Diagnosing and Treating Depression in the Elderly

J. Craig Nelson, M.D.

As the population of people over 65 years of age increases, clinicians will see more cases of late-life depression. Currently, the rates of depression in the elderly are higher for nursing home patients and other medical inpatients and outpatients than for the noninstitutionalized, non–medically ill elderly. Depression in the elderly may be difficult to diagnose because of factors such as late onset, comorbid medical illness, dementia, and bereavement, but depression is not a natural part of aging. People who are depressed have increased suffering, impaired functioning, and increased mortality. Fortunately, antidepressants have been shown to effectively treat late-life depression. While monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs) are efficacious for treating depression in the elderly, their side effect profiles may be difficult and even dangerous for some older patients. However, serotonin selective reuptake inhibitors (SSRIs) and other second generation antidepressants appear to be both effective and better tolerated in the elderly. Since elderly patients may be more sensitive to drugs, clinicians may need to closely monitor these patients for dosing, side effects, and drug-drug interactions. *(J Clin Psychiatry 2001;62[suppl 24]:18–22)*

The World Health Organization expects that within 25 years people in all countries will have a life expectancy of over 50 years.[1] Concurrently, people over 65 years of age will make up 10% of the total world population. As our population grows older, clinicians will begin to see more depressed, elderly patients. Even now, depression in the elderly is not unusual; the Epidemiologic Catchment Area (ECA) Study estimates that depressive symptoms are present in 15% of community residents over the age of 65 years.[2] Although the ECA study found lifetime prevalence rates for major depression were lower in patients over the age of 65 years than in younger patients, the prevalence of major depression in nursing home patients and other medical inpatients and outpatients is higher, ranging from 9% to 42%.[3]

DIAGNOSING DEPRESSION IN THE ELDERLY

Unfortunately, depression is often viewed by both patients and clinicians as an inevitable part of aging. Older patients may not complain of depression or may not recognize that they are experiencing depressive symptoms because somatic symptoms may predominate, patients may not feel sad, or they may attribute symptoms to comorbid medical illnesses. The result is that these patients are undertreated and their depression underrecognized. However, despite the difficulty of diagnosing depression in older patients, these patients can be effectively treated. Diagnosing depression in the elderly may be further confounded because of special issues like late onset, dementia, medical illness, and bereavement, but an awareness of these issues can make diagnosis less difficult.

Late Onset

Late-onset depression may differ from early-onset depression. (Late-onset refers to depression that first appears in old age, not to depression that appears earlier and continues into old age.) Evidence suggests that compared with patients with early-onset depression, patients with late-onset depression are less likely to have a family history of depression but are more likely to have cognitive impairment, cerebral atrophy, deep white matter changes, medical comorbidity, and higher mortality.[2] In some patients, late-onset depression has been linked to forms of brain pathology, such as leukoariosis, and general vascular pathologies, such as carotid artery stenosis and cardiovascular disease. Patients with late-onset depression may be more resistant to treatment than patients with early-onset depression although the treatments employed are the same.

Dementia

Dementia frequently coexists with depression and can complicate diagnosis in the elderly. Depression can occur in the presence of both vascular and Alzheimer's dementia. Unfortunately for clinicians, depression and dementia have some similar symptoms like lack of energy, loss of interest in pleasurable activities, and sleep disturbance.[4]

From the Department of Psychiatry, Yale University School of Medicine, New Haven, Conn.

Supported by an unrestricted educational grant from Pfizer Inc.

Reprint requests to: J. Craig Nelson, M.D., Yale-New Haven Hospital, 20 York St., New Haven, CT 06504.

