Key Words: depression, elderly, diagnosis, drug therapy

Depression in the Elderly

By William M. McDonald, MD, Carl Salzman, MD, and Alan F. Schatzberg, MD

ABSTRACT *~ Depression is prevalent in the elderly and associated with increased morbidity and mortality. Diagnosis can be complicated by the presence of concomitant medical and/or psychiatric disorders, and it is important to exclude a number of factors, such as neurological disease, hormonal causes, chronic illness, or substance abuse, particularly alcohol. Although comorbid medical illness may contribute to depressive illness, depressive disorders are not a consequence of aging. Most classes of antidepressants that are effective in adult patients are effective in the elderly and, in general, they have shown comparable efficacy in terms of response rates. However, antidepressants vary in terms of their tolerability profiles, and treatment of the elderly is complicated by their sensitivity to medication side effects and the potential for serious adverse events, such as falling or delirium. A correct dosing strategy is particularly important for the elderly, whose treatment should usually start at low doses of antidepressants and increase slowly. It is possible to successfully treat elderly patients with depressive disorder, and antidepressant therapy should be selected on the basis of prior response to treatment, the adverse-event profile, and the potential for drug-drug interactions. Treatment should also take into account the likelihood of achieving and maintaining remission of symptoms in order to restore the patient to a baseline level of functioning appropriate for their age.*
Psychopharmacology Bulletin. *2002;36(Suppl 2):112-122*

Introduction

Major depression is a chronic and often recurrent disorder that affects up to 6% of the general population.[1] Despite popular belief, depression is not as frequent in the elderly. Among the community-dwelling elderly ≥65 years of age, the prevalence of major depression is only 1% to 3%, although clinically significant symptoms of anxiety and depression are observed in 8% to 15% of this group.[2,3] However, among hospitalized or residential elderly patients, the incidence of depression is significantly greater, and has been reported to be as high as 45% of those receiving surgical or medical treatment.[4]

Depression in the elderly is often not recognized by physicians and frequently undertreated.[5,6] This is primarily due to the presence of comorbid disorders (such as

Dr. McDonald is director of the Fuqua Center for Late-Life Depression at Emory University in Atlanta. Dr. Salzman is professor of psychiatry at the Massachusetts Mental Health Center at Harvard Medical School in Boston. Dr. Schatzberg is Kenneth Norris Jr. professor and chair of the Department of Psychiatry at Stanford University School of Medicine in California.

To whom correspondence should be addressed: Alan F. Schatzberg, MD, Stanford University School of Medicine, Room 300, 401 Quarry Road, Stanford, CA 94305-5548; Tel: 650-723-6811; Fax: 650-498-5294; E-mail: afschatz@stanford.edu

arthritis, diabetes mellitus, cancer, cardiovascular diseases, visual/auditory impairment, and neurological disorders) that may mask the symptoms of depression.[7,8] Coronary artery disease and cerebrovascular disease are commonly associated with depression. In patients with coronary artery disease and comorbid depression, depression has been shown to predict future cardiac events and increase mortality.[9] Up to 50% of geriatric patients reported feeling depressed in the first year following a stroke.[10] Similarly, approximately 50% of elderly patients reported feeling depressed following hip-fracture surgery.[11]

Depression has been reported to lead to impairment of physical and social functioning, and increased health service utilization in both elderly and younger patients.[12,13] Furthermore, in elderly patients with impaired vision, depression was actually found to be more strongly associated with development of disability than loss of vision itself.[14]

