Pharmacotherapy of Affective Disorders in Old Age

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Objective: To present a clinical guide for the selection of safe and effective pharmacological treatment for depressed geriatric patients.

Method: A review of the use of antidepressants in the elderly is presented based on clinical experience and a search of MEDLINE and PsychInfo data bases. Emphasis is placed on the following newer antidepressants: fluvoxamine, sertraline, paroxetine, nefazodone, venlafaxine, and moclobemide.

Results: With the advent of newer antidepressants, physicians have been given a wider range of generally safer antidepressant medications. Although these medications appear to have a more favourable side effect profile in elderly patients, this review is limited because there are few published studies of the use of these newer antidepressants in the elderly.

Conclusion: Depression is a common psychiatric problem in old age, but it can usually be treated successfully. Although the use of antidepressants in geriatric populations is more likely to be complicated by poorly tolerated side effects and drug interactions than in younger patients, this review should help clinicians use currently available medications to the best advantage of their geriatric patients.

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Key Words: elderly, antidepressants, selection of antidepressants, review, tricyclics, fluoxetine, fluvoxamine, sertraline, paroxetine, nefazodone, venlafaxine, moclobemide

Depression is a common psychiatric problem in old age. When strict DSM-III criteria are applied, approximately 3% of the elderly living in the community suffer from major depression (1,2); however, 15% to 20% of community-dwelling elderly have clinically significant depressive syndromes (3,4). Depressive disorders are prevalent in nursing homes (occurring between 2 and 6 times more frequently than among old people living in the community) (5) and in medical settings (11% to 13% major depression; 23% to 29% “minor” depression), where the diagnosis and treatment of depression are complicated by concurrent medical problems (6–9). Depression is also responsible for the majority of geriatric admissions to psychiatric services of general hospitals and acute care psychiatric facilities (10).

Geriatric depression is often difficult to recognize as patients tend initially to present with somatic complaints, anxiety, or loss of concentration and memory problems (11,12) rather than depressed mood. Depression is associated with high morbidity, causing more impairment in physical functioning (except for serious heart disease), more pain (except for arthritis), and more impairment in social functioning than most chronic medical conditions (13); depression is also associated with increased risk for suicide (14) and increased mortality from causes unrelated to suicide (15).

Major depression can usually be treated successfully in the elderly. Approximately 60% of elderly patients treated for an acute major depressive episode show clinical improvement during antidepressant drug trials of 6 to 12 weeks’ duration (16), and studies reporting on the one-year outcome of geriatric depressed inpatients indicate that 57% to 68% are well at follow-up (17–20). Although “minor” depressions (clinically significant depressive syndromes that do not meet the DSM-III-R criteria for major depression) are more prevalent than major depressions and have a significant impact on functioning and quality of life, geriatric research is still very much lacking in this area; studies on younger populations, however, seem to indicate that pharmacotherapy can help many of these patients (21,22). Similarly, depression complicating bereavement (23) or dementia (24), 2 common conditions in geriatric practice, can respond favourably to antidepressant therapy. Evidence is also mounting that depression which complicates chronic medical illnesses can also be treated successfully, with remission rates as high as 75% by 29 weeks of treatment (25). Clinicians should
Therefore remain optimistic when treating depressed elderly patients.

While the successful treatment of depression in the elderly usually results from a combination of psychotherapeutic, social, and medical interventions, this paper will focus on the pharmacological treatment of depressive disorders.

Clinical Guide for the Selection of Antidepressants for Geriatric Patients

Determining the best antidepressant treatment options for individual geriatric patients requires careful consideration of several clinical issues, which are listed in Table 1. Treatment strategies will vary according to the type of depression, from antidepressants for unipolar major depression, to mood stabilizers (which may have to be combined with an antidepressant) for bipolar illness, to electroconvulsive therapy (ECT) for delusional depression (26). If a rapid improvement in symptoms is required, such as in severe depression with refusal to eat or depressive stupor, ECT can literally be life-saving (27).

Reviewing the patient’s previous response to treatment helps us avoid medications that have not helped or were poorly tolerated and consider those which were beneficial. Many geriatric patients have had a previous good response to tricyclic antidepressants (TCAs), such as amitriptyline or imipramine, which may be too anticholinergic or hypotensive to be considered in old age. In this case, their active metabolites, nortriptyline or desipramine, or one of the newer antidepressants may be considered instead. Since most elderly patients have medical problems, it is important to select an antidepressant that is unlikely to complicate or worsen these problems. For example, we tend to avoid TCAs for patients who have cardiovascular problems or dementia.