Thus, when trying to make a diagnosis of depression in patients with dementia, clinicians may want to look at when and how symptoms are experienced. Symptoms of dementia develop over a period of years, while depression usually develops over a few weeks or months. Severe and persistent dysphoria is indicative of major depression, whereas mild dysphoria or apathy is common in Alzheimer's patients and so does not necessarily indicate depression.[4] In the late stages of dementia, clinicians may have to rely on the observations of family members and caretakers to diagnose depression. Evidence suggests diagnosing depression is important because treatment for depression may also improve cognitive function.[4]

Medical Illness

Separating the symptoms of medical illness from those of depression can be challenging for clinicians. Like dementia, medical conditions are often comorbid with depression in the elderly and should be diagnosed independently. Because some physical symptoms could be caused by medical illness, ideational symptoms like guilt, hopelessness, and suicidal thinking may be more specific. When faced with patients presenting with both medical illness and depression, clinicians should remember that depression is not a normal consequence of medical illness. Many patients cope with debilitating and terminal illnesses without developing depression. However, depressive syndromes can appear as a physiologic reaction to an illness.[5] For example, a depressive syndrome may be precipitated by a medication used to treat a medical illness.

Bereavement

Losing jobs, homes, and loved ones are common stressors in later life. Bereavement is that condition which results from the loss of a spouse or loved one. Among people 65 years of age and over, more than 50% of women and 13% of men have lost at least 1 spouse.[4] After the death of a husband or wife, most people grieve for a period of time, but, eventually, they return to their normal level of functioning. For some people, however, bereavement may turn into depression. The DSM-IV[6] recognizes that symptoms of bereavement are similar to those of major depression but indicates that a diagnosis of depression should not be given unless the symptoms persist 2 months after the loss. The diagnosis of depression is suggested, however, by the presence of feelings of worthlessness, suicidal ideation, psychomotor retardation, and marked functional impairment. Even in major depression, recognizing that bereavement was a precipitating factor may be important in making treatment decisions.

TREATING DEPRESSION IN THE ELDERLY

Quality of life suffers when depression goes untreated. Depressed people have a diminished sense of well-being, and their ability to enjoy or even perform daily activities is impaired. For many clinicians and their elderly patients, symptoms such as anhedonia may be ascribed to aging, and the depression goes untreated. Pharmacotherapy has been shown to be an effective treatment for depression in the elderly, and it specifically improves quality of life. Several studies have shown antidepressants to be safe treatments for late-life depression.[7–14] Serotonin selective reuptake inhibitors (SSRIs) and other new, or second generation, antidepressants appear to be more tolerable and easier to use in the elderly than older agents, monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants (TCAs).

MAOIs and TCAs

Although MAOIs have been shown to effectively treat depression in the elderly,[7] they are rarely used. Orthostatic hypotension is a common side effect for MAOIs, as it is with the TCAs. In addition, their interactions with foods containing high amounts of tyramine and with indirect sympathomimetic drugs may lead to hypertensive crisis. MAOIs interacting with SSRIs may lead to serotonin syndrome. These potentially life-threatening food and drug interactions are the reasons that many clinicians rarely use MAOIs to treat patients with late-life depression.

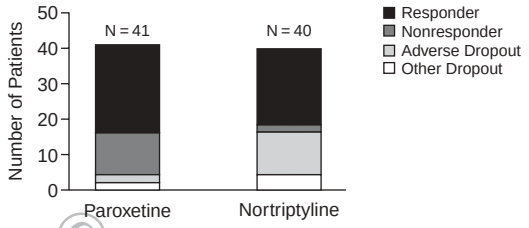
For many years, TCAs were the standard treatment for late-life depression, but their side effect profile and potential toxicity make them difficult, even dangerous, for older patients to take. Orthostatic hypotension is most common and can lead to falls causing head injuries and broken hips. Other side effects common to TCAs are dry mouth, urinary retention, constipation, and blurred vision. Other limiting side effects of TCAs in the elderly are memory loss and confusion. Further, TCAs often affect the cardiovascular system causing delayed ventricular conduction and increased heart rate (8 to 10 bpm). If taken in overdose, TCAs can cause considerable morbidity and mortality. For example, fatal arrhythmias are common in overdose. When taking TCAs, patients with ischemic heart disease are also at risk for sudden death due to arrhythmias.

SSRIs

While TCAs have potentially dangerous effects on cardiovascular function, SSRIs have little or no effect. Patients taking SSRIs have a slight decrease in heart rate, but conduction and blood pressure are not affected. Similarly, a 6-week, double-blind study[8] compared the TCA nortriptyline with the SSRI paroxetine in 81 patients with DSM-III-R–defined nonpsychotic unipolar major depression and ischemic heart disease. Although both drugs were efficacious for treating depression, paroxetine was better tolerated than nortriptyline and was less likely to affect the cardiovascular system (Figure 1).

