorder and an early dementing disorder, and the differential diagnosis can challenge even the most experienced clinician. Not only may cognitive symptoms of the two disorders overlap (e.g., forgetting, poor concentration, losing things), but other symptoms, such as low energy and social withdrawal, also may be common to both. Paradoxically, patients with a primary mood disorder may minimize complaints of dysphoria and emphasize problems with memory, while the primary cognitively impaired individu-

als will do everything possible to hide and compensate for their cognitive disturbances (e.g., by making lists) while not masking their disappointment or demoralization.

Treatable causes of dementia should be ruled out by a thorough history (including family history for dementing disorders) and physical examination, complete blood count, chemistry panel, serum B_{12} and folate levels, rapid plasma reagin (RPR) test, heavy metal screen, toxicology screen, and HIV antibody screen. Neuroimaging studies should be considered if there is evidence of, or risk factors for, focal neurologic impairment such as marked personality change, step-wise progression of dementia, focal motor deficits, history of cerebrovascular or significant cardiovascular disease, or previous history of a primary neoplasm.

For patients presenting with both mood and cognitive disturbances, the diagnosis of a depressive episode should be considered whenever anhedonia, an emphasis on personal failures, feelings of worthlessness, or suicidal ideation are present; when there is a past personal or family history of mood disorders; when there is a recognizable onset and/or moderately rapid progression of symptoms; when remote memory is affected; and when "soft" neurologic signs (e.g., glabellar or snout reflexes, or sundowning) are not present.[35] If the correct diagnosis remains in doubt, a full trial of antidepressant treatment is warranted.

Adverse Life Events

In addition to loss of health and cognitive abilities, the elderly face myriad adverse life losses: of jobs, money, homes, abilities, hopes and dreams, and friends and family. Many of these losses can lead to fear, demoralization, or loneliness. In vulnerable persons, they can contribute to the onset, worsening, or persistence of a mood disorder. Because the elderly, their family, and even health care providers can understand how difficult these life experiences are, they tend to consider that depression occurring in the wake of such adverse life events is normal. This uninformed perspective works against making the diagnosis of a clinical depression and interferes with the effective treatment of this painful and potentially life-threatening condition. Whenever major depression occurs, even if precipitated by horrific life events, it should be considered an illness and treated accordingly.

A case in point is spousal bereavement, a ubiquitous life event which has been associated with prolonged personal suffering, declining mental and physical health, and increased mortality risk.[36,37] Among people aged 65 or over, more than 50% of all women and 13% of men have been widowed at least once. Twenty percent of elderly widows and widowers meet criteria for major depressive syndrome 2 months after their loss, and in about one third of these, the depression lasts a year or longer.[38] Bereaved persons who are depressed have worse health, more functional and social difficulties, and more protracted grief than bereaved persons who are not depressed.[39] Risk factors for prolonged depression after bereavement include previous and family history of depression, intense depressive symptoms soon after the loss, and poor general medical health.[40]

As a rule of thumb, if a major depressive syndrome occurs within the first 2 months after bereavement and lasts less than 2 months, it should be considered part of normal bereavement and not aggressively treated. However, even within the first 2 months, the depression should be considered a clinically important, treatable syndrome if it is severe or associated with psychomotor retardation, is accompanied by feelings of worthlessness or suicidal ideation, or occurs in a person with a history of a previous major depressive episode. Even when the depression is mild, if it persists 2 or more months after the loss, treatment should be considered. It is an error to regard major depression, in any circumstances, as a normal response to adversity. It is always a serious illness.

MORBIDITY AND MORTALITY

Depression causes great suffering for patients and their families. It interferes with basic abilities to think, eat, sleep, love, interact with others, maintain a sense of purpose, experience gratification, and maintain self-responsibility.[2] Although not specifically dealing with late-life depression, the medical outcome studies have demonstrated that major depressive symptoms are associated with as much social and physical dysfunction, days spent in bed, and even physical pain, as any other chronic medical illness, with the possible exception of advanced coronary artery disease.[41] The World Health Organization has recently estimated that by the year 2020, depression will be the second leading cause of disability in the world.

When depression is comorbid with a general medical illness, each may adversely effect the clinical picture, course, response to treatment, and prognosis of the other illness. For example, a comorbid medical illness increases the chronicity and refractoriness to treatment of major depression.[18,42] Several studies show lower recovery rates for depressed patients with heart disease,[43] stroke,[44] hip fracture,[45] and dementia[46] compared with nondepressed patients. When depression strikes a person suffering from a comorbid general medical illness, dysfunction and pain are magnified, motivation is disrupted, compliance is minimized, and recovery is compromised.

The most serious consequence of untreated depression is death. An important risk factor for death after a myocardial infarction[47] or a cerebrovascular accident[44] is depression. Nursing home residents with major depression exhibit between 1.5 and 3 times the death rate of nondepressed residents.[13] Perhaps the major cause of increased mortality in the depressed elderly is suicide. The suicide rate for the elderly is approximately twice that for other age groups and is especially high in elderly white

males. Risk factors for suicide in depressed elderly persons include a history of suicide attempts, comorbid general illness, alcohol use, anxiety, panic, agitation, feelings of hopelessness or worthlessness, and perhaps most important, lack of appropriate treatment for depression.

