Therapy Choices for Late-Life Depression

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Late-life depression has a chronic course and is often complicated by coexistent medical conditions, of which anxiety is the most common. Clinical evidence exists for the efficacy of tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs) in late-life depression. Unlike TCAs, SSRIs benefit from a benign tolerability profile and are not associated with adverse cardiovascular effects, anticholinergic activity, or significant sedative properties. The choice of SSRI for late-life depression should take into account pharmacokinetic differences between SSRIs that confer additional safety and tolerability advantages.

(Primary Care Companion J Clin Psychiatry 2000;2[suppl 5]:39–43)

Late-life depression has a chronic course and is often recurrent, requiring long-term treatment. Elderly patients with depression commonly have concomitant medical illness for which they may already be receiving medication. Effective treatment of late-life depression must be well tolerated to encourage patients to comply with treatment and have little potential for drug interactions. Thus, in addition to efficacy, tolerability is an important determinant of choice of antidepressant therapy in elderly patients with depression.

This review examines the clinical evidence for the efficacy and tolerability of tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and newer antidepressants to assess the most appropriate choice of therapy for late-life depression.

TRICYCLIC ANTIDEPRESSANTS

Once considered standard treatment of depression, TCAs have been less widely studied in elderly depressed subjects than in younger adults with depression. The number of controlled studies specifically in the elderly is very limited. Open treatment studies are notoriously unreliable, and evidence of efficacy can only be derived from adequately sized placebo-controlled studies or from reference comparator studies if superior efficacy is demonstrated. Comparator studies that do not control for an underlying placebo response rate are sometimes difficult to interpret.

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Presented at the symposium "Depression in the Elderly: Clinical Considerations and Therapeutic Approaches," which was held April 7, 1999, in Florence, Italy, and supported by an unrestricted educational grant from SmithKline Beecham Pharmaceuticals.

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A few well-conducted, short-term, placebo-controlled studies of TCAs have been performed involving small numbers of patients aged ≥ 60 years; these showed that imipramine,[1–4] amitriptyline,[5] and nortriptyline[6] were more effective than placebo in late-life depression. A few larger active comparator studies (N > 100) have also been conducted with amitriptyline[7,8] and imipramine,[9] showing equivalent efficacy between TCAs and comparator agents.

It is also difficult to generalize from the results of studies that have a high discontinuation rate. This is a particular problem with the TCA studies in the elderly depressed population because the TCAs are associated with a very high rate of discontinuations due to side effects. As a result, some questions remain about the effectiveness of TCAs in elderly depression.

As a class, TCAs cause side effects that make their use problematic in the older patient. TCAs prolong cardiac conduction times and have a direct negative ionotropic effect on the myocardium. They increase bundle-branch block, can produce ventricular tachycardia, and can lead to sudden death.[10,11] Their use has particular risks for patients with heart disease.[12] TCAs also cause orthostatic hypotension, which increases the risk of falls and possible fractures in the elderly. All TCAs have anticholinergic activity which, in addition to cardiac depressant effects, predictably causes dry mouth, urinary retention, and constipation. TCAs also have significant sedative properties and, even when taken at night, cause daytime drowsiness and may impair memory and psychomotor function. Because of their wide pharmacologic activity, TCAs are associated with considerable morbidity and mortality if taken in overdose.[13,14]

SELECTIVE SEROTONIN REUPTAKE INHIBITORS

The introduction of SSRIs in the 1990s was significant for older depressed patients.[15] By comparison with TCAs,

SSRIs lack cardiovascular, anticholinergic, and sedative effects and are far less toxic when taken in overdose.[13,14] In a meta-analysis not restricted to the elderly, Montgomery et al.[16] examined 42 published, randomized, controlled studies comparing SSRIs and TCAs with respect to discontinuation rates due to side effects and lack of efficacy. Seven of the trials were placebo-controlled, and these were considered in an additional separate analysis. There was no significant difference between the 2 classes of antidepressant for the rate of discontinuation due to lack of efficacy (overall analysis: 6% SSRIs vs. 5% TCAs; placebo-controlled studies: 7% SSRIs vs. 6% TCAs). However, the rate of discontinuation attributed to side effects was significantly greater with TCAs than with SSRIs in the overall analysis (19% vs. 15%, respectively; $p < .01$) and when limited to the placebo-controlled studies (27% vs. 19%, respectively; $p < .01$). Thus, although of similar efficacy, there are clear differences between the tolerability profiles of SSRIs and TCAs.

