Practical Considerations for the Treatment of Depression in Elderly and Very Elderly Long-Term Care Patients

Carl Salzman, M.D.

Depression in the elderly and very elderly, especially those in long-term care facilities, often is more difficult to treat than depression in young or middle-aged adults. Because this population may be more sensitive to the common adverse effects of many antidepressant drugs, particularly the anticholinergic side effects, administration of pharmacologic therapy for depression in the elderly requires careful consideration of the side effect profiles of the various classes of antidepressant medication.

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Clinical depression, although a serious public health problem in the elderly, is not a normal consequence of aging[1] and is often underdiagnosed and undertreated in this population.[2–4] Multiple pathways contribute to late-life depression, including neurobiological and psychological factors, multiple physical illnesses, as well as common social and economic problems.[5] It is now accepted that the elderly, defined as individuals older than 65 years, actually constitute a very heterogeneous population cohort. Individuals older than 75 or 80 years are referred to as "old-old" compared with those aged 65 to 75 years, who are referred to as "young-old." As the population continues to age, there is a growing group of people older than 90 years and even centenarians; these individuals may be termed the "oldest-old." It is remarkable that so few controlled studies on the use of antidepressant drugs in patients aged 75 years or older have been conducted, because the oldest-old is the fastest growing age group in the world. Americans now are living well into their 80s, and it is no longer unusual for people to live into their 90s. Because many of the old-old and oldest-old live in long-term care facilities, it is also surprising that relatively few studies are available that describe elderly patients with depression living in long-term care or assisted-living facilities. This article briefly reviews the treatment of major and nonmajor depression in individuals older than 75 years, with particular reference to those living in assisted-care facilities. Three groups of antidepressants are considered: (1) tricyclic antidepressants (TCAs), (2) selective serotonin reuptake inhibitors (SSRIs), and (3) miscellaneous atypical antidepressants.

PHARMACOTHERAPY OF MAJOR DEPRESSIVE DISORDER IN ELDERLY PATIENTS

Tricyclic Antidepressants

The TCAs are effective medications for major depressive disorder in the elderly and very elderly. Blood levels necessary to achieve the therapeutic effect in the very elderly are the same as in younger adults,[6] although most older people are more sensitive to the therapeutic as well as toxic effects of TCAs.

Reviews of TCA therapy in the elderly have been presented elsewhere.[2,7] Only a few studies have investigated the benefits of pharmacologic therapy in patients older than 75 or 80 years. One of the most influential and important studies was conducted by Katz and colleagues,[8,9] who reported on the clinical effects and pharmacokinetics of the TCA nortriptyline in 24 very elderly patients (mean age = 84 years) living in an institutional setting and characterized as having chronic illness and functional disability. Nortriptyline was effective in this population, and the investigators found no clinically significant differences in nortriptyline kinetics in the elderly patients compared with those found in younger and healthier patients.

Although the TCAs are effective as antidepressants, altered pharmacokinetics and adverse effects may interfere with the usefulness of TCAs in treating the very elderly patient with depression. Hydroxy metabolites of TCAs, which are potentially cardiotoxic to the very elderly, may be present at higher plasma levels in the elderly because the renal excretion of these metabolites is decreased by advanced age.[10] It is possible, therefore, for elderly patients to develop cardiotoxic side effects from elevated hydroxy metabolite levels, even when plasma drug levels are within

From the Department of Psychiatry, Harvard Medical School, Boston, Mass.

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Reprint requests to: Carl Salzman, M.D., Massachusetts Mental Health Center, 74 Fenwood Rd., Boston, MA 02115.

the therapeutic range. It is useful for clinicians to remember that renal excretion of water-soluble hydroxy metabolites may also be delayed by concomitant illness or other medications that may impair renal clearance (e.g., nonsteroidal anti-inflammatory drugs). An electrocardiogram can be used to monitor hydroxy metabolite levels at baseline and during treatment with TCAs. When hydroxy metabolite levels approach the toxic range, the QRS complex (or corrected QT interval [QTc]) widens, thereby providing an early warning sign of impending cardiac toxicity.