TREATMENT

The goals of treatment are to reduce symptoms, restore optimal functioning, and prevent relapse or recurrence. Before treatment is begun, a thorough psychiatric and medical history should be done to confirm the diagnosis and identify any other conditions that need to be addressed. Medical, laboratory, and electrocardiogram (ECG) examinations will further help rule out medical causes, identify conditions that may alter one's approach or choice of treatments, and provide baseline information. Although the relative effectiveness of psychotherapy versus pharmacotherapy versus both is still controversial in late-life depressive episodes, most studies suggest that combined or integrative modalities often are more effective than monotherapy.[48–50]

Psychotherapy

Both cognitive-behavioral and interpersonal therapies are effective in treating some elderly patients with major depression.[49,51] Many experts in the field of mood disorders recommend the combined use of medications and psychotherapy to treat an affective illness.[48] Shuchter et al.[52] have described an approach that integrates elements of supportive, cognitive, interpersonal, and family therapies with the use of antidepressant medications. The cornerstone of this approach is the awareness that major depression and dysthymia are biopsychosocial disorders, and that well-educated patients are the best patients. Thus, the first step in the treatment of depression is intensive psychoeducation and support for the patients and their families. This involves explaining the diagnosis of depression in understandable language; emphasizing that depression is not a shameful weakness but instead is an illness that requires careful medical attention and treatment; informing patients of the expected benefits and risks of treatment, including side effects and what to do if they occur; counseling about the course of depression and the need to continue taking medication beyond the immediate resolution of symptoms; and telling patients and families how to contact their physician should the need arise. In addition, the therapist maintains a hopeful, positive perspective; seeing the patient regularly and being available by phone; discouraging major life changes until the depression is attenuated; minimizing the use of alcohol and drugs, while taking advantage of as much light, good nutrition, exercise, and the use of other coping techniques as feasible for the patient; and maintaining vigilance for suicide throughout the course of the illness.

There are some unorthodox psychosocial interventions—unique to late life—that can occasionally be employed. For example, it is often useful to recommend pets, especially for individuals who no longer have a regular companion or someone for whom to care. Similarly, while one rarely would advocate physical contact with young patients, it may be extremely therapeutic to touch elderly patients, who are often isolated from physical, human contact. In certain circumstances, a small amount of alcohol with dinner may be encouraged, especially if it enhances socialization and well-being, or helps with sleep, and is not otherwise unsafe or contraindicated.[27]

Psychotherapy may be the treatment of choice for mild depression or when it has been helpful in the past, but its use should be monitored and adjusted as warranted by clinical response. It also can be useful in patients for whom pharmacologic treatment may not be suitable because of side effects, interaction among medications, or comorbid medical conditions. In patients with moderate to severe depression, psychotherapy can help augment medication.

Pharmacotherapy

For patients in late life with moderate-to-severe major depression, pharmacotherapy is the mainstay of treatment. Although the data on treatment of dysthymia in late life are sparse, antidepressant medications probably are also indicated.[4] Several studies have demonstrated the safety and efficacy of antidepressant medications in the "young-old" (55–70 years) and healthy-old, but few studies have addressed antidepressant use in the very old or in the medically frail, elderly population that is increasingly represented in many clinical practices. A few studies have supported the effectiveness of antidepressants in stroke patients,[53] in those with Alzheimer's Disease,[32] and in institutionalized oldest-old patients with depression.[15]

The pharmacotherapeutic treatment of late-life depression is more similar than dissimilar to the treatment of depression in younger adults. However, several features of the elderly and their response to medication provide unique challenges. These can be divided into pharmacokinetic and pharmacodynamic factors, the effects of chronic illness and end-organ changes, and the tendencies in late life for polypharmacy and noncompliance.

First, aging is associated with *pharmacokinetic changes* that generally result in higher and more prolonged plasma concentrations of most medications in the elderly compared with younger patients. These pharmacokinetic changes include altered absorption, distribution, metabolism, and excretion of medications. The most clinically significant alterations, however, occur in hepatic and renal functions. Hepatic clearance of antidepressant medications is, in general, decreased in the elderly due to reduced hepatic blood flow and enzyme activity. Renal clearance also is reduced by the aging process as well as by disease or the use of other medications. Thus, the elderly are vulnerable

Table 5. Principles of Pharmacologic Management for the Elderly

Work with other general medical physicians to eliminate redundant or unnecessary medications and keep lines of communication between providers open
Choose a medication with minimal antihistaminic, anticholinergic, and antiadrenergic side effects
Choose a medication that minimizes cardiovascular risk
Choose a medication that has minimal significant drug-drug interactions for the specific patient
Choose a medication that maximizes the likelihood of compliance
Begin with low doses
Gradually and slowly increase doses as necessary
Monitor for safety (eg, use baseline and follow-up electrocardiograms) and compliance
Use additional resource people (eg, family, caretakers) as necessary

to higher plasma levels and prolonged elimination half-lives, resulting in greater and longer-lasting toxic effects for any given dose of medication.[54]

Second, *pharmacodynamic changes* associated with aging make the elderly more sensitive to any given blood level of a medication than younger individuals. In particular, for any given concentration of medication, the elderly experience more sedation, more severe anticholinergic effects, and a greater tendency to orthostatic changes.[54] The combination of pharmacokinetic and pharmacodynamic changes means that for any given dose of medication, the elderly have higher blood levels for longer times, and for any given blood level of medication, they are apt to have more side effects.

Third, these developmental alterations in pharmacokinetics and pharmacodynamics are compounded by the effects of *chronic illness* and *physiologic end-organ changes*. In the cardiovascular system, for example, decreased baroreceptor sensitivity predisposes to orthostatic hypotension, and diminished reserve in cardiac conduction predisposes to heart block.[55]

Fourth, *polypharmacy* in the elderly is quite common. Many elderly patients take multiple medications, incurring the potential for serious and multiple drug-drug interactions. The average elderly patient takes six to eight different prescribed medications per day,[56] and 33% of nursing home residents take more than eight different medications daily.[57] In addition, the elderly are prone to use several nonprescription medications on a regular or as-needed basis. The more medications an individual takes, the more likely he or she is to be *noncompliant* with the medication. Indeed, 45% to 70% noncompliance rates have been reported for the elderly.[58] Ten percent of elderly patients take medications prescribed for others, 20% do not take medications currently prescribed,[57] and 40% stop medications too soon.[59]

Because of these unique features of late life, several principles of pharmacologic management apply to the treatment of depression in the elderly. Table 5 summarizes these principles. The main point is that treatment of depression in the elderly is important and potentially lifesaving, but must be done cautiously and with an appreciation for the unique characteristics of advanced age. These principles suggest beginning with low doses and gradually increasing doses on the basis of clinical efficacy and evolving side effects, monitoring for safety and compliance, and employing the aid of additional resource people as necessary.