Meta-analysis of randomized, controlled, double-blind studies of antidepressants in the elderly showed comparable response rates for TCAs and SSRIs.[17] There were no statistically significant differences between the treatments. However, adverse event rates and dropout rates were higher in the elderly patients prescribed TCAs. The 4.7% difference in rates of discontinuation due to adverse events between TCAs and SSRIs, while not statistically significant probably because of variability in small patient numbers, is in accord with, or somewhat higher than, the significant differences reported in similar analyses. Patients included in clinical trials may be an unrepresentative sample, but a study of consecutive presenters in primary care also indicated more factors that mitigate against the use of TCAs in the elderly.[18]

Metabolic diversity in disposition between SSRIs confers pharmacokinetic differences.[19,20] Pharmacokinetic characteristics that may be of particular importance, should switching or termination of treatment be required, include parent drug half-life and the relative activity and persistence of metabolites (Table 1). Some SSRIs have one or more active metabolites. One of the active metabolites of citalopram, didemethylcitalopram, is cardiotoxic in dogs; however, the levels of the metabolite in humans are low, and the clinical relevance of this finding is still under discussion.[21] Only fluvoxamine and paroxetine benefit from both a lack of active metabolites and a half-life optimal for once-daily dosing. Drug-drug interactions have been reported for all SSRIs, and particular care is needed in the presence of concomitant medication depending on which CYP450 isoenzymes are involved in the metabolism of both SSRIs and other medications.

The clinical efficacy of individual SSRIs in late-life depression has been assessed in several open-label, placebo-controlled and active comparator studies, and these are discussed below.

Table 1. Comparative Pharmacokinetic Profiles of SSRIs[a]

		Metabolite(s)		
SSRI	Half-Life	Active (N[b])	Half-Life	Potency[c]
Citalopram	33 h	✓ (2)	49–100 h	2–4 times less
Fluoxetine	1–3 d	✓ (1)	7–15 d	Equipotent
Fluvoxamine	15 h	✕	…	…
Paroxetine	24 h	✕	…	…
Sertraline	25 h	✓ (1)	66 h	8 times less

[a]Data from Grundemar et al.[22] Symbols: ✓ = present, ✕ = absent, … = not applicable.
[b]Number of active metabolites.
[c]Relative to parent.

Fluoxetine

In a study of moderate-to-severe late-life depression, 671 outpatients aged more than 60 years were randomly assigned to receive fluoxetine or placebo for 6 weeks.[23] The overall response to treatment in this study was low. On the primary efficacy measure, there was no significant difference between fluoxetine and placebo. However, on the secondary measure of response rate (50% reduction in Hamilton Rating Scale for Depression [HAM-D] score), there was a significant advantage for fluoxetine compared with placebo (43.9% vs. 31.6%; $p = .002$). The tolerability of fluoxetine was shown by the similar rates of discontinuation due to adverse events with fluoxetine and placebo (11.6% vs. 8.6%). A smaller short-term, placebo-controlled study by Evans et al.[24] in a more usual patient population also reported the antidepressant efficacy and tolerability of fluoxetine in 82 depressed individuals aged more than 65 years who had coexistent physical illness. The response rate was 67% in the fluoxetine group compared with 38% in the placebo group, according to a 50% reduction in HAM-D scores.

Small short-term comparative trials have suggested that fluoxetine is as effective as amitriptyline,[25,26] doxepin,[27] and trazodone[28] in elderly patients with depression.

Fluvoxamine

Efficacy in late-life depression has been demonstrated in a short-term, placebo-controlled comparative study with fluvoxamine in 76 patients aged 60–71 years.[4] At week 4, equivalent efficacy was observed for fluvoxamine and imipramine, which were both significantly better than placebo, according to HAM-D and Clinical Global Impressions (CGI) scales. Two smaller comparative studies of depressed patients aged 65 years or more have reported possible similar efficacy of fluvoxamine and dothiepin ($N = 52$)[29] or mianserin ($N = 57$)[30] according to the Montgomery-Asberg Depression Rating Scale (MADRS), following 6 weeks of therapy.

Paroxetine

The efficacy of paroxetine in late-life depression has been assessed in double-blind comparisons with TCAs involving 800 patients aged 60 years or more (Table 2).