Although depression is common among hospitalized geriatric patients, the relationship between depressive symptoms and long-term mortality is only beginning to be understood. A prospective study of 573 patients, ≥70 years of age (mean=80 years of age), who were hospitalized with medical illnesses, experienced significantly greater 3-year mortality if they exhibited more than six depressive symptoms (56%), compared with those that had less than six depressive symptoms (40%; $P<.001$).[15] Furthermore, the patients with six or more depressive symptoms exhibited greater comorbid illness, functional impairment, and cognitive impairment. Although greater levels of illness severity, coexisting illness, and functional dependence explained part of the association with mortality, depressive symptoms remained a predictor of mortality even after adjustment for one additional comorbid medical disorder.[15] Similarly, an elevated risk of death in depressed versus nondepressed nursing home residents was found in a 1-year follow-up study of 454 consecutive patients, newly admitted to eight nursing homes. Indeed, major depressive disorder (MDD),[16] which was diagnosed in 12.6% of patients, increased the likelihood of death by 59% and was considered a risk factor for mortality over a 1-year period, independent of selected physical health measures.[17] Clearly, such strong associations between MDD and increased morbidity and mortality point to the need to achieve and maintain remission with effective and well-tolerated antidepressant treatment regimens in elderly depressed patients.

The Diagnosis of Depression in the Elderly

The criteria used to diagnose MDD include a 2-week period of loss of interest and pleasure, and depressed mood accompanied by conditions, such as anxiety, somatic complaints, and cognitive impairment. However, the diagnosis of depression in late life can be problematic as indicators,

such as appearance, mood, sleep disturbance, appetite, and energy, may be unreliable, particularly in those >75 years of age. In contrast, increased irritability, withdrawal from social interaction, anxiety, and cognitive impairment are seen as important indicators of depression in older adults, particularly the very elderly.[13,18] The first critical step in the clinical evaluation of depression in geriatric patients is to rule out possible physical causes, whether these are neurological (eg, Parkinson's disease, stroke, or dementia), hormonal (eg, thyroid or estrogen imbalance), or a consequence of chronic illnesses (eg, cancer, cardiovascular disease, or diabetes mellitus). In addition, because many elderly patients take multiple medications, it is important to rule out drug-related adverse events, drug-drug interactions, or hidden substance abuse (especially alcohol abuse), which might also contribute to their depressive symptoms.

A variety of scales exist for the screening of depression in late life. The Geriatric Depression Scale (GDS) is one such instrument that has become widely used in a variety of clinical, research, and cultural settings. In the United Kingdom, the GDS has been recommended as a suitable scale to screen for depression by the Royal College of Physicians, the British Geriatric Society, and the Royal College of General Practitioners.[19] In recent years, the use of shorter versions has become attractive, as they can substantially reduce administration time in clinical practice. In one study, 64 outpatients (aged ≥60 years) diagnosed with depressive disorder (*International Classification of Diseases*, Tenth Edition [ICD-10] criteria), were evaluated using a range of short GDS scales with 15, 10, and 4 items.[20] The results indicated that the GDS-15 and GDS-10 versions are reliable screening instruments for MDD, as defined by both the ICD-10 and *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition[21] criteria.

More recently, a new form of the GDS scale, the GDS-12-Revised (R), has been developed. This 12-item scale is suitable for older people living in nursing homes and residential care settings, and those with significant cognitive impairment.[22] A total of 308 newly admitted residents of 30 nursing and residential homes in northwest England were assessed using the GDS-12-R scale and the results compared with scores from the GDS-15, the Mini-Mental State Examination, and the Affect Balance Scale. The 12-item scale was shown to have greater internal reliability than the 15-item version and was not affected by the presence of moderate-to-high levels of cognitive impairment. Overall, the use of short GDS versions may provide primary care physicians with brief, easy-to-administer diagnostic tools that should help to increase the detection rate of depression among the elderly.

However, it is important to remember that scales are for screening and not diagnostic purposes, and they may have limited value in the elderly

population. Indeed, older individuals may find it difficult to openly discuss feelings of depression, helplessness, hopelessness, and worthlessness during a single visit with a clinician whom they do not know well.[23] A study of nursing home residents 74–99 years of age (mean age=88.4 years) compared nurse-derived ratings of depression in residents with ratings from direct interviews and patient self-reports.[24] Using the Cornell Scale for Depression and the 30-item GDS, it was found that, for nonmajor forms of depression, nurse-derived symptom ratings correlated poorly with ratings from direct-patient interviews.