Selecting an Appropriate Medication

All of the antidepressant medications listed in Table 6 are roughly equivalent in their overall efficacies. Choosing between them is best done on the basis of previous response and side effect profiles.

Monoamine oxidase inhibitors (MAOIs). The MAOIs are effective for a full range of mood disorders, including atypical depressive episodes, anergic depression in bipolar patients, mild as well as severe depressive episodes, and depressive episodes associated with anxiety and panic.[62] In addition, MAOIs effectively treat depression in the elderly.[63] Common side effects include anxiety, agitation, insomnia, sedation, weight gain, edema, sexual dysfunction, palpitations, and tachycardia. The most serious common side effect seen in the elderly is orthostatic hypotension. However, because of interactions with food containing high amounts of tyramine, drug interactions with indirect sympathomimetic medications potentially leading to hypertensive crises, or drug interactions with other serotonin antagonists potentially leading to serotonin syndrome, the MAOIs rarely are used in the elderly. The newest available MAOI, selegeline, a selective monoamine oxidase type B inhibitor, is less likely to exhibit these food and drug interactions when used in the low doses recommended for the treatment of Parkinson's disease.[64] However, in the higher doses that may be necessary for antidepressant efficacy,[64] selegeline loses its specificity and has the same potential for serious food and drug interactions as other MAOIs. Even in therapeutic doses, it is contraindicated with meperidine and other opiates, and with TCAs and SSRIs, as serotonin syndrome has been reported to occur with these combinations.

Tricyclic and tetracyclic antidepressants (TCAs). Until recently, the TCAs were the first-line treatment for depressive episodes in late life. They are effective for a broad range of depressive disorders and may be more effective than many of the newer antidepressant medications for the most severe forms of depressive disorders. Their efficacy in late-life depression has been amply demonstrated by several placebo-controlled studies.[55] However, because of the many troublesome side effects, and some serious toxic reactions, their use as front-line medications for depression in late life has been largely replaced by the newer medications.

Many of the side effects of the TCAs can be explained on the basis of their affinities for histaminic, muscarinic,

Table 6. Antidepressant Medications in Treating the Elderly*

Class/Agent	Dose Range (mg/d)[a] Initial	Usual	Relative Receptor Affinities[b] Histaminic/H_1	Muscarinic	Adrenergic/α_1	Toxicity: Delay in Cardiac Conduction	Toxicity: Lethal in Overdose
Tricyclic antidepressants (TCAs)							
Tertiary amine (eg, imipramine)	10–25	25–100	+++	++	+++	+++	++++
Secondary amine (eg, nortriptyline)	10	20–100	++	++	++	+++	++++
Serotonin selective reuptake inhibitors							
Fluoxetine	10	10–50	0	0	0	0	0
Paroxetine	10	10–40	0	++	0	0	0
Sertraline	25	25–150	0	0	+	0	0
Norepinephrine/dopamine reuptake inhibitor							
Bupropion SR	100	150–300	0	0	0	0	0
Serotonin/norepinephrine reuptake inhibitor							
Venlafaxine	50	50–225	0	0	0	0	0
5-HT_2 Antagonists serotonin and norepinephrine reuptake inhibitors							
Nefazodone	100	100–400	0	0	++	0	0
Trazodone	25	75–300	0	0	+++	0	0
α_2 Antagonist/5-HT_2 antagonist							
Mirtazapine	7.5–15	15–45	+++	0	+	0	0

*Abbreviations for relative effects: ++++ = very strong, +++ = strong, ++ = moderate, + = mild, 0 = minimal.
[a]Dosage guided by general medical conditions, hepatic and renal function, electrocardiographic changes, side effects, and clinical response.
[b]Estimates from Richelson[60] and Frazer.[61]

and adrenergic receptors. Because of the TCAs' high affinities for H_1 receptors, they are prone to cause the antihistaminic side effects of weight gain and sedation, each of which the elderly are particularly vulnerable to experience. Their affinity for muscarinic receptors lead to peripheral anticholinergic side effects of dry mouth, blurry vision, urinary retention, constipation, and aggravation of glaucoma, all potentially rate-limiting side effects in the elderly. A central anticholinergic side effect, memory disturbance, also is common in elderly patients taking TCAs. When the full central anticholinergic syndrome of agitation, confusion, listlessness, and disorientation occurs, it may be misdiagnosed as dementia or increased depression and therefore worsened by inappropriate treatment. The sensitivity of older individuals to a central anticholinergic syndrome is enhanced not only by the pharmacokinetic and pharmacodynamic factors described above, but also by the multiple other medications the elderly often take that have additional, often unrecognized, anticholinergic properties.[65] The affinity of TCAs for α_1 adrenergic receptors explains certain drug-drug interactions, reflex tachycardia, and, most importantly, the side effect of orthostatic hypotension. The elderly are more vulnerable than younger individuals to clinically significant orthostasis, which can lead to falls, head injuries, and broken hips. Especially vulnerable are individuals with preexisting heart disease and/or congestive heart failure and those taking antidepressant medications. Other troublesome side effects of the TCAs at any age are sexual dysfunctions, gastrointestinal disturbances, and switching to hypomania or mania. Because of all these unfortunate side effects, compliance is more of an issue with TCAs than with other classes of antidepressants.[66]

The secondary amine TCAs are more commonly prescribed in the elderly because they tend to be less antihistaminic, anticholinergic, and antiadrenergic than the tertiary amine TCAs. Desipramine is the least sedating and least anticholinergic and can be given during the day. Nortriptyline causes less orthostatic hypotension than the other TCAs and has been the most extensively studied TCA in elderly populations,[67] including one study in oldest-old (≥ 80 years old) nursing home residents. While nortriptyline was effective in the frail elderly living in nursing homes, dropout rates because of cardiovascular side effects were common.[15] Unfortunately, while desipramine and nortriptyline are better tolerated than tertiary amine tricyclics, they probably are no safer in terms of serious cardiac events or lethality in overdose.