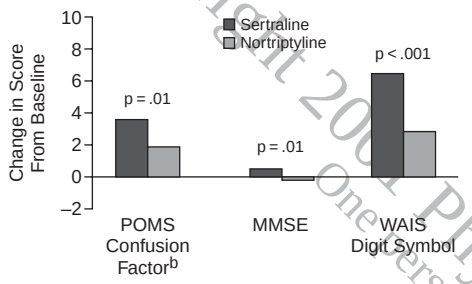
SSRIs are also more likely than TCAs to improve cognition. Bondareff et al.[9] used a double-blind, parallel

Figure 1. Intent-to-Treat Outcomes With Paroxetine or Nortriptyline in 81 Depressed Patients With Ischemic Heart Disease[a]



[a]Data from Nelson et al.[8]

Figure 2. Effects on Cognition in Patients Treated With Sertraline or Nortriptyline[a]



[a]Data from Bondareff et al.[9] Abbreviations: POMS = Profile of Mood States, MMSE = Mini-Mental State Examination, WAIS = Wechsler Adult Intelligence Scale.
[b]Negative POMS scores changed to positive to show improvement.

group design to compare nortriptyline with the SSRI sertraline in 210 outpatients 60 years of age and older. The 12-week study found that sertraline-treated patients had improved cognition whereas nortriptyline-treated patients had less improvement or their cognition declined (Figure 2). Patients taking sertraline in this study also showed greater improvement in energy and quality of life measures than the nortriptyline-treated patients. All of the available SSRIs have been demonstrated to be more effective than placebo in the treatment of late-life depression,[10–14] (Table 1) Thus, the choice of which to use should be based on other criteria.

Although several side effect differences among the SSRIs have been claimed, few consistent differences have been confirmed. In fact, most side effects appear to be related to the increased availability of serotonin. Thus if the SSRIs are compared at doses that have equivalent effects on serotonin uptake blockade, similar side effects would be expected. More consistent differences emerge when the SSRIs are compared with other drug classes.

There are clear differences among SSRIs with respect to their elimination half-life and drug-drug interactions.[15] With the exception of fluoxetine, the SSRIs have elimination half-lives ranging from about 16 to 35 hours, allowing for once a day administration. Fluoxetine has a longer

Table 1. Placebo-Controlled Studies of SSRIs in Late-Life Depression[a]

Drug	N	Age (y)	Weeks	Results
Fluoxetine[b]	671	≥ 60	6	Fluoxetine > Placebo
Fluvoxamine[c]	76	60–71	4	Fluvoxamine > Placebo
Citalopram[d]	149	≥ 65	6	Citalopram > Placebo
Paroxetine[e]	215	≥ 60	12	Paroxetine > Placebo
Sertraline[f]	752	≥ 60	8	Sertraline > Placebo

[a]Abbreviation: SSRI = selective serotonin reuptake inhibitor.
[b]Data from Tollefson and Hollman.[10]
[c]Data from Wakelin.[11]
[d]Data from Nyth et al.[12]
[e]Data from Pitts et al.[14]
[f]Data from Schneider et al.[13]

half-life of about 2 to 3 days for the parent and 5 days for the metabolite. Because of its longer half-life, fluoxetine can be given less frequently and discontinuation symptoms are less likely to occur if doses are missed than other agents. Alternatively, fluoxetine takes longer to discontinue than other agents if side effects occur, mania is induced, or it is necessary to switch to other agents.

The other clear differences among the SSRIs are their effects on the cytochrome P450 system. Paroxetine and fluoxetine are potent inhibitors of the CYP2D6 pathway. Fluoxetine also has meaningful effects on the CYP2C9 pathway. Fluvoxamine is a potent inhibitor of CYP1A2. Citalopram and sertraline do not appear to have meaningful pharmacokinetic interactions.