Older adults are sensitive to the adverse effects of psychotropic drugs and eliminate these drugs more slowly as they age. Clinicians should choose antidepressants that will be well tolerated and unlikely to cause disastrous complications such as falls and fractures from hypotension or delirium from anticholinergic activity.

Each class of antidepressant comes with its own list of potential drug interactions, with monoamine oxidase inhibitors (MAOIs) having the longest list of potentially severe drug interactions. Since most of the elderly take drugs regularly for their medical problems, it is important to select an antidepressant that is unlikely to interact with these medications. Clinicians should also inquire about over-the-counter (OTC) medications that may have anticholinergic or sedating properties and about OTC nonsteroidal antiinflammatory drugs, particularly if lithium is being considered. TCAs also potentiate the effects of alcohol, and while abstinence is the best recommendation, patients who are unlikely to comply with this recommendation should be given antidepressants that are less likely to interact with alcohol, such as sertraline (28), paroxetine (29), or nefazodone (30).

TCAs and MAOIs (31) are much more lethal in overdose than selective serotonin reuptake inhibitors (SSRIs), reversible MAOIs (RIMAs), or serotonin noradrenaline reuptake inhibitors (SNRIs) and should be avoided if the risk for suicide is high. In geriatric practice, we tend to select drugs that have a reasonable elimination half-life in order to avoid prolonged side effects or drug interactions; for example, fluoxetine and its active metabolite norfluoxetine can cause drug interactions and side effects for a few weeks after its discontinuation, so there is a need for a washout period of at least one month when switching from fluoxetine to TCAs, MAOIs, or other SSRIs.

Drugs that have a unit dose smaller than the average therapeutic dose allow for a gradual titration toward the therapeutic dose from a low starting dose. This is necessary because there are large interindividual variations in dose-response range for the elderly (32). Some of the currently available SSRIs, for example, fluoxetine, paroxetine, and sertraline, were initially difficult to titrate for patients who needed very low doses, but smaller unit doses are now available.

The patient’s symptom profile should also be considered with the view of avoiding drugs that are more likely to worsen symptoms which the patient finds particularly troublesome. For example, SSRIs are more likely to cause nausea and

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worsen an already poor appetite, while TCAs are more likely to worsen an already preoccupying constipation. Drugs can also be selected on the basis that their particular side effect profile, such as sedation, will have a beneficial effect on the patient’s symptoms. This process of selection should not be followed to the detriment of more important considerations, however, such as overall side effect profile and tolerability.

The cost of medication is another practical consideration. It is obvious that compliance will be poor if the patient cannot afford the prescribed medication. Drugs that appear to cost little, however, such as TCAs, may be associated with high indirect costs such as those of the complications they cause (falls, cardiovascular and cognitive complications) and those associated with poor long-term compliance due to annoying side effects. The costs associated with relapses due to poor compliance (need for intensive treatment, hospitalization, and sometimes suicide) can be significantly higher than the savings achieved on drug costs.

Clinicians may also wish to consider the patient’s familial response to antidepressant treatment, considering treatments that were useful to first-degree relatives, including children, but this area has been poorly studied. In addition, the seasoned clinician will list symptoms that could later be misconstrued as side effects and document any “baseline” electrocardiogram (ECG) abnormality or postural hypotension prior to prescribing antidepressants.

Review of Major Classes of Antidepressants

TCAs

Among the TCAs, only desipramine and nortriptyline will be reviewed because they have a more favourable side effect profile: desipramine is the least anticholinergic of the tricyclics, and nortriptyline causes less orthostatic hypotension than imipramine or amitriptyline (33). All TCAs, including desipramine, have more anticholinergic activity than the newer antidepressants and are more likely to cause serious problems in the elderly, including significant impairments in psychomotor performance (34) that are not seen with SSRIs such as fluvoxamine or sertraline (28,34–36). When prescribing TCAs, clinicians need to monitor blood pressure for postural hypotension and to perform an ECG, remembering the cardiotoxicity of TCAs in “overdose.” Patients deficient in cytochrome enzyme P450 2D6, which metabolizes some TCAs, may have high serum levels at relatively low doses, but serum level monitoring is available to verify that therapeutic drug concentrations have been reached while remaining below toxic levels. TCAs can cause hyponatremia through inappropriate secretion of antidiuretic hormone (syndrome of inappropriate antidiuretic hormone [SIADH]), of which there are several case reports in the literature (37). TCAs interact with several drugs that are commonly prescribed to the elderly, including antihypertensives, anticholinergics, anticoagulants, and anticonvulsants. Clinically, we have also noted a lowering of glycemia in some of our diabetic elderly patients when TCAs are added.