The most serious adverse effects of the TCAs are their cardiotoxicity and lethality in overdose. In therapeutic doses, the TCAs can increase heart rate, decrease heart rate variability, slow cardiac conduction, and produce orthostasis. They act as quinidine-like antiarrhythmics and therefore are contraindicated in patients with left bundle branch block or second degree A-V block, and should not be used within the first several months, if at all, after a myocardial infarction. At least part of the cardiotoxicity is related to the accumulation of the hydroxy metabolites of TCAs. A product of hepatic hydroxylation, these water soluble metabolites have no particular therapeutic benefits, but are thought to be cardiotoxic. Because of deficits in renal clearance, they tend to accumulate in the elderly.[54]

Furthermore, since most laboratories do not measure hydroxy metabolites, blood drug levels are not an effective means of monitoring the cardiotoxic potential of TCAs in the elderly. Thus, for all elderly patients, pretreatment ECGs are mandatory, and frequent ECG monitoring during treatment with TCAs is important.

Serotonin Selective Reuptake Inhibitors (SSRIs). As a class, the SSRIs are about equally effective as the TCAs, except perhaps in severely ill, depressed patients with melancholia,[68] and are much more tolerable, simple to use, and safe. In addition, they can be quite effective for comorbid anxiety states and can be given once daily, and the starting dose often is the therapeutic dose. Each of the SSRIs currently available in the United States for the treatment of depression has been demonstrated to be more effective than placebo and at least equally effective as TCAs for the treatment of major depression in late life.[69] In addition, they are better tolerated than the TCAs and have fewer serious side effects.

Unlike the TCAs, the SSRIs have minimal antihistaminic, anticholinergic, and antiadrenergic effects; have relatively benign cardiovascular profiles; and generally are safe in overdose. The most common side effects are activation (anxiety and insomnia), gastrointestinal distress, and headaches. Decreased libido, retarded ejaculation, and orgasmic dysfunction are common with these agents and may lead to premature discontinuation or poor compliance. To varying degrees, each of the SSRIs inhibits hepatic cytochrome P450 enzymes, potentially leading to increased blood levels, side effects, and prolonged durations of side effects of coadministered medications. This is particularly problematic for medications that do not have alternate metabolic pathways and that have narrow therapeutic-toxicity indices such as the TCAs.[70] SSRI withdrawal symptoms most commonly include dizziness, lethargy, paresthesia, nausea, vivid dreams, irritability, and lowered mood.[71]

The most dangerous adverse reaction with the SSRIs, serotonin syndrome, occurs when different classes of serotonin agonists are given simultaneously. This condition of serotonin hyperstimulation consists of neuromuscular symptoms (e.g., tremor, hyporeflexia, myoclonus), central nervous system symptoms (e.g., activation, anxiety, agitation, confusion), autonomic nervous system symptoms (e.g., fever, sweating, shivering), and gastrointestinal symptoms (e.g., diarrhea and abdominal pain). In severe cases, fatalities have occurred. The best treatment is prevention. Thus, patients should be monitored for these symptoms when using high doses of an SSRI, or when employing an augmentation strategy. SSRIs are contraindicated with MAOIs, including selegeline, and should be used cautiously with meperidine, dextromethorphan, serotonin-agonist diet pills, and tryptophane.[72]

Although the SSRIs are more similar to than different from each other, each of the SSRIs has some unique characteristics that may impart advantages or disadvantages for specific patients. For example, fluoxetine is the longest acting SSRI, with an elimination half-life of 48 to 96 hours. It has active, long-acting metabolites and takes 21 to 60 days to reach steady state. These pharmacokinetic characteristics result in fewer withdrawal symptoms upon rapid discontinuation and minimal physiologic effects after a missed dose; however, they also produce more prolonged side effects and drug interactions even after fluoxetine is stopped. Both sertraline and paroxetine have elimination half-lives of about 24 hours and reach steady state in 7 to 14 days. Paroxetine does not have an active metabolite. A standard dose of fluoxetine or paroxetine produces higher plasma drug levels in the elderly than in younger individuals.[73] Plasma sertraline levels may be more comparable to those seen in younger subjects.[74] While sertraline may be slightly more dopaminergic than the others, paroxetine may be more anticholinergic.[60] Of the three, paroxetine has been studied the most extensively in the elderly, and its safety in patients with cardiac disease is most established. Compared with fluoxetine and sertraline, paroxetine has a greater tendency to be mildly sedating and is less likely to be anxiogenic.

Bupropion. Unlike the SSRIs, bupropion does not inhibit synaptic serotonin reuptake; rather, it is a modest inhibitor of norepinephrine and dopamine reuptake. It down-regulates noradrenergic firing of the locus ceruleus and decreases turnover of norepinephrine. Like the SSRIs, bupropion is an effective antidepressant that is both safer and better tolerated than the TCAs. Bupropion may be less apt than other antidepressants to induce hypomanic/manic states,[75,76] does not decrease REM sleep, does not cause sexual side effects,[77] and appears to be associated with minimal drug-drug interactions. It lacks significant antihistaminic, anticholinergic, and antiadrenergic properties; does not cause significant confusion or impair thinking abilities; has a relatively benign cardiovascular profile; and appears reasonably safe in overdose. Bupropion doses of 150 to 450 mg/day are more effective than placebo, and similar to fluoxetine[78,79] and imipramine,[80,81] in the treatment of late-life depression.