It is essential that in addition to a thorough historical and physical evaluation of the patient, further information is obtained from family, friends, and caregivers as these groups may contribute important diagnostic information. It is critically important to identify elderly patients with symptoms of depression and rule out possible physical causes in order to allow the selection of suitable treatments, with the aim of restoring the patient to a baseline level of functioning appropriate for their age.

Treatment of Depression in the Elderly

Although depression is one of the most common disorders in the primary care setting, undertreatment is widespread, with fewer than 10% of patients receiving appropriate treatment.[25] In general, most antidepressants are as effective in the elderly as they are in younger adults, and depressed elderly patients should be treated aggressively (adequate dose for a sufficient duration) with an appropriate antidepressant that enables them to return to normal functioning. However, the improvement in symptoms may be slower than that observed in middle-aged patients.[6] Several age-related factors can complicate the pharmacologic management of depression in elderly patients.[26] For example, older individuals may have impaired hepatic and/or renal function; reduced hepatic metabolism and renal clearance can produce higher drug-plasma concentrations and prolong the elimination half-lives of some antidepressants and their metabolites. It is also highly likely that an elderly patient will be taking other prescription and over-the-counter medications as a consequence of comorbid medical illnesses. Thus, there may be an increased risk of drug-drug interactions.[26]

In addition to these age-related factors, noncompliance among the elderly depressed population may be as high as 70%. The adverse-event profile of an antidepressant needs to be considered if compliance is to be improved. Antidepressants shown to have a good tolerability profile and low rate of discontinuation have become an important consideration in the selection of therapy for elderly patients.[27] There is a wealth of literature on the use of antidepressants among the elderly that have been extensively reviewed elsewhere.[28,29] Although the focus has tended towards medically stable outpatients under 80 years of age,[26] studies in this "old-old" cohort do exist.[28-30]

When selecting antidepressant medication, the ultimate goal is to achieve and maintain remission—a virtually symptom-free state—while minimizing the risk of adverse events. Realistically, the beneficial outcomes easily achieved from the treatment of depression in the elderly include minimizing illness severity and symptoms, reducing relapse and recurrence, reducing the healthcare burden, preventing suicide, and improving patient quality of life, daily functioning, and overall health status. Prior response to treatment, the adverse-event profile, potential for drug interactions, and factors that improve compliance with treatment, need to be taken into consideration when prescribing an antidepressant. Moreover, many elderly patients experience adverse reactions to doses that are therapeutic for younger adults; therefore, antidepressant therapy should begin at low doses, increasing slowly to the optimum dosage to ensure full therapeutic benefit. Conversely, some geriatric patients may require the full therapeutic dose. Elderly patients should therefore be treated on an individual basis following a full assessment of each patient's characteristics; as a result, the time taken to achieve response and remission in this population will be longer. Furthermore, although studies have demonstrated the efficacy of antidepressants in the elderly, several meta-analyses and controlled studies have found the magnitude of therapeutic response to be small compared with placebo.[3,29]

The most widely used agents in the pharmacologic treatment of depression in the elderly are tricyclic antidepressants (TCAs), and selective serotonin reuptake inhibitors (SSRIs)[27]; more recently, the serotonin and norepinephrine reuptake inhibitors (SNRIs) and selective norepinephrine reuptake inhibitor (NRI) have been shown to be efficacious in the elderly depressed population.[31-33] Most studies have shown similar efficacy (approximately 60%) for SSRIs and TCAs when used at appropriate doses in elderly patients.[34,35] However, in general, TCAs tend to be used at sub-optimal dosages because of their poor tolerability.[27] This is in contrast to newer antidepressant therapies, which tend to be used at appropriate therapeutic dosages because they generally have a better tolerability profile in this patient population.