The overall advantages of TCAs are their proven efficacy and low cost. Their multiple side effects, however, often lead to complications and premature discontinuation, an important problem for geriatric patients who need long-term treatment to avoid relapse or recurrence.

Desipramine. For geriatric outpatients, the usual starting dose of desipramine will be 25 mg/day, with weekly increases of 25 mg until limiting side effects or therapeutic effects occur. This titration allows clinicians to identify those patients who will tolerate and respond to only a low dose while proceeding at a reasonable pace towards a therapeutic dose for those who require higher doses. The therapeutic dose is usually 100 to 150 mg/day but can be as low as 25 mg/day and as high as 250 mg/day. With desipramine, patients are told to report postural dizziness, urinary retention, and eye pain immediately for prompt medical attention. Clinicians should watch for postural hypotension and occasional hypertension. Desipramine can cause tremors, agitation and insomnia, and may need to be prescribed in the morning.

Nortriptyline. Nortriptyline has been the most frequently studied antidepressant in elderly patients (16), including patients over the age of 80 (38) and patients who had strokes (39). For geriatric outpatients, the average starting dose of nortriptyline will be 25 mg/day, with weekly monitoring and increases of 10 mg until limiting side effects or therapeutic effects occur. Nortriptyline seems to have a therapeutic window, where blood levels below or above the therapeutic range are less efficacious. The same therapeutic window seems to apply to the elderly, but the dose range of the medication to obtain therapeutic blood levels again show great variability in this population, averaging between 60 mg/day and 90 mg/day, with a range from 25 to more than 100 mg/day.

MAOIs

MAOIs, particularly phenelzine, have proven efficacy in treating geriatric depression (40–42). Over the years, MAOIs have provided a useful alternative to TCAs, particularly for patients who could not tolerate their anticholinergic activity. MAOIs have also helped many patients suffering from treatment-resistant depression. Their most troublesome side effects include insomnia and postural hypotension, which can appear a few weeks after initiation of treatment. Less common but important side effects include neuropathy secondary to vitamin B6 deficiency, weight gain, and generalized edema. On a practical note, however, the most important problem with MAOIs is their potential to cause severe hyperadrenergic states with tyramine-containing foods (especially aged cheese) and potentially fatal reactions with several drugs including OTC cold and sinus remedies, asthma inhalants, meperidine, and sympathomimetic amines. The need for dietary restrictions, concerns about potential drug interactions, and lethality in overdose tend to limit their use because we now have several safer alternatives.
**SSRIs**

SSRIs currently available in Canada include fluoxetine, fluvoxamine, sertraline, and paroxetine. Generally speaking, the advantages of SSRIs over TCAs come from their more favourable side effect profile, causing less anticholinergic activity, orthostatic hypotension, arrhythmia, or tachycardia. In addition, SSRIs are relatively safe in case of overdose (43,44). In the most recent consensus report of the American Association for Geriatric Psychiatry on the diagnosis and treatment of late-life depression, Schneider presented an extensive review of controlled trials that included geriatric patients and concluded that the efficacy of SSRIs is equivalent to that of TCAs in elderly patients, with about 60% of patients responding to treatment (45). The side effect profile of SSRIs includes nausea, diarrhea, insomnia, headaches, agitation, anxiety, and sexual dysfunction. SSRIs also seem to have the potential to worsen Parkinsonism, although they do not consistently do so (46,47). As with TCAs and MAOIs, there have been several case reports of hyponatremia (SIADH) in geriatric patients treated with SSRIs (48,49), occasional reports of hypomania, and rare cases of seizures (50,51). Potential drug interactions of SSRIs come from their effect on the drug-metabolizing isoenzymes of the cytochrome P450 and will be reviewed separately, with each SSRI.