Perhaps the major advantage of bupropion in late life is its relatively benign cardiovascular side effect profile. Bupropion has been used safely in patients who had previously experienced treatment-limiting postural hypotension TCA treatment[82]; and it is significantly less likely than imipramine to induce orthostasis in patients with or without congestive heart failure.[83] Even in patients with preexisting heart disease, bupropion is reasonably safe and well tolerated. In such patients, bupropion does not appear to affect pulse rate or left ventricular function, prolong cardiac conduction, or exacerbate preexisting ventricular arrhythmias. Furthermore, some patients with cardiovascular intolerance to TCAs may be safely treated and maintained with bupropion.[84]

Although not yet studied in late life, the sustained-release (SR) formulation of bupropion may be especially useful for depression in the elderly. With the SR formulation, doses of up to 200 mg can be safely prescribed at any one time. Given the fact that many elderly patients may respond to as little as 150 to 200 mg of bupropion SR daily, it is likely that single daily dosing, for at least some patients treated with bupropion SR, will be possible. Also, with the SR formulation, the risk of seizures is no greater than the risk with SSRIs or with any other class of antidepressant medication.[97]

Other medications. Other antidepressant medications may have some role in the treatment of late-life depressive episodes. Venlafaxine inhibits the reuptake of both serotonin and norepinephrine.[85] Thus far, no controlled studies have demonstrated its efficacy or safety in late-life depression. In young persons with depression, venlafaxine has a broad spectrum of efficacy; its side effects are largely referable to its potent effect on serotonin reuptake, and, like the SSRIs, it may be associated with serotonin syndrome. It is not highly protein bound, and drug interactions appear minimal. Venlafaxine is the only antidepressant medication associated with dose-related increases in diastolic blood pressure. In most young patients, this poses little risk and is readily handled by dosage adjustment. However, whether this is the case in the elderly, or in patients with preexisting cardiovascular disease, remains to be determined.

Trazodone, a 5-HT_2 antagonist, once was considered a drug of choice in geriatric depression because of its lack of anticholinergic side effects, minimal effects on cardiac conduction, and relative safety in overdose. However, the arrival of the SSRIs and bupropion have ended its first-line use, and it now is largely relegated to adjunctive treatment (for sedation or augmentation) with other antidepressant medications. Several studies demonstrate trazodone's efficacy,[86] but many studies highlight the frequency of residual symptoms and the high dropout rates due to side effects.[54] In particular, older individuals may be quite sensitive to the sedation, impaired cognition, and orthostatic hypotension often seen with trazodone.

Nefazodone also antagonizes 5-HT_2 receptors. In addition, it is a modest serotonin and weak norepinephrine reuptake inhibitor. No clinical trials of nefazodone in older individuals have yet been published. Insofar as one can extrapolate from studies in younger individuals, nefazodone should be an effective and relatively safe antidepressant for the elderly and has solid anxiolytic properties.[87] Like bupropion, nefazodone is not associated with decreased REM sleep or sexual disturbances. The most common side effects are dizziness, sedation, and constipation. Visual trails have been reported. Because nefazodone is a modest inhibitor of the cytochrome P450 3A4 enzyme, its use is contraindicated in patients taking terfenadine, astemizole, and cisapride, and it should be used cautiously with patients taking triazolam or alprazolam.

The most recent antidepressant to be approved by the FDA, mirtazapine, is an α_2 antagonist.[88] There have been no published studies of mirtazapine in late-life depression. Because it has a high affinity for histamine receptors, mirtazapine is associated with somnolence and weight gain. Other common side effects include dizziness, dry mouth, and constipation. In 3 of almost 3000 patients studied in premarketing trials in the United States, serious blood dyscrasias (agranulocytosis or neutropenia) were found.[98] Its role in the overall treatment of late-life depression is yet to be determined.

Stimulants often are considered adjuncts in the management of late-life depression. Evidence for their efficacy as a single agent for the treatment of major depression and dysthymia is scant. Amphetamines have been used to rapidly mobilize medically ill, depressed, older patients; to neutralize hypotensive effects of antidepressant medications; and to augment treatment in partial responders.[89] Side effects include activation, tachycardia, elevated blood pressure, and possible tolerance and/or dependence. In high doses or with chronic use of stimulants, psychoses can develop and withdrawal depression is always a potential hazard.

Electroconvulsive therapy (ECT). Several studies have demonstrated the efficacy and safety of ECT.[90] It appears to work as well in the elderly as in younger individuals and without any increase in medical complications. ECT may be the treatment of choice for some patients with severe, melancholic, psychotic, or refractory depression. One study found that patients treated with ECT live longer than comparable patients not treated with ECT.[91] The most common side effects are confusion and memory problems and occasional, mild, transient cardiac arrhythmias. Even older depressed patients with preexisting heart disease usually respond well to ECT.[92] One of the major problems associated with ECT is the high recurrence rate of depressive episodes, especially in patients who have been refractory to antidepressant medications.[93] The effectiveness of maintenance ECT in the elderly has not been established.

Augmentation. Because of the problems associated with polypharmacy in the elderly, augmentation should be avoided whenever possible. If a patient does not respond to an adequate dose and duration of an antidepressant, it is best to switch to another agent, generally one from a different class of medications, before adding another medication. After a few such trials, however, a partial responder may be converted to a full responder with appropriate augmentation. To date, there are no controlled studies of thyroid hormone, carbamazepine, valproic acid, or even stimulant augmentation in late-life depression. Similarly, the efficacy and safety of combining two different antidepressant medications have not been systematically studied in older individuals. On the other hand, several studies demonstrate a modest effect of lithium augmentation of

TCAs in the elderly.[54] In responders, the necessary lithium dose is about one third to one half that of younger adults.

Although unsubstantiated by controlled studies, perimenopausal or postmenopausal women, we are convinced, sometimes respond better to antidepressant medication when given low doses of estrogen. While the literature on this strategy is limited,[94] estrogen may have a role in serotonin receptor binding.

Duration of Pharmacologic Treatment

In younger individuals, medication should be given for at least 4 to 6 weeks before the depression is considered refractory to treatment. In elderly individuals, that duration should be doubled.[95] If the patient feels better after 8 to 12 weeks, medication should be continued and periodically reassessed for at least 6 more months. Once the patient has achieved full recovery for at least 6 months, medication can be gradually discontinued unless maintenance treatment is indicated. Depending on past history and the clinical situation, such treatment can last from years to a lifetime.[96] Maintenance should be considered for anyone who has any of the following characteristics: a history of recurrent (three or more) depressive episodes; particularly severe, disabling, or life-threatening episodes; residual depressive symptoms; or a comorbid dysthymic disorder. The maintenance dose of medication is generally the same as the dose used to treat the acute episode. The goal of maintenance treatment is to prevent the recurrence of further episodes.