Special issues for the SSRIs in the elderly. Hyponatremia, weight loss, and balance problems can prove problematic in older patients taking SSRIs. Liu et al.[16] reviewed reports of hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone and found 736 cases. Although actual rates of hyponatremia are not well established because the population at risk is unknown, about three-fourths of all the cases reported were in patients over 65 years of age. Hyponatremia can occur with many psychotropic drugs including the SSRIs.

Although weight gain is more of a concern in younger patients, weight loss during acute treatment is an important issue in the elderly. Older patients commonly experience appetite and weight loss during their depression. As a result, the clinician is often struggling to maintain nutrition during initial treatment. Two studies[17,18] noted considerable weight loss during acute treatment with fluoxetine. This effect may be greater for fluoxetine. A comparison study found more weight loss with fluoxetine than sertraline although the difference was not large, –3.2 lb (–1.44 kg) versus –1.7 lb (–0.76 kg), respectively, $p < .018$.[19]

A major problem with the TCAs in older patients was orthostatic hypotension and falls. Although the SSRIs do not cause hypotension, a provocative report[20] found increased rates of falls in elders treated with SSRIs that were similar to those associated with the TCAs. The latter comparison, however, appeared seriously flawed. The mean dose of the SSRI was 16 mg/day of fluoxetine, or its

equivalent, which would be within a therapeutic range. The average dose of amitriptyline, or its equivalent, was 37 mg/day, well below a therapeutic dose. Further, in this retrospective study, there was no control for the effects of the disorder on gait. In other words, the SSRIs were usually prescribed in this nursing home sample for treatment of behavior disturbance associated with dementia or depression. It is not clear to what extent impulsive behavior in dementia or motor disturbance in depression may contribute to falls. It has been suggested that SSRIs impair balance although studies of this mechanism have been mixed.[21–23]

Other Second Generation Antidepressants

A group of second generation antidepressants other than SSRIs, such as bupropion, venlafaxine, nefazodone, and mirtazapine, has also proven to be efficacious in treating depression in the elderly.[24–27] Double-blind, comparison studies by Cassano et al.[26] of nefazodone and maprotiline and Høyberg et al.[27] of mirtazapine and amitriptyline found the second generation antidepressants to be as effective as the older agents.

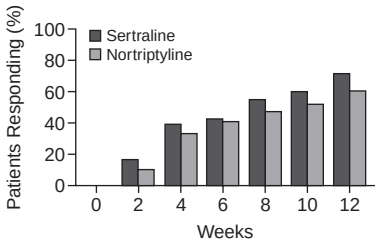
When treating their elderly patients with new antidepressants like bupropion, venlafaxine, nefazodone, and mirtazapine, clinicians may need to weigh the benefits and costs of each drug for individual patients. Bupropion, a norepinephrine reuptake blocker, is nonsedating and does not cause sexual dysfunction. Further, bupropion does not cause confusion or impaired thinking. However, bupropion may be difficult for elderly patients to take because of its b.i.d. dosing, and it is an inhibitor of the CYP2D6 pathway.[28] Venlafaxine functions as a 5-HT reuptake blocker at low doses and as a norepinephrine reuptake blocker at high doses.[29] Venlafaxine appears to have no significant drug interactions and may have greater efficacy at high doses. However, high doses also cause more side effects and sustained increases in blood pressure in about 9% of patients.[30] Nefazodone, a 5-HT_2 antagonist, has beneficial effects on sleep and has no treatment-emergent anxiety or sexual dysfunction. A drawback for elderly patients taking nefazodone may be sedation. Also, this drug has twice-daily dosing and may require dose titration. Finally, nefazodone is a moderately potent inhibitor of the CYP3A4 metabolic pathway. Mirtazapine is an α_2 antagonist that appears to have the following advantages in the elderly: beneficial effect on sleep, no treatment-emergent anxiety, weight maintenance, and no significant drug interactions. Mirtazapine may cause sedation in patients and the doses may have to be titrated.