**Fluoxetine.** Fluoxetine was the first SSRI available in North America. Geriatric randomized clinical trials comparing fluoxetine with a number of different antidepressants show no significant difference in efficacy as measured at end point. One should note that many of these trials were too short in duration (4 to 6 weeks) to see the full therapeutic effect of these antidepressants in the elderly, explaining the rather high endpoint Hamilton Depression Rating Scale (HDRS) scores and low response rates in most of these studies. For example, a double-blind comparison of paroxetine (20 to 30 mg) and fluoxetine (20 to 40 mg) in 106 elderly outpatients (age 61 to 85 years) over a period of 6 weeks showed comparable efficacy but high endpoint HDRS scores of 20 and 23, respectively (52). Roose and others (53) studied 22 hospitalized elderly patients (average age 73 years) with severe unipolar depression (average HDRS score of 26) and heart disease who were treated with fluoxetine and compared the outcome with that of 42 comparable patients (average age 70 years and average HDRS score of 28) who were treated with nortriptyline. The intent-to-treat response rate was 67% for the nortriptyline group and only 23% for the fluoxetine group, but this nonrandomized trial was very short (4 to 6 weeks). Similarly, in a large geriatric trial (54), a double-blind comparison of fluoxetine 20 mg/day with placebo in 671 elderly outpatients (average age 68 years) showed relatively low response rates (44% with fluoxetine versus 32% with placebo) and remission rates (32% for fluoxetine and 19% for placebo), but the duration of the trial was short (6 weeks). An earlier double-blind trial comparing fluoxetine 20 mg with amitriptyline 75 mg over a period of 5 weeks in 28 geriatric inpatients (average age 68 years) showed significant improvements in HDRS scores relative to baseline values, with endpoint HDRS scores of 14 and 10 for the 2 drugs, respectively (55). Another relatively large trial compared fluoxetine with doxepin in 157 elderly depressed patients over a period of 6 weeks. Dropout rates were high, particularly for the doxepin group, and endpoint HDRS scores were 16 and 17, a significant improvement over baseline scores. Fluoxetine had fewer total side effects than doxepin (56). The issue of what constitutes a proper geriatric dose of fluoxetine remains controversial. Studies were done mostly with the fixed dose of 20 mg/day, but clinical experience suggests that many elderly patients will do best with lower doses or a longer interval (that is, every 2 days).

Side effects from fluoxetine are those typical of the SSRIs and include nervousness and anxiety, insomnia, and nausea, which are all common symptoms of depression in old age, creating confusion as to how to titrate the dosage, up or down. An added difficulty is that side effects may persist several days after the discontinuation of fluoxetine. In addition, there has been one well-documented case report of atrial fibrillation and bradycardia with fluoxetine in an elderly patient with cardiac disease (57), a case of bradycardia likely due to the potentiation of pimozide (58) and a case of delirium believed to be due to high serum total fluoxetine concentration (59).

Fluoxetine inhibits the cytochrome isoenzymes P450 2D6 and 2C19 and therefore can potentiate drugs that are metabolized by the same isoenzymes, namely, some antipsychotics, TCAs, citalopram, paroxetine, venlafaxine, metabolites of nefazodone and trazodone, barbiturates, β-blockers, codeine, dextromethorphan, ethylmorphine, and type 1C antiarrhythmics (60). Two cases of toxic reactions during the coadministration of fluoxetine and phenytoin have been reported by Jalil (61). Interactions between fluoxetine and other serotonergic drugs, such as lithium, tryptophan, and MAOIs, are potentially serious and can lead to the serotonergic syndrome because of synergistic pharmacodynamic effects (62). Fluoxetine may also weakly inhibit the isoenzyme 3A4, which metabolizes terfenadine, astemizole, carbamazepine, quinidine, and lidocaine, but there seem to be no clinical reports of clear drug interactions with drugs metabolized by this isoenzyme.