Table 2. Double-Blind Randomized Studies of Paroxetine, Showing Equivalent Efficacy to Comparator Antidepressants in Elderly Subjects

Comparator	N	Age (y)	Duration (wk)	Equivalent Efficacy[a]	Study
Doxepin	271	≥ 60	6	Yes	Dunner et al, 1992[31]
Imipramine	198	≥ 60[b]	8	Yes	Katona et al, 1998[32]
Amitriptyline	101	≥ 65	6	Yes	Hutchinson et al, 1992[33]
Amitriptyline	91	≥ 65	6	Yes	Geretsegger et al, 1995[34]
Clomipramine	79	≥ 60	6	Yes	Guillibert et al, 1989[35]
Mianserin	60	≥ 60	6	Yes	Dorman, 1992[36]

[a]Assessed by Hamilton Rating Scale for Depression, Montgomery-Asberg Depression Rating Scale, and Clinical Global Impressions measures.
[b]Includes patients with dementia.

Dunbar[37] performed a meta-analysis of 10 double-blind comparative studies enrolling 736 elderly patients (aged ≥ 65 years) who were randomized to receive paroxetine or a TCA (or related antidepressant) for 5 to 6 weeks. Paroxetine was found to be significantly better than active comparators, leading to improvements in mean HAM-D, MADRS, and CGI scores. Adverse events were less frequent ($p \leq .05$) with paroxetine, including anticholinergic side effects ($p \leq .05$).

In treating elderly patients with depression, many of whom have heart disease, there is a clear requirement for antidepressant therapy that is not associated with adverse cardiovascular effects. Paroxetine provided efficacious treatment of depression without compromising cardiac function in depressed subjects with clinically stable ischemic heart disease.[38]

The efficacy of paroxetine has also been compared with that of fluoxetine in 106 depressed patients aged 61–85 years.[39] Following 6 weeks of treatment, mean total HAM-D and MADRS scores decreased in both groups. Improvement in depressive symptoms tended to occur more rapidly in the paroxetine group, with a significant difference in mean HAM-D score favoring paroxetine after 3 weeks ($p = .03$). After 6 weeks, there were significantly more responders to paroxetine as shown by a ≥ 50% reduction in HAM-D and MADRS total scores ($p < .05$). More rapid improvement in cognitive function was observed with paroxetine. No significant difference in tolerability or safety was observed between the 2 SSRIs.

Sertraline

The majority of data on sertraline in late-life depression come from open-label studies. The efficacy of sertraline was examined in a large open-label study in 1437 patients aged 60 years or more.[40] By the end of the 8-week study, the mean reduction from baseline MADRS score was 61% ($p < .001$), with a 70% response rate, as assessed by a reduction of ≥ 50% on this measure. Side effects were reported by 23% of patients treated with sertraline, although side effects rarely led to withdrawal from the study (5.1%). In 2 small open-label studies (7–10 weeks), sertraline improved symptoms of depression (according to HAM-D and Beck Depression Inventory [BDI]) in elderly depressed patients with coexistent Parkinson's disease ($N = 15$)[41] or non–insulin dependent diabetes mellitus ($N = 28$).[42] In an 8-week, double-blind comparison with amitriptyline, the efficacy of sertraline was assessed in 241 patients aged 65 years or more.[43] The 2 antidepressants were reported to have similar efficacy, measured by improvement in symptoms of depression according to HAM-D and MADRS. However, 35% of amitriptyline patients withdrew from the study because of treatment-related side effects (compared with 28% of patients on sertraline), and amitriptyline was associated with a greater incidence of anticholinergic and gastrointestinal effects.

Citalopram

In a 6-week, placebo-controlled study enrolling 149 depressed patients (aged ≥ 65 years) with or without coexistent dementia, citalopram significantly improved symptoms of depression compared with placebo, according to HAM-D, MADRS, and CGI scores.[44] An 8-week comparison of citalopram and amitriptyline in 305 patients (aged ≥ 65 years) has shown comparable efficacy of the 2 antidepressants according to MADRS, HAM-D, and CGI scores.[45] Anticholinergic side effects were more common among amitriptyline-treated patients. In a long-term (up to 12 months) open-label study of 123 depressed subjects aged 58–96 years, the efficacy of citalopram has been assessed, with improvements in symptoms of depression measured by CGI score.[46]

NEWER ANTIDEPRESSANTS

Several newer antidepressants have been studied in late-life depression with variable results.