SUMMARY

Depression and dysthymia are prevalent, serious, and treatable disorders in late life. Optimal treatment includes educating the patient and family about depression and its treatment, selecting the appropriate combination of psychotherapeutic and pharmacologic interventions, and monitoring closely for compliance, response, and side effects. Treatment must be geared toward not only reversing the acute episode, but also preventing further episodes of this otherwise debilitating, chronic, recurring, and malignant illness.

Drug names: alprazolam (Xanax), astemizole (Hismanal), bupropion (Wellbutrin), carbamazepine (Tegretol and others), cisapride (Propulsid), desipramine (Norpramin), fluoxetine (Prozac), imipramine (Tofranil), meperidine (Demerol and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), selegiline (Eldepryl), sertraline (Zoloft), terfenadine (Seldane), trazodone (Desyrel), triazolam (Halcion), valproic acid (Depakene and others), venlafaxine (Effexor).

REFERENCES

1. Aging America, Trends and Projections. Washington, DC: U.S. Senate Special Committee on Aging, the American Association of Retired Persons, the Federal Council on the Aging, and the U.S. Administration on Aging; 1991:7
2. Diagnosis and treatment of depression in late life: NIH Consensus Development Panel on Depression in Late Life. JAMA 1992;268(8):1018–1024
3. Robins LN, Regier DA, eds. Psychiatric Disorders in America: The Epidemiologic Catchment Area Study. New York, NY: The Free Press, 1991
4. Blazer DG. Depression in Late Life, 2nd ed. St. Louis, Mo: Mosby; 1993
5. Murrell SA, Himmelfarb S, Wright K. Prevalence of depression and its correlates in older adults. Journal of Epidemiology 1983;117:173–185
6. Berkman LF, Berkman CS, Kasl S, et al. Depressive symptoms in relation to physical health and functioning in the elderly. Journal of Epidemiology 1986;124:372–388
7. Kennedy GJ, Kelman HR, Thomas C, et al. Hierarchy of characteristics associated with depressive symptoms in an urban elderly sample. Am J Psychiatry 1989;146:220–225
8. Boorson S, Barnes RA, Kukull WA, et al. Symptomatic depression in elderly medical outpatients, I: prevalence, demography, and health services utilization. J Am Geriatr Soc 1986;34:341–347
9. Barrett JE, Barrett JA, Oxman TE, et al. The prevalence of psychiatric disorders in a primary care practice. Arch Gen Psychiatry 1988;45:1100–1106
10. Koenig HG, Meador KG, Cohen HG, et al. Depression in elderly hospitalized patients with medical illness. Arch Intern Med 1988;148:1929–1936
11. O'Riordan TGB, Hayes JP, Shelley R, et al. The prevalence of depression in an acute geriatric medical assessment unit. Int J Geriatr Psychiatry 1989; 4:17–21
12. Rapp SR, Walsh DA, Parisi SA, et al. Detecting depression in elderly medical inpatients. Journal of Counselling in Clinical Psychology 1988;36: 509–513
13. Parmelee PA, Katz IR, Lawton MP. Depression among institutionalized aging: assessment in prevalence estimation. J Gerontol A Biol Sci Med Sci 1989;44:M22–M29
14. Ames D. Depression among elderly residents of local-authority residential homes: its nature and efficacy of intervention. Br J Psychiatry 1990; 156:667–675
15. Katz IR, Parmelee PA. Depression in elderly patients in residential care settings. In: Schneider LS, Reynolds CF, Lebowitz BD, et al, eds. Diagnosis and Treatment of Depression in the Elderly: Results of the NIH Consensus Development Conference. Washington, DC: American Psychiatric Press; 1994:437–468
16. Lebowitz BD. Diagnosis and treatment of depression in late life: an overview of the NIH consensus statement. Am J Geriatr Psychiatr 1996;4(1, suppl):S3–S6
17. Cole MG, Bellavance F. The prognosis of depression in old age. Am J Geriatr Psychiatry 1997;5:4–14
18. Murphy E. The course and outcome of depression in late life. In: Schneider LS, Reynolds CF, Lebowitz BD, et al, eds. Diagnosis and Treatment of Depression in the Elderly: Results of the NIH Consensus Development Conference. Washington, DC: American Psychiatric Association; 1994:81–98
19. Dorgan CA, ed. Statistical Record of Health & Medicine. New York, NY: International Thomson Publishing Company; 1995
20. Cohen-Cole SA, Stoudemire A. Major depression and physical illness. Psychiatr Clin North Am 1987;10:1–17
21. Zubenko GS, Mulsant BH, Rifai AH, et al. Impact of acute psychiatric inpatient treatment on major depression in late life and prediction of response. Am J Psychiatry 1994;151:987–994
22. Brown RP, Sweeny J, Loutsch E, et al. Involutional melancholia revisited. Am J Psychiatry 1984;141:24–28
23. Ruegg RG, Zisook S, Swerdlow NR. Depression in the aged. Psychiatr Clin North Am 1988:11(1):83–99
24. Blazer DG. Depression in elderly: myths and misconceptions. Psychiatr Clin North Am 1997;21(1):111–119
25. Massie MJ, Holland JC. Depression and the cancer patient. J Clin Psychiatry 1990;51(7, suppl):12–17
26. Cavanaugh SV. Diagnosing depression in the hospitalized patient with chronic medical illness. J Clin Psychiatry 1984;45(3, sec 2):13–17
27. Kathol RG, Mutgi A, Williams J, et al. Diagnosis of major depression in cancer patients according to four sets of criteria. Am J Psychiatry 1990; 147:1021–1024
28. Salzman C. Antidepressant treatment in the elderly. Presented at the West Coast Geriatric Psychiatry Conference; September 28–October 1, 1995; San Diego, Calif
29. Folstein MF, Folstein SE, McHugh PR. Mini-mental state: a practical method for grading the cognitive status of patients for the clinician. J Psychiatr Res 1975;12:189–198
30. Reifler BV, Larson E, Hanley R. Coexistence of cognitive impairment and depression in psychiatric outpatients. Am J Psychiatry 1982;139:623–626