**Fluvoxamine.** Fluvoxamine is an SSRI that is generally well tolerated by the elderly as it has little or no effect on ECG and blood pressure and very little anticholinergic activity. It can be given in a single daily dose and has a reasonable elimination half-life of approximately 18 hours. Wakelin (63) analyzed data from 8 placebo-controlled studies that included 76 severely depressed patients between the ages of 60 and 71 years. Patients were randomly assigned to imipramine, fluvoxamine, or placebo and treated over a 4-week period. Both fluvoxamine and imipramine were superior to placebo in lowering HDRS scores from baseline and providing improvement scores on the Clinical Global Impression Scale, although the duration of treatment was very short. In a double-blind study of fluvoxamine (100 to 200 mg) versus mianserin (40 to 80 mg) in 57 elderly patients, both drugs
improved the symptoms of depression after 6 weeks of treatment, causing a statistically significant decrease in Montgomery-Asberg Depression Rating Scale (MADRS) scores compared with baseline (64). Rahman and others (65) studied 52 elderly patients (> 64 years) with major depressive episode and compared the efficacy of fluvoxamine (100 to 200 mg) with dothiepin (100 to 200 mg) over a period of 6 weeks. MADRS scores were improved by 63.5% in the fluvoxamine group and 60% in the dothiepin group.

Clinical experience suggests that fluvoxamine should be initiated at 50 mg/day for most geriatric patients, with weekly increments of 25 mg as tolerated in a single evening dose. The usual therapeutic dose of fluvoxamine in the elderly seems to be between 100 mg/day and 150 mg/day (range of 50 to 250 mg). This is the same dose range used in published open-label studies, including a large primary care study (66,67). The main side effects reported in these studies are nausea, dry mouth, constipation, drowsiness or sedation, headaches, and dizziness without significant postural hypotension (64,65). A recent analysis of 4843 elderly patients (65 to 97 years) enrolled worldwide in different trials with fluvoxamine (50 to 300 mg) showed that 46% of the patients reported at least one adverse event, and 18.5% discontinued participation in the study because of an adverse event. The most frequent side effects were nausea (15%), somnolence (6.5%), asthenia (6.5%), dry mouth (5%), insomnia (5%), dizziness (5%), constipation (5%), nervousness (4%), and headaches (4%) (68).

As with other SSRIs, there is a risk of serotonergic syndrome when combining SSRIs such as fluvoxamine with MAOIs or other serotonergic drugs, including lithium. There is a well-documented case report of the doubling of plasma levels of trimipramine when fluvoxamine was added (69), warranting some caution when adding fluvoxamine to TCAs before a proper wash out. Another case report documents the potentiation of theophylline by fluvoxamine (70). Other drugs such as warfarin, phenytoin, and tobutamide can also be affected by fluvoxamine, warranting close monitoring of serum drug levels and glycemia. One of our patients had a rapid lengthening in coagulation time when fluvoxamine was added. Because of the apparent inhibition of the isoenzymes 1A2 and 2C19, there may be interactions with propranolol, barbiturates, citalopram, clomipramine, imipramine, amitriptyline, clozapine, theophylline, and warfarin. Other possible interactions include bromazepam, carbamazepine, and other drugs that are metabolized through 3A4 (60,71).

Sertraline. Sertraline is an SSRI that is generally well tolerated by the elderly as it has little or no effect on ECG (72) and blood pressure and very little anticholinergic activity. It can be given in a single daily dose and has a reasonable elimination half-life of approximately 25 hours. The efficacy of sertraline seems to be comparable to that of other antidepressants in the limited geriatric studies available. Cohn and others (73) reported the results of an 8-week double-blind study of sertraline (50 to 150 mg/day, n = 161) and amitriptyline (50 to 150 mg/day, n = 80) in 241 elderly patients (mean age 70 years). There was no significant difference in the response rate between the 2 groups: 69% of the sertraline patients and 62.5% of the amitriptyline patients responded to treatment on the basis of the HDRS criterion, while 79% and 73%, respectively, were rated as improved on the Clinical Global Impression Scale (73). Another study comparing sertraline (50 to 150 mg) with nortriptyline (25 to 100 mg) in 208 elderly patients (average age 68 years) over a period of 12 weeks showed response rates of 83% and 80%, with endpoint HDRS scores of 10 and 11. Interestingly, sertraline produced more improvement on measures of attention and memory (74). Another study compared sertraline to fluoxetine in 236 elderly patients (average age 68 years) over a period of 12 weeks: both drugs had good efficacy, with endpoint HDRS scores of 11 for both groups (75).