Tricyclic Antidepressants

TCAs are the most extensively studied class of antidepressant drug in the elderly. TCAs can be subdivided into two groups: tertiary amines (including amitriptyline, clomipramine, doxepin, imipramine, and trimipramine) and secondary amines (desipramine, nortryptyline, protriptyline). Before treatment with a TCA is initiated, the patient should be evaluated for cardiac disease, endocrinopathies, cerebrovascular or degenerative brain disease, glaucoma, and prostatic hypertrophy; elderly patients are more likely to experience toxic effects and adverse events from TCAs

due to age-related pharmacokinetic and pharmacodynamic changes. There is no demonstrable difference in efficacy between the TCAs desipramine and nortriptyline. Both TCAs have two important advantages in geriatric patients: first, there is extensive clinical and research data on their safety and efficacy, and second, plasma levels can be used to determine the therapeutic dose of medication and assess patient compliance.[28] Nortriptyline is the most extensively studied TCA in the elderly, with response rates of approximately 60%.[36] A recent double-blind study of 210 depressed outpatients ≥60 years old compared nortriptyline with the SSRI sertraline, and showed that the efficacy of both was similar: 61% of the nortriptyline-treated patients and 72% of the sertraline-treated patients responded to treatment (reduction ≥50% in total score on the Hamilton Rating Scale for Depression [HAM-D]).[34,37]

The most common adverse events associated with TCAs are dry mouth, blurred vision, sedation (anticholinergic adverse events), weight gain, orthostatic hypotension (which can lead to falls and hip fractures), and cardiac toxicity. The secondary amines are better tolerated than the tertiary amines, as they are less likely to induce these adverse events. Some of these adverse events can be of concern, thus TCAs may be contraindicated in elderly patients.[26,27]

Selective Serotonin Reuptake Inhibitors

Studies of SSRIs, including paroxetine, fluoxetine, citalopram, and sertraline, have proven to be effective in geriatric patients. A 6-week, double-blind study of fluoxetine in depressed outpatients ≥60 years of age demonstrated the safety and efficacy of fluoxetine relative to placebo.[38] Fluoxetine produced significantly greater response (44% versus 32%; P=.002) and remission (32% versus 19%; P<.001) rates. A double-blind comparison of fluoxetine and sertraline in 236 outpatients (≥60 years of age) showed that both drugs were effective, with 12-week response rates of 71% for fluoxetine and 73% for sertraline.[39] Similarly, in a 6-week, double-blind, parallel-group study of 106 patients (≥65 years of age) with acute major depression, fluoxetine and paroxetine were shown to be effective (as assessed by a ≥50% reduction in HAM-D total score). At week 6, a significantly (P<.05) greater proportion of patients responded to treatment with paroxetine, compared with those treated with fluoxetine.[40] Fluoxetine, paroxetine, and sertraline have also been examined in 50 "very old" depressed nursing home residents 80–98 years of age (mean=89 years of age).[41] At 12-week follow-up of an open-label trial, 42% of patients had at least a 50% decrease in HAM-D score. All three antidepressants were well tolerated, and there were no significant differences between each medication.

While TCAs and SSRIs are similar in efficacy, SSRIs are better tolerated by the elderly and associated with fewer anticholinergic and cardiovascular adverse events than TCAs; the choice of SSRI is left to clinical experience. The adverse-event profile of SSRIs differs from TCAs, with gastrointestinal upset, insomnia, sedation, nervousness, and sexual dysfunction being the most common side effects. SSRI-induced adverse events also tend to be dose-related and it is therefore recommended that elderly patients start on low doses and increase the medication gradually.[29] In addition, adverse events often diminish in frequency and/or severity with continued treatment.[26]