Mirtazapine and venlafaxine have a mixed pharmacologic profile, acting at both noradrenergic and serotonergic sites. In a 6-week, placebo-controlled comparative study not restricted to elderly individuals ($N = 150$), mirtazapine was more effective than trazodone in improving symptoms of depression, as assessed by MADRS and HAM-D scores.[47] Clinical experience with mirtazapine has shown antidepressant efficacy similar to that of the TCA amitriptyline.[8]

Few placebo-controlled or active comparator data have been published for venlafaxine in late-life depression. A 6-week, double-blind comparative study assessed the efficacy of venlafaxine or doxepin in 92 patients with depression, aged 64–87 years. The 2 antidepressants showed comparable efficacy, with significant decreases in HAM-D and MADRS scores compared with baseline ($p = .05$).[48] Long-

term, open-label studies of around 200 patients aged 65 years or more have examined the efficacy and safety of venlafaxine for late-life depression and have reported that the drug is both effective and safe.[49–51] However, clinical experience with venlafaxine in nonelderly patients has shown a potential for pressor effects at high doses. Dose-dependent increases in diastolic and systolic blood pressure have been attributed to venlafaxine.

The norepinephrine reuptake inhibitor reboxetine has been compared with imipramine in a double-blind randomized study of 256 depressed patients aged 56–94 years.[52] Reboxetine was as effective as imipramine in alleviating symptoms of depression according to HAM-D, MADRS, and CGI measures, but was better tolerated than the TCA. Patients in the reboxetine-treatment group experienced a lower incidence of hypotension and related side effects, and there were fewer withdrawals due to adverse events.

DEPRESSION WITH ASSOCIATED ANXIETY

An estimated 60% to 90% of patients with depression also have symptoms of anxiety, and anxiety most commonly complicates persistent depression.[53] A community survey—Depression Research in European Society II (DEPRES II)—identified within a cohort of subjects with symptoms of depression, different types of depressed patient according to coexistent factors such as anxiety, chronic physical problems, sleep difficulties, and tiredness.[54] The patient type with depression and associated anxiety had the highest number of depression symptoms and experienced the most disruption of normal life, compared with other patient types.

Anxiety and confusion are often reported by elderly patients, particularly when depression is present. Comorbidity of depression and anxiety results in more severe symptoms of depression, reduced response to conventional therapy, and a poorer prognosis than depression without concomitant anxiety. An antidepressant that can improve symptoms of anxiety in elderly patients with depression is of particular use.

Dunbar[37] conducted a meta-analysis of randomized, double-blind studies of paroxetine versus active controls (amitriptyline, clomipramine, doxepin, mianserin) in 736 patients aged more than 65 years. Symptoms of anxiety associated with depression measured on the HAM-D psychic and somatic anxiety items were similarly improved with paroxetine or active comparator following 5 to 6 weeks of treatment. However, paroxetine was associated with significantly fewer sedative effects than the TCAs ($p \leq .05$). The efficacy of paroxetine (compared with placebo or active control) in improving anxiety associated with depression has also been demonstrated in studies not restricted to elderly patients, including a meta-analysis of more than 4500 subjects[55] and a 6-week, double-blind randomized study (N = 717) comparing paroxetine, imipramine, and placebo.[56]

CONCLUSIONS

Late-life depression presents a challenge to clinicians as it requires long-term treatment, often in the presence of concomitant medical illness of which anxiety is the most prevalent. The willingness of the patient to accept and comply with antidepressant treatment of an adequate dosage and for a sufficient period of time is a key determinant of antidepressant effectiveness and is largely dictated by tolerability. Both TCAs and SSRIs have demonstrated efficacy in late-life depression, but acceptable tolerability has been more difficult to achieve in older patients. Unlike TCAs, SSRIs are not associated with significant side effects in elderly patients, making SSRIs the most appropriate option for effective treatment of late-life depression. Within-class differences exist between SSRIs, which confer additional safety and tolerability advantages for paroxetine and fluvoxamine in particular.

Drug names: amitriptyline (Elavil and others), citalopram (Celexa), clomipramine (Anafranil and others), doxepin (Sinequan and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nortriptyline (Pamelor and others), paroxetine (Paxil), reboxetine (Vestra), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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Discussion

Therapy Choices for Late-Life Depression

Dr. Salzman: Fluvoxamine is not widely used in the United States to treat depression in the elderly. In the United States, the drug reputed to have the most GI side effects is sertraline. However, if you look at the one postmarketing study of fluoxetine versus sertraline carried out in 1990, the side effect profiles were similar *[Fisher S, et al. J Clin Psychiatry 1995;56:288–296]*.