31. Himmelhoch JM, Auchenbach R, Fuchs CZ. The dilemma of depression in the elderly. J Clin Psychiatry 1982;43(9, sec 2):26–32
32. Riefler BV, Teri L, Raskind M, et al. Double-blind trial of imipramine in Alzheimer's disease patients with and without depression. Am J Psychiatry 1989;146:45–49
33. Cummings JL. Depression and Parkinson's disease: a review. Am J Psychiatry 1992;149:443–454
34. Alexopoulos GS, Meyers BS, Young RC, et al. The course of geriatric depression with "reversible dementia": a controlled study. Am J Psychiatry 1993;150:1693–1699
35. Kramer SI, Riefler BV. Depression, dementia and reversible dementia. Clin Geriatr Med 1992;8:289–297
36. Stroebe W, Stroebe M. Bereavement and Health. New York, NY: Cambridge University Press; 1987
37. Kaprio J, Koskenvuo M, Rita H. Mortality after bereavement: a prospective study of 95,647 widowed persons. Am J Public Health 1987;77: 283–287
38. Zisook S, Shuchter SR. Bereavement. In: Current Psychiatric Therapy, II. Philadelphia, Pa: Saunders; 1997:248–252
39. Zisook S, Shuchter SR. Uncomplicated bereavement. J Clin Psychiatry 1993;54:365–372
40. Zisook S, Shuchter SR. Major depression associated with widowhood. Am J Geriatr Psychiatry 1993;147:316–326
41. Wells KB, Stewart A, Hays RD, et al. The functioning and well-being of depressed patients: results from the Medical Outcomes Study. JAMA 1989; 262:914–919
42. Kennedy GJ, Kelman HR, Thomas C. Persistence and remission of depressive symptoms in late life. Am J Psychiatry 1991;148:174–178
43. Dalack GW, Roose SP. Perspectives on the relationship between cardiovascular disease and affective disorder. J Clin Psychiatry 1990;51(7, suppl): 4–9
44. Morris PL, Robinson RG, Andrzejewski P, et al. Association of depression with 10 year poststroke mortality. Am J Psychiatry 1993;150(1):124–129
45. Mossey JM, Knott K, Craik R. The effects of persistent depressive symptoms on hip fracture recovery. J Gerontol A Biol Sci Med Sci 1990;45(5):M163–M168
46. Pearson JL, Teri L, Riefler BV, et al. Functional status and cognitive impairment in Alzheimer's patients with and without depression. J Am Geriatr Soc 1989;37:1117–1121
47. Frasure-Smith N, Lesperance F, Talajic M. Depression following myocardial infarction. JAMA 1993;270:1819–1825
48. Frank E, Karp JF, Rush AJ. Efficacy of treatments for major depression. Psychopharmacol Bull 1993;29:457–475
49. Niederehe G. Psychosocial treatments with depressed older adults: a research update. Am J Geriatr Psychiatry 1996;4(suppl 1):S66–S78
50. Reynolds CF, Frank E, Perel JM, et al. Combined pharmacotherapy and psychotherapy in the acute and continuation treatment of elderly patients with recurrent major depression: a preliminary report. Am J Psychiatry 1992;149:1687–1692
51. Thompson LW, Gallagher D, Breckenridge JS. Comparative effectiveness of psychotherapies for depressed elders. J Consult Clin Psychol 1987;55: 385–390
52. Shuchter SR, Downs N, Zisook S. Biologically Informed Treatment for Depression. New York, NY: Guilford Press; 1996
53. Robinson RG, Morris PLP, Fedoroff JP. Depression and cerebrovascular disease. J Clin Psychiatry 1990;51(7, suppl):26–31
54. Salzman C. Clinical Geriatric Psychopharmacology. Baltimore, Md: Williams & Wilkins; 1992
55. Finch CE. Neuroendocrine and autonomic aspects of aging. In: Finch CE, Hayflick L, eds. Handbook of the Biology of Aging. New York, NY: Van Nostrand Reinhold; 1977:262–280
56. Salzman C. Medication compliance in the elderly. J Clin Psychiatry 1995;56(1, suppl):18–22
57. Lamy PP, Salzman C, Nevis-Oelsen J. Drug prescribing patterns, risks, and compliance guidelines. In: Salzman C, ed. Clinical Geriatric Psychopharmacology, 2nd ed. Baltimore, Md: Williams & Wilkins; 1992:15–37
58. Ostrum RE, Hammarlund ER, Christensen DB, et al. Medication usage in an elderly population. Med Care 1988;23:157–170
59. Jackson JE, Ramsdell JW, Renvall M, et al. Reliability of drug histories in a specialized geriatric outpatient clinic. J Gen Intern Med 1984;4:39–43
60. Richelson E. Synaptic effects of antidepressants. J Clin Psychopharmacol 1996;16(suppl 2):1S–9S
61. Frazer A. Pharmacology of antidepressants. J Clin Psychopharmacol 1997; 17(suppl 1):2S–18S
62. Zisook S. A clinical overview of monoamine oxidase inhibitors. Psychosomatics 1985;26:240–251
63. Georgotas A, McCue RE, Friedman E, et al. A placebo-controlled comparison of nortriptyline and phenelzine in maintenance therapy of elderly depressed patients. Arch Gen Psychiatry 1989;46:783–786
64. Sunderland T, Cohen RM, Molchan S. High-dose selegiline in treatment-resistant older depressive patients. Arch Gen Psychiatry 1994;51:607–615
65. Tune L, Carr S, Hoag E, et al. Anticholinergic effects of drugs commonly prescribed for the elderly: potential means for assessing risk of delirium. Am J Psychiatry 1992;149:1393–1394
66. Simon GE, VonKorff M, Heiligenstein JH, et al. Initial antidepressant choice in primary care: effectiveness and cost of fluoxetine vs. tricyclic antidepressants. JAMA 1996;275:1897–1902
67. Schneider LS. Pharmacologic considerations in the treatment of late-life depression. Am J Geriatr Psychiatr 1996;4(suppl 1):S51–S65
68. Roose SP, Glassman AH, Attia E, et al. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. Am J Psychiatry 1994;151:1735–1739
69. Newhouse PA. Use of serotonin selective reuptake inhibitors in geriatric depression. J Clin Psychiatry 1996;57(suppl 5):12–22
70. Nemeroff CB, DeVane CL, Pollock BG. Newer antidepressants and the cytochrome P450 system. Am J Psychiatry 1996;153:311–320
71. Coupland NJ, Bell CJ, Potokar JP. Serotonin reuptake inhibitor withdrawal. J Clin Psychopharmacol 1996;16:356–362
72. Sporer KA. The serotonin syndrome: implicated drugs, pathophysiology and management. Drug Saf 1995;13:94–104
73. Preskorn SH. Recent pharmacologic advances in antidepressant therapy for the elderly. Am J Med 1993;94(suppl 5A):2S–12S
74. Sprouse J, Clarke T, Reynolds L, et al. Comparison of the effects of sertraline and its metabolite methylsertraline on blockade of central 5-HT reuptake in vivo. Neuropsychopharmacology 1996;14:225–231
75. Sachs GS, Lafer B, Stoll AL, et al. A double-blind trial of bupropion versus desipramine for bipolar depression. J Clin Psychiatry 1994;55:391–393
76. Haykal RF, Akiskal HS. Bupropion as a promising approach to rapid cycling bipolar II patients. J Clin Psychiatry 1990;51:450–455
77. Walker PW, Cole JO, Gardner EA, et al. Improvement in fluoxetine-associated sexual dysfunction in patients switched to bupropion. J Clin Psychiatry 1993;54:459–465
78. Mildener B, Kramer-Ginsberg E, Greenwald B, et al. Fluoxetine and bupropion in old-old depressives. In: New Research Program and Abstracts of the 145th Annual Meeting of the American Psychiatric Association; May 4, 1992; New York, NY. Abstract NR103:72
79. Giakas WJ, Miller HL, Hensala JD, et al. Fluoxetine versus bupropion in geriatric depression. In: New Research Program and Abstracts of the 146th Annual Meeting of the American Psychiatric Association; May 26, 1993; San Francisco, Calif. Abstract NR479:180
80. Kane JM, Cole K, Sarantakos S, et al. Safety and efficacy of bupropion in elderly patients: preliminary observations. J Clin Psychiatry 1983;44(5, sec 2):134–136
81. Branconnier RJ, Cole JO, Ghazvinian S, et al. Clinical pharmacology of bupropion and imipramine in elderly depressives. J Clin Psychiatry 1983;44(5, sec 2):130–133
82. Farid FF, Wenger TL, Tsai SY, et al. Use of bupropion in patients who exhibit orthostatic hypotension on tricyclic antidepressants. J Clin Psychiatry 1983;44(5, sec 2):170–173
83. Roose SP, Glassman AH, Giardina EGV, et al. Cardiovascular effects of imipramine and bupropion in depressed patients with congestive heart failure. J Clin Psychopharmacol 1987;7:247–251
84. Roose SP, Dalack GW, Glassman AH, et al. Cardiovascular effects of bupropion in depressed patients with heart disease. Am J Psychiatry 1991; 148:512–516
85. Schweizer E, Weise C, Clary C, et al. Placebo-controlled trial of venlafaxine for the treatment of major depression. J Clin Psychopharmacol 1991; 11:233–236
86. Gerner R, Estabrook W, Steuer J, et al. Treatment of geriatric depression with trazodone, imipramine, and placebo: a double-blind study. J Clin Psychiatry 1980;41:216–220
87. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996;57(suppl 2):53–62
88. Bremner JD. A double-blind comparison of Org 3770, amitriptyline, and