Monoamine Oxidase Inhibitors

Monoamine oxidase inhibitors (MAOIs) are not widely used among elderly patients, as they are associated with a poor tolerability profile. However, they are effective antidepressants, with 50% to 65% of geriatric patients responding to the MAOI phenelzine.[26] Phenelzine, and other older nonselective MAOIs, are associated with a range of adverse events that include peripheral edema, weight gain, insomnia, sexual dysfunction, and orthostatic hypotension.[26] In contrast, moclobemide, a selective inhibitor of monoamine oxidase type A, is well tolerated in the elderly. The drug has also been shown to have comparable efficacy in both young and elderly patients with depression,[36] with response rates of 56% to 74% compared with fluoxetine, which exhibited response rates of 48% to 69%.[42,43] Although moclobemide appears to have a reasonable tolerability profile for the treatment of depression in the elderly, it has a short duration of action and requires a three times/day dosage, which may decrease patient compliance in the elderly.[26]

Bupropion

Bupropion, a unique aminoketone antidepressant that affects noradrenergic/dopaminergic function,[44] has little or no affinity for muscarinic or histamine receptors, minimal cardiovascular effects, and does not cause sexual dysfunction.[26] The adverse side effects associated with bupropion include agitation, headaches, dizziness, tremor, insomnia, anorexia, and nausea.[26] This agent has been shown to be effective and well tolerated in depressed outpatients. However, until recently, no well-controlled studies had been conducted in elderly outpatients with depression.[44] The results of a 6-week, randomized, double-blind, parallel-group study in 100 depressed patients (60–88 years of age) demonstrated that sustained-release (SR) bupropion and paroxetine produced similar response rates (71% and 77%, respectively; ≥50% reduction in HAM-D total score). Bupropion SR was associated with a lower incidence of adverse events, which sug-

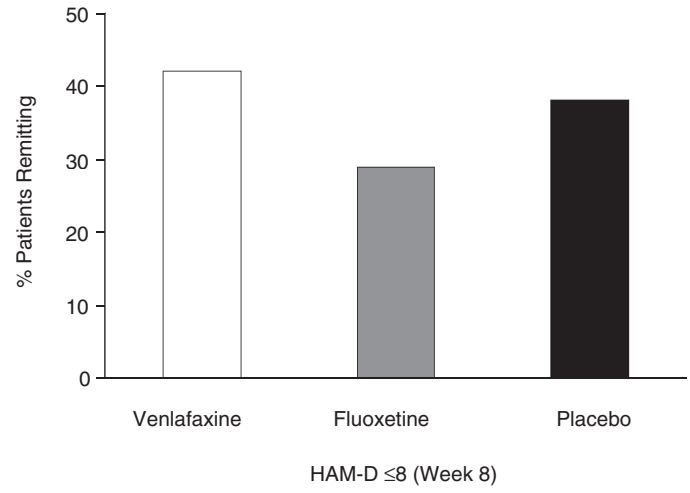
gests that it might represent a useful nonserotonergic treatment alternative in elderly depressed patients.[44] The daily dosage for elderly patients is in the range of 75–450 mg, although seizures have been reported with doses >400 mg/day of bupropion, but not bupropion SR.[29]

Selective Norepinephrine Reuptake Inhibitors

The SNRI, venlafaxine, has been shown to have comparable antidepressant efficacy in the young and in a subset of over 350 geriatric patients.[36] Furthermore, venlafaxine extended release (XR) is as well tolerated in elderly patients as it is in younger patients.[36] Although past clinical experience has indicated that the different classes of antidepressants have comparable efficacy in terms of response, it is now increasingly evident that achieving remission of depressive symptoms and preventing relapse and recurrence is critical in the treatment of depression. However, there is still a relative paucity of data available on the proportions of patients who achieve remission in relation to those who simply respond to treatment. Recent randomized, double-blind, placebo-controlled comparative studies of venlafaxine/venlafaxine XR and SSRIs have indicated that it is possible to achieve high levels of remission in

FIGURE

Remission (HAM-D Score ≤8) in Elderly Depressed Patients Who Received 8 Weeks of Treatment With Venlafaxine, Fluoxetine, or Placebo



*Remission indicated by HAM-D ≤8.
HAM-D=Hamilton Rating Scale for Depression.