It is worth noting that there are no data to support the idea that paroxetine has clinically relevant anticholinergic activity. There are 2 in vivo studies, one published by the Pittsburgh group *[Pollock BG, et al. Am J Psychiatry 1998;155:1110–1112]* and my own unpublished data that clearly show that paroxetine is not associated with meaningful anticholinergic blood levels in the elderly.

Dr. Sadavoy: There is a movement among payers, government, and others to see selective serotonin reuptake inhibitors (SSRIs) as all the same. What should we be saying about differentiation among the SSRIs?

Dr. Salzman: There are certainly data in young and middle-aged adults showing that if you don't respond to one SSRI you may respond to another. No such data exist in the elderly, and we need them. I suspect it is true that some elderly people will respond to one and not another.

Dr. Montgomery: I fail to see the logic of restricting the number of treatments so that only one SSRI is available on the formulary. It is unhelpful to the individual. I have enough experience with patients who fail to respond to fluoxetine but then respond to paroxetine, and vice versa, to know that we do not have evidence to justify this approach.

Dr. Salzman: I would add that we already have that model in medicine, taking the nonsteroidal anti-inflammatory drugs as an example. Although they act in the same way, any rheumatologist could tell you that there are differences among them, and they have to try a number to find the one that works in the patient.

Dr. Montgomery: We seem to have agreement that formularies should be open and include all other medications.

Dr. Thompson: Does the increase in blood pressure with venlafaxine cause any problems in the elderly?

Dr. Montgomery: The evidence of increased blood pressure comes exclusively from high-dose studies, over 200 mg, and the studies I reviewed used lower doses. I am not aware of data suggesting that older patients are more vulnerable to the blood pressure rises. You see an increase of 2 mm Hg against placebo with imipramine and other tricyclics, but you are looking at much higher rises, up to 5 mm Hg, with venlafaxine at doses higher than 300 mg.

Dr. Salzman: Hypertension is a heterogeneous response. There is no clinical experience, either open or controlled, on the elderly response.

Dr. Zisook: You didn't present any studies on bupropion. Is that used in Europe?

Dr. Montgomery: Bupropion was never licensed anywhere in Europe, and so we have no data on its efficacy overall. I am not aware of any placebo-controlled evidence of efficacy of bupropion in the elderly.

Dr. Zisook: In the United States, there are some older small studies, not terribly well done. One of the larger ones is an imipramine-controlled study that showed equivalency.

Dr. Salzman: My reading of the data and my sense of the American state of the art is that tricyclics are still considered to be effective. Some would argue that they are more effective than the SSRIs, but no one would say they are less effective. On a risk/benefit basis, there are greater risks with tricyclic antidepressants (TCAs) and, if the benefits are equally good, clearly you would use an SSRI first.

If you look at geriatric studies, most have final Hamilton Rating Scale for Depression (HAM-D) scores in the 12 to 13 range. Virtually none has final scores under 7 or 8, which suggests to me that the patients are partial responders in the clinical setting, although in a research setting they meet the criterion of a 50% reduction. When you look at the SSRI studies and TCA studies on the basis of the final HAM-D score rather than a percentage reduction in the score, there is an impression that the TCAs may do a little bit better.

Dr. Montgomery: Going along with that, in a meta-analysis, there is around a 1-point difference in favor of TCAs compared with SSRIs, but that is thought to be explained by sedative effects of TCAs on the sleep item, because the difference disappears if you exclude the 3 sleep items on the HAM-D.

Dr. Salzman: But we have to remember that we are talking about a difference based on the HAM-D score in a heterogeneous population. If we turn to clinical practice, we can see that clinicians in the United States are clearly voting for SSRIs in the elderly as in younger adults, because they work and they are safer. For back-up drugs, they are using nortriptyline or the secondary amines and venlafaxine. I would certainly recommend an SSRI first, but I would then go to nortriptyline or venlafaxine rather than a second SSRI.

Dr. Zisook: Depending on the clinical picture, I might consider bupropion as a second-line agent, although there are fewer data to support it.

Dr. Salzman: If there was a partial response, I would consider augmentation with bupropion or trazodone, rarely a benzodiazepine.

Dr. Zisook: What about lithium augmentation?

Dr. Salzman: I know the data well. Lithium augmentation has not been convincingly demonstrated in the elderly. In 6 double-blind studies, there is a 50% response rate and a 50% nonresponse rate, and the side effects of lithium in the elderly are a problem. There are better augmentation strategies.