Annoying side effects of TCAs, particularly constipation and dry mouth, can become severe problems in the elderly, leading to bowel obstruction and diminished ability to eat. Central nervous system (CNS) anticholinergic side effects, which usually consist of decreased memory and attention, can progress to a delirious state with severe symptoms of cognitive impairment, nighttime confusion (sundowning), and delirium. It is not unusual for these CNS side effects to be misdiagnosed as dementia. Orthostatic hypotension, another common adverse effect of TCAs, may cause falls, which can be serious or even fatal in this age group. Oversedation from TCA therapy is another potential problem because it prevents elderly patients from leading a full life and participating in activities.

To prevent these common adverse effects of TCA therapy, relatively low starting doses followed by gradual dose increases are recommended. Although elderly depressed patients usually respond to lower doses than do younger and middle-aged adults, there is considerable variability in metabolism and response to TCAs, so some patients may require full therapeutic doses to achieve therapeutic blood TCA levels. Thus, the correct dose level is usually achieved by balancing emerging therapeutic response, adverse effects, and blood levels or changes in the electrocardiogram. Once the depression begins to lift, elderly patients should not prematurely discontinue treatment because maximum therapeutic response may take longer to develop in the elderly than it does in younger and middle-aged adults. Unless serious adverse effects occur, clinicians should then maintain elderly patients on treatment with their antidepressant medications to prevent relapse. Modest doses of TCAs are effective in treating depressed elderly patients who are also demented.

Selective Serotonin Reuptake Inhibitors

The SSRIs have become the preferred first-line antidepressant therapy for most elderly patients.[11–16] For all but the most severe depression, SSRIs and TCAs have comparable efficacy. However, easier administration, reduced need for dosage adjustment, less severe adverse effect profiles, and greater acceptance of the SSRIs favor these agents over the TCAs.[5] Whether SSRIs and TCAs are equally effective in treating the most severe psychotic or melancholic depressed elderly patient is still controversial.

All SSRIs are useful for late-life depression. In a recent large, double-blind study, Orengo and colleagues[17] found the SSRI fluoxetine to be an effective and well-tolerated antidepressant in elderly patients of varying ages, levels of depression, and psychiatric diagnoses who were admitted to a geropsychiatric inpatient unit. Among the SSRIs, only paroxetine has been studied in very elderly patients; paroxetine use in patients older than 80 years had greater efficacy than placebo (C.S., unpublished data, 1999) with virtually no adverse effects (see below). Another recent study compared serum anticholinergicity of 61 elderly depressed patients (mean age = 73.2 years) randomly assigned to double-blind treatment with paroxetine (N = 31) or nortriptyline (N = 30) and found that paroxetine has approximately one fifth the anticholinergic potential of nortriptyline at therapeutic plasma concentration levels in elderly patients.[18] The investigators also found that complaints of dry mouth and tachycardia were significantly more frequent and severe in the nortriptyline group. Data from Europe suggest that the SSRIs may also be useful in elderly patients with depression who also have comorbid cognitive impairment or dementia.[19,20] If the primary depression is well treated, elderly patients may experience improved cognition, although the underlying dementia may still be present. Unlike treatment with a TCA, SSRI treatment will not worsen cognition owing to anticholinergic toxicity.

The SSRIs differ in rates of hepatic clearance.[11] Fluoxetine and citalopram have relatively long half-lives, whereas the half-lives of sertraline, fluvoxamine, and paroxetine are shorter. The elimination half-life of an SSRI bears no relationship to its therapeutic properties, and whether a long half-life increases the risk of adverse effects in the elderly is unknown. Long half-life compounds have the advantage of high compliance and steady blood levels should a dose be missed, whereas short half-life SSRIs have the advantage of dosing flexibility. Recommended starting doses for an elderly patient, based on clinical experience rather than published data, are between one third and one half of that for young and middle-aged adults. As with the TCAs, clinicians usually "start low and go (increase) slow" (i.e., use low initial doses and increase the dose gradually) with SSRI dosing, maintaining long-term therapy to reduce the risk of relapse.