Adapted from: Schatzberg AF, Cantillon M. Antidepressant early response and remission with venlafaxine or fluoxetine in depressed geriatric outpatients. Poster presented at: Annual Meeting of the College of International Neuropsychopharmacology; 2000; Brussels, Belgium.

McDonald WM, Salzman C, Schatzberg AF. *Psychopharmacology Bulletin*. Vol 36. Suppl 2. 2002.

elderly patients with depression. For example, a large-scale, 8-week study of venlafaxine (n=104) versus fluoxetine (n=100) and placebo (n=96) found that 48% to 57% of depressed geriatric outpatients responded to treatment (>50% improvement in HAM-D score) and 29% to 42% achieved remission (HAM-D score ≤8; Figure).[45]

Furthermore, active drug treatments were well tolerated, and patients treated with venlafaxine did not experience more adverse events than those on fluoxetine or placebo. A separate 8-week study compared venlafaxine with SSRIs (fluoxetine, paroxetine, or fluvoxamine) and placebo in depressed adults, including a cohort of elderly patients ≥65 years of age (n=65). It was found that response and remission (HAM-D score ≤7) rates for venlafaxine and SSRIs were superior to placebo at week 8, irrespective of gender or age. However, the differences in response rates between antidepressant and placebo in the subgroup of patients ≥65 years of age were not statistically significant.[32] The high placebo response rate observed in these studies, consistent with the findings of other recent trials in elderly depressed patients, makes the data difficult to interpret in this heterogeneous population.

Venlafaxine also has a favorable drug-interaction profile. Studies have shown that it has minimal inhibition of cytochrome P450 isoenzymes[46] and low protein binding, compared with antidepressant therapies.[47]

Clearly, there is a need for further studies to determine how well, and how quickly, remission of depressive symptoms can be achieved with a wider range of antidepressants in an attempt to achieve and maintain remission of depression in late life.

Conclusion

Effective treatment of depression in the elderly population presents a challenge to the clinician. Accurate diagnosis is critical, but can be difficult because comorbid medical illness frequently masks the symptoms of depression in older patients. Choosing an antidepressant that is efficacious and well tolerated will remain the cornerstone of clinical practice in treating depression in late life. Therapy should begin with low dosages and increase slowly to the optimum therapeutic dose of antidepressant or the highest tolerated dose. The primary aim of drug treatment in the elderly should be the same as that in younger adults, namely, achieving remission and maintaining the resolution of depressive symptoms in order to enable patients to function normally. ✤

Acknowledgment

This work was supported by an educational grant from Wyeth.