Dosing and Duration of Treatment

Dosing in the elderly usually proceeds cautiously because of concern with tolerability. It should be noted, however, that most studies of late-life depression have been conducted in the "young-old," patients between 60 and 75 years of age. In these studies, with few exceptions, usual starting doses of antidepressants were employed.[3] In the "old-old," patients over 75 or 80 years of age, and in those patients with active medical illness, while there is less systematic data, it is prudent to proceed more slowly, starting with low doses. The aim is to determine if the patient can tolerate the medicine. Old and frail patients are not only more likely to experience side effects, but the consequences may be more severe. For example, a little gait instability may result in a fall and a hip fracture, or a little cognitive impairment can result in delirium. These concerns lead to the adage, *start low and go slow*; however, because these older patients often require usual final doses, be sure to *keep going*.

Older patients may take longer to respond than younger patients. This was first suggested by Georgotas and McCue,[31] who noted that older patients improved considerably during a 2-week extension of a 7-week clinical trial. More recently, Bondareff et al.[9] noted progressive improvement over a 12-week trial in older depressed patients treated with sertraline and nortriptyline (Figure 3). For example at 6 weeks, only 43% and 41% of the sertraline- and nortriptyline-treated patients had responded with 50% improvement. Yet at 12 weeks, 72% and 61% of the respective groups had responded. It should also be noted that in this study there was no suggestion of more rapid response with the TCA. This study indicates the importance of providing an adequate duration of treatment. The study also helps to explain low response rates reported in some studies of brief duration.[9]

Figure 3. Response Over 12 Weeks of Patients Treated With Sertraline or Nortriptyline[a]



[a]Data from Bondareff et al.[9] Response defined as ≥ 50% change in Hamilton Rating Scale for Depression.

SUMMARY

As the population of people over 65 years of age continues to increase, clinicians will be faced with the challenge of diagnosing and treating more late-life depression. Depression in the elderly is often difficult to diagnose because it is not recognized by the patient and the somatic symptoms that predominate may be mistaken for medical illness. However, depression is not a natural part of aging and can be treated effectively with antidepressants. While MAOIs and TCAs are efficacious for treating depression

in the elderly, their side effect profiles make them less tolerable than the newer antidepressants. SSRIs and other second generation antidepressants appear to be both effective and tolerable in the elderly. Since elderly patients may be more sensitive to drugs, clinicians may need to closely monitor these patients for dosing, side effects, and drug-drug interactions.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin), citalopram (Celexa), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Pamelor and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

Disclosure of off-label usage: The author of this article has determined that, to the best of his knowledge, fluvoxamine is not approved by the U.S. Food and Drug Administration for the treatment of depression.