The most common adverse effects of SSRIs in the elderly are agitation and sedation. Because adverse effects may be more intense during the first several days of SSRI therapy, some elderly patients may discontinue the medication, although some elderly patients can take full therapeutic doses almost immediately. Drug interactions between the SSRIs and other compounds that share hepatic metabolizing enzymes may be more common in the older age group because these patients tend to take several medications simultaneously. This is especially true during long-term maintenance antidepressant treatment because concurrent medications may change over time.

Atypical Antidepressants

The third general group of antidepressant drugs used in elderly patients with depression are the atypical antidepressants, including bupropion, venlafaxine, nefazodone, and mirtazapine. Although the number of elderly patients studied while taking each of these medications is significantly less than that for the TCAs and SSRIs, clinical experience suggests that each of these drugs is effective in the elderly.[21,22] Prescribing principles are the same for atypical antidepressant drugs as for the TCAs and SSRIs, i.e., "start low and go slow." None of these drugs have been studied in patients older than 75 years.

Each medication has advantages and disadvantages. Bupropion has no anticholinergic side effects and does not cause orthostatic hypotension, properties that are advantageous to the elderly.[22] However, it tends to be activating, and very high doses are associated with a significantly greater risk of seizures than with other agents. Venlafaxine resembles a TCA in pharmacologic properties but lacks anticholinergic effects. It may be quite effective, but headache, nausea, and elevated blood pressure emphasize the need for caution when venlafaxine is given to very elderly patients. Nefazodone and mirtazapine are useful for bedtime sedation but may cause daytime drowsiness.

TREATMENT OF NONMAJOR DEPRESSION IN ELDERLY PATIENTS

Nonmajor depression in the elderly often goes unrecognized. Katz and colleagues[23] conducted a study of 209 nursing home residents and found that 18% suffered from dysphoria. Another study, by Nobler and colleagues,[24] reported a higher incidence of outpatient dysthymia in elderly patients (mean age = 67 years). Symptoms of nonmajor depression, which may interfere with the quality of life as much as major depression does, commonly include dysphoria, mixed anxiety, variable sadness, increased irritability, and increased social withdrawal. The diagnostic distinction between unhappiness and nonmajor depression may be difficult to determine because the patient may not be able to provide enough useful information to make the differentiation. Often, the best person to determine whether the patient's level of unhappiness has reached clinically significant severity is the 24-hour caregiver.

Nonmajor depression may be treated without medication, using techniques such as expressive movement, group, reminiscence, problem-solving, and group-cognitive therapies.[25–30] A recent study examined the effect of 8 weeks of planned socialization and leisure activities in 31 elderly nursing home residents (mean age = 78.7 years) with either minor depression or mild-to-moderate major depression. Approximately half of the patients were able to resume social interaction similar to their pre–nursing home pattern, suggesting that a psychosocial intervention enhancing socialization according to each patient's choice had a positive therapeutic impact.[31] It seems that each form of nonpharmacologic therapy has been successful in improving the quality of life of nursing home residents, suggesting that, to avoid unnecessary medical risks, patients suffering from minor depression should try nonpharmacologic therapy before undergoing drug treatment.[32]

My colleagues and I conducted a randomized, double-blind, placebo-controlled trial of paroxetine in elderly nursing home residents with nonmajor depression (A. Burrows, M.D., C. Salzman, M.D., A. Satlin, M.D., et al., unpublished data, 1999). The study design included a 1-week placebo run-in, 8 weeks of double-blind treatment with paroxetine or placebo, weekly monitoring of safety and global improvement or deterioration, and psychometric assessments performed at baseline and at weeks 4 and 8. The overall preliminary results showed a high placebo response and little difference between the 2 treatment groups. However, when response was originally defined according to evidence of specific rating scale improvements, paroxetine was significantly more effective than placebo. Our data support those of Nobler and colleagues,[24] who reported that SSRI therapy is effective in 60% of elderly patients with dysthymia.

CONCLUSIONS

All antidepressant therapies seem to be effective in the treatment of elderly and very elderly patients with major depression in long-term care facilities. If drug selection is based on side effect profiles, the SSRIs offer the most favorable adverse effect profile. Regardless of which antidepressant is selected, dosing should start low and increase slowly to reduce the risks of adverse effects. It seems that psychotropic medication as well as nonpharmacologic therapies are effective for treating elderly patients with nonmajor depression.

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

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