References

1. Angst J. Epidemiology of depression. *Psychopharmacology (Berl)*. 1992;106(suppl):S71-S74.
2. Blazer D. Depression. In: Beers MH, Berkow R, eds. *The Merck Manual of Geriatrics*. Whitehouse Station: Merck & Co.; 2000:310-322.
3. Salzman C, Schneider LS, Alexopoulos G. Pharmacological treatment of depression in late life. In: Bloom FE, Kupfer DJ, eds. *Psychopharmacology—The Fourth Generation of Progress*. New York, NY: Raven Press; 1995:1471-1477.
4. Finch JL, Ramsay R, Katona CL. Depression and physical illness in the elderly. *Clin Geriatr Med*. 1992;8:275-287.
5. Lebowitz BD, Pearson JL, Schneider LS, et al. Diagnosis and treatment of depression in late life. Consensus statement update. *JAMA*. 1997;278:1186-1190.
6. Reynolds CF, Frank E, Kupfer DJ, et al. Treatment outcome in recurrent depression: a post hoc comparison of elderly ('young old') and midlife patients. *Am J Psychiatry*. 1996;153:1288-1292.
7. Volz HP, Möller HJ. Antidepressant drug therapy in the elderly-a critical review of the controlled clinical trials conducted since 1980. *Pharmacopsychiatry*. 1994;27:93-100.
8. McDonald WM, Salzman C. Geriatric psychopharmacology. In: Michels R, Cooper AM, Guze, et al., eds. *Psychiatry Consultation-Liaison Psychiatry and Behavioral Medicine*, vol II. 1994;138:1-23.
9. Musselman D, McDonald WM, Nemeroff CB. Anxiety and depression in patients with cardiovascular disease. In: Fuster, Alexander, O'Rourke, eds. *Hurst's Textbook of Cardiology*, 10th ed. New York, NY: McGraw-Hill; 2001:2227-2250.
10. Starkstein SE, Robinson RG. Affective disorders and cerebral vascular disease. *Br J Psychiatry*. 1989;154:170-182.
11. Mossey JM, Knott K, Craik R. The effects of persistent depressive symptoms on hip fracture recovery. *J Gerontol Med Sci*. 1990;45:M163-M168.
12. 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.
13. Salzman C. Depressive disorders and other emotional issues in the elderly: current issues. *Int Clin Psychopharmacol*. 1997;12(suppl 7):S37-S42.
14. Rovner BW, Zisselman P, Shmuely-Dulitzki Y. Depression and disability in older people with impaired vision: a follow-up study. *J Am Geriatr Soc*. 1996;44:181-184.
15. Covinsky KE, Kahana E, Chin MH, Palmer RM, Fortinsky RH, Landefeld CS. Depressive symptoms and 3-year mortality in older hospitalized medical patients. *Ann Intern Med*. 1999;130:563-569.
16. *Diagnostic and Statistical Manual of Mental Disorders*. 3rd ed.rev. Washington DC: American Psychiatric Association; 1987.
17. Rovner BW, German PS, Brant LJ, Clark R, Burton L, Folstein MF. Depression and mortality in nursing homes. *JAMA*. 1991;265:993-996.
18. Koenig HG, Cohen HJ, Blazer DG, Krishnan KR, Sibert TE. Profile of depressive symptoms in younger and older medical inpatients with major depression. *J Am Geriatr Soc*. 1993;41:1169-1176.
19. Evans M, Mottram P. Diagnosis of depression in elderly patients. *Adv Psychiatr Treatment*. 2000;6:49-56.
20. Almeida OP, Almeida SA. Short versions of the geriatric depression scale: a study of their validity for the diagnosis of a major depressive episode according to ICD-10 and *DSM-IV*. *Int J Geriatr Psychiatry*. 1999;14:858-865.
21. *Diagnostic and Statistical Manual of Mental Disorders*. 4th ed. Washington DC: American Psychiatric Association; 1994.
22. Sutcliffe C, Cordingley L, Burns A, et al. A new version of the geriatric depression scale for nursing and residential home populations: the geriatric depression scale (residential) (GDS-12R). *Int Psychogeriatr*. 2000;12:173-181.
23. Katz IR, Miller D, Oslin D. Diagnosis of late-life depression. In: Salzman C, ed. *Clinical Geriatric Psychopharmacology*, 3rd ed. Baltimore: Williams & Wilkins; 1998:153-183.
24. Burrows AB, Satlin A, Salzman C, Nobel K, Lipsitz LA. Depression in a long-term care facility: clinical features and discordance between nursing assessment and patient interviews. *J Am Geriatr Soc*. 1995;43:1118-1122.
25. Hirschfeld RM, Keller MB, Panico S, et al. The National Depressive and Manic-Depressive Association consensus statement on the under-treatment of depression. *JAMA*. 1997;277:333-340.
26. Flint AJ. Choosing appropriate antidepressant therapy in the elderly. A risk-benefit assessment of available agents. *Drugs Aging*. 1998;13:269-280.
27. Emslie G, Judge R. Tricyclic antidepressants and selective serotonin reuptake inhibitors: use during pregnancy, in children/adolescents and in the elderly. *Acta Psychiatr Scand*. 2000;403(suppl):26-34.