REFERENCES

1. World Health Organization. Fifty facts from The World Health Report 1998. Available at: www.who.int/whr/1998/factse.htm. Accessed March 5, 2001
2. NIH Consensus Development Panel on Depression in Late Life. Diagnosis and treatment of depression in late life. JAMA 1992;268:1018–1024
3. Nelson JC. Treatment of major depression in the elderly. In: Nelson JC, ed. Geriatric Psychopharmacology. New York, NY: Marcel Dekker; 1998: 61–97
4. Zisook S, Dunn LB. Dementia and bereavement: adverse life experiences complicating depression in later life. Primary Care Companion J Clin Psychiatry 2000;2(suppl 5):25–31
5. Zisook S, Downs NS. Diagnosis and treatment of depression in late life. J Clin Psychiatry 1998;59(suppl 4):80–91
6. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Washington, DC: American Psychiatric Association; 1994
7. 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
8. Nelson JC, Kennedy JS, Pollock BC, et al. Treatment of major depression with nortriptyline and paroxetine in patients with ischemic heart disease. Am J Psychiatry 1999;156:1024–1028
9. Bondareff W, Alpert M, Friedhoff AJ, et al. Comparison of sertraline and nortriptyline in the treatment of major depressive disorder in late life. Am J Psychiatry 2000;157:729–736
10. Tollefson GD, Holman SL. Analysis of the Hamilton Depression Rating Scale factors from a double-blind, placebo-controlled trial of fluoxetine in geriatric major depression. Int Clin Psychopharmacol 1993;8:253–259
11. Wakelin JS. Fluvoxamine in the treatment of the older depressed patient; double-blind, placebo-controlled data. Int Clin Psychopharmacol 1986;1: 221–230
12. Nyth AL, Gottfries CG, Lyby K, et al. A controlled multicenter clinical study of citalopram and placebo in elderly depressed patients with and without concomitant dementia. Acta Psychiatr Scand 1992;86:138–145
13. Schneider LS, Clary CM, Finkel SI, et al. Sertraline in the treatment of elderly depression: results of a large, multicenter, placebo-controlled trial. In: New Research Program and Abstracts of the 153rd Annual Meeting of the American Psychiatric Association; May 16, 2000; Chicago, Ill. Abstract NR290:134
14. Pitts CD, Morton NH, Goodwin W, et al. Paroxetine in the treatment of depression in elderly patients. In: New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association; June 4, 1998; Toronto, Ontario, Canada. Abstract NR696:256
15. Pollock BG. Drug interactions. In: Nelson JC, ed. Geriatric Psychopharmacology. New York, NY: Marcel Dekker; 1998:43–60
16. Liu BA, Mittmann N, Knowles SR, et al. Hyponatremia and the syndrome of inappropriate secretion of antidiuretic hormone associated with the use of selective serotonin reuptake inhibitors: a review of spontaneous reports. Can Med Assoc J 1996;155:519–527
17. Brymer C, Winograd CH. Fluoxetine in elderly patients: is there cause for concern? J Am Geriatr Soc 1992;40:902–905
18. Robinson RG, Schultz SK, Castillo C, et al. Nortriptyline versus fluoxetine in the treatment of depression and in short-term recovery after stroke: a placebo-controlled, double-blind study. Am J Psychiatry 2000;157:351–359
19. Newhouse PA, Krishnan RR, Doraiswamy PM, et al. A double-blind comparison of sertraline and fluoxetine in depressed elderly patients. J Clin Psychiatry 2000;61:559–568
20. Thapa PB, Gideon P, Cost TW, et al. Antidepressants and the risk of falls among nursing home residents. N Engl J Med 1998;339:875–882
21. Laghrissi-Thode F, Pollock BG, Miller MC, et al. Double-blind comparison of paroxetine and nortriptyline on the postural stability of late-life depressed patients. Psychopharmacol Bull 1995;31:659–663
22. Laghrissi-Thode F, Pollock BG, Miller MC, et al. Comparative effects of sertraline and nortriptyline on body sway in older depressed patients. Am J Geriatr Psychiatry 1995;3:217–228
23. Li X, Hamdy R, Sandborn W, et al. Long-term effects of antidepressants on balance, equilibrium, and postural reflexes. Psychiatry Res 1996;63: 191–196
24. Weihs KL, Settle EC Jr, Batey SR, et al. Bupropion sustained release versus paroxetine for the treatment of depression in the elderly. J Clin Psychiatry 2000;61:196–202
25. Dierick M. An open-label evaluation of the long-term safety of oral venlafaxine in depressed elderly patients. Ann Clin Psychiatry 1996;8:169–178
26. Cassano GB, Fazzari G, Giannelli A, et al. Nefazodone versus maprotiline in elderly depressed patients. In: New Research Program and Abstracts of the 151st Annual Meeting of the American Psychiatric Association; June 4, 1998; Toronto, Ontario, Canada. Abstract NR707:259
27. Høyberg OJ, Maragakis B, Mullin J, et al. A double-blind multicentre comparison of mirtazapine and amitriptyline in elderly depressed patients. Acta Psychiatr Scand 1996;93:184–190
28. Wellbutrin (bupropion). Physicians' Desk Reference. Montvale, NJ: Medical Economics; 2001:1485–1489
29. Thase ME. Is venlafaxine more effective than the SSRIs? mage- and meta-analyses of 17 controlled studies. Presented at the 39th annual meeting of the American College of Neuropsychopharmacology; Dec 10–14, 2000; San Juan, Puerto Rico
30. Thase ME. Effects of venlafaxine on blood pressure: a meta-analysis of original data from 3744 depressed patients. J Clin Psychiatry 1998;59: 502–508
31. 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