placebo in major depression. J Clin Psychiatry 1995;56:519–525
89. Satel SL, Nelson JC. Stimulants in the treatment of depression: a critical overview. J Clin Psychiatry 1989;50:241–249
90. Mulsant BH, Rosen J, Thornton JE, et al. A prospective naturalistic study of electroconvulsive therapy in late-life depression. J Geriatr Psychiatry Neurol 1991;4:3–13
91. Philibert RA, Richards L, Lynch CF, et al. Effect of ECT on mortality and clinical outcome in geriatric unipolar depression. J Clin Psychiatry 1995; 56:390–394
92. Zielinski RJ, Roose SP, Devanand DP, et al. Cardiovascular complications of ECT in depressed patients with cardiac disease. Am J Psychiatry 1993; 150:904–909
93. Sackheim HA, Prudic J, Devanand DP, et al. The impact of medication resistance and continuation pharmacotherapy on relapse following response to electroconvulsive therapy in major depression. J Clin Psychopharmacol 1990;10:96–104
94. Oppenheim G, Zohar J, Sharpiro B, et al. The role of estrogen in treating resistant depression. In: Zohar J, Belmaker RH, eds. Treating Resistant Depression. New York, NY: PMA Publishing; 1987:357–366
95. Georgotas A, McCue RE. The additional benefit of extending an antidepressant trial past seven weeks in the depressed elderly. Int J Geriatr Psychiatry 1989;4:191–195
96. Reynolds CF III. Treatment of depression in special populations. J Clin Psychiatry 1992;53(9, suppl):45–53
97. Dunner DL, Zisook S, Billow AA, et al. A prospective safety surveillance study for bupropion sustained release in the treatment of depression. J Clin Psychiatry. In press
98. Physicians' Desk Reference. Montvale, NJ: Medical Economics; 1997