28. Alexopoulos GS, Salzman C. Treatment of depression with heterocyclic antidepressants, monoamine oxidase inhibitors, and psychomotor stimulants. In: Salzman C, ed. *Clinical Geriatric Psychopharmacology*. 3rd ed. Baltimore: Williams & Wilkins; 1998:184-244.
29. Small GW, Salzman C. Treatment of depression with new and atypical antidepressants. In: Salzman C, ed. *Clinical Geriatric Psychopharmacology*. 3rd ed. Baltimore, Md: Williams & Wilkins; 1998:184-244.
30. Salzman C. Practical considerations for the treatment of depression in elderly and very elderly long-term care patients. *J Clin Psychiatry*. 1999;60(suppl 20):30-33.
31. Mahapatra SN, Hackett D. A randomized, double-blind, parallel-group comparison of venlafaxine and dothiepin in geriatric patients with major depression. *Int J Clin Pract*. 1997;51:209-213.
32. Entsuah R. Huang H, Thase M. Response and remission rates in different subpopulations with major depressive disorder administered venlafaxine, selective serotonin reuptake inhibitor, or placebo. *J Clin Psychiatry*. 2001;62:869-877.
33. Aguglia E. Reboxetine in the maintenance therapy of depressive disorder in the elderly: a long-term open study. *Int J Geriatr Psychiatry*. 2000;15:784-793.
34. Bondareff W, Alpert M, Friedhoff AJ, Richter EM, Clary CM, Batzar E. Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. *Am J Psychiatry*. 2000;157:729-736.
35. Dunbar GC, Cohn JB, Fabre LF, et al. A comparison of paroxetine, imipramine and placebo in depressed out-patients. *Br J Psychiatry*. 1991;159:394-398.
36. Goldberg RJ. Antidepressant use in the elderly. Current status of nefazodone, venlafaxine and moclobemide. *Drugs Aging*. 1997;11:119-131.
37. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry*. 1960;23:56-22.
38. Tollefson GD, Bosomworth JC, Heiligenstein JH, Potvin JH, Holman S. A double-blind, placebo-controlled clinical trial of fluoxetine in geriatric patients with major depression. The Fluoxetine Collaborative Study Group. *Int Psychogeriatr*. 1995;7:89-104.
39. Newhouse PA, Krishnan KR, Doraiswamy PM, Richter EM, Batzer ED, Clary CM. A double-blind comparison of sertraline and fluoxetine in depressed elderly outpatients. *J Clin Psychiatry*. 2000;61:559-568.
40. Schöne W, Ludwig M. A double-blind study of paroxetine compared with fluoxetine in geriatric patients with major depression. *J Clin Psychopharmacol*. 1993;13(suppl 2):34S-39S.
41. Trappler B, Cohen CI. Use of SSRIs in 'very old' depressed nursing home residents. *Am J Geriatr Psychiatry*. 1998;6:83-89.
42. Altamura A, Aguglia E. Moclobemide vs fluoxetine in elderly outpatients with major depression or dysthymia: a double-blind trial. *Eur Psychiatry*. 1994;9:163.
43. Bugarski-Kirola D, Zivkovic D, Stankovic Z, Damjanovic A. Fluoxetine versus moclobemide in elderly depressed patients. *Eur Neuropsychopharmacol*. 1996;1(suppl 6):20.
44. Weihs KL, Settle EC Jr, Batey SR, Houser TL, Donahue RM, Ascher JA. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. *J Clin Psychiatry*. 2000;61:196-202.
45. Schatzberg AF, Cantillon M. Antidepressant early response and remission with venlafaxine or fluoxetine in depressed geriatric outpatients. Poster presented at: Annual Meeting of the College of International Neuropsychopharmacology; 2000; Brussels, Belgium.
46. Ereshefsky L. Drug-drug interactions involving antidepressants: focus on venlafaxine. *J Clin Psychopharmacol*. 1996;16(suppl 2):37S-50S.
47. Ereshefsky L, Dugan D. Review of the pharmacokinetics, pharmacogenetics, and drug interaction potential of antidepressants: focus on venlafaxine. *Depress Anxiety.* 2000;1:30-44.