The usual starting dose for sertraline is 50 mg orally in the morning or 25 mg in the very frail elderly. Now that 25-mg dosing is available, it seems easiest to titrate the dosage every 1 to 2 weeks by 25 mg as tolerated. Our clinical experience is that an effective geriatric dose is usually 50 to 100 mg/day (range 25 to 200 mg). Side effects are those typical of SSRIs (nausea, anorexia, insomnia), with loose stools or diarrhea indicating that the titration may be too rapid or the dose too high. Single doses of sertraline 50 mg were compared with amitriptyline 50 mg and placebo in 12 healthy elderly subjects to measure effects on a variety of cognitive and motor functions, including reaction time/driving, number recall, list learning, name–face association, facial recognition, and digit symbol test: performance after sertraline was significantly better than after amitriptyline and comparable to that after placebo (76).

Sertraline seems to be a less potent inhibitor of the hepatic isoenzyme P450 2D6 than fluoxetine or paroxetine (60,77) and should be less likely to affect the metabolism of some antipsychotics, TCAs, opiates, antiarrhythmics, and β-blockers. Specific studies examined the possible interaction profile of sertraline with haloperidol (78), atenolol (79), digoxin (80), carbamazepine (81), and phenytoin (82) and showed no clinically significant interactions with these drugs. Combining sertraline with MAOIs is not recommended, and there is a theoretical risk of causing a serotonergic syndrome when adding sertraline to other serotonergic drugs. While studies initially did not detect any increase in warfarin concentrations when sertraline was added, coagulation time can nevertheless increase, and monitoring is required.

Paroxetine. Paroxetine is a potent and selective inhibitor of serotonin reuptake that is also weakly anticholinergic, but it is less so than the TCAs. It seems to have little or no effect on ECG or blood pressure and is less toxic than TCAs in overdose. Paroxetine can be taken in a single daily dose and has a reasonable elimination half-life that is longer and more variable in the elderly than in younger adults (83,84).

In a French double-blind study comparing paroxetine (20 mg) with clomipramine (60 mg) in 83 elderly patients (mean age 71 years) for 5 weeks, both groups showed a
similar degree of improvement on all rating scales, with endpoint MADRS scores of 11 and 13, respectively (85). Paroxetine was also as efficacious as fluoxetine in the 6-week double-blind study of 106 depressed geriatric outpatients reported by Schone and Ludwig (86). In a 6-week study of 90 geriatric outpatients (mean age 72) in general practice, Hutchinson and others found paroxetine 30 mg to be as efficacious as amitriptyline 100 mg and to be better tolerated (87). Dorman compared paroxetine 30 mg with mianserin 60 mg in a 6-week double-blind study of 60 depressed outpatients over the age of 65. Both drugs were efficacious, with endpoint HDRS scores of 12 and 16, respectively, and with paroxetine having a more beneficial effect on sleep (88). Dunner and others studied 271 geriatric outpatients (mean age 68 years) suffering from depression and compared paroxetine (mean dose 23 mg) with doxepin (mean dose 105 mg) over a period of 6 weeks (89). Paroxetine was as effective as doxepin in alleviating depression, resulting in HDRS endpoint scores of 12 and 13, fewer anticholinergic side effects, but more reports of nausea and headache. Geretsegger and others (90) also studied a geriatric inpatient population (average age 71 years), comparing paroxetine (n = 44) with amitriptyline (n = 47) over a period of 6 weeks: paroxetine was as effective as amitriptyline, having a 64% response rate compared with 58% for amitriptyline. Guilbert and others (91) studied 79 elderly depressed patients (mean age 69 years) and compared paroxetine (30 mg) with clomipramine (75 mg) over a period of 6 weeks: the response rate with paroxetine (65%) was comparable to that of clomipramine (72%). Dunbar, in a metaanalysis of 10 studies of elderly patients, most of which have been described in this paper, concluded that paroxetine is as effective as active controls amitriptyline, clomipramine, doxepin, and mianserin (92).

Clinical use of paroxetine indicates that the average geriatric therapeutic dose is approximately 20 mg/day and probably less in very old (over 80 years of age), debilitated, and frail elderly patients. The recent addition of the 10- to 20-mg tablets of paroxetine will allow for a gradual titration starting at 10 mg for most elderly with the possibility of increasing the dose by 5 mg at regular intervals (every 2 weeks, since steady states take 7 to 14 days) until there is a satisfactory response or unacceptable side effects. The positive effects of paroxetine on sleep and anxiety are useful clinically, but paroxetine’s mild anticholinergic activity combined with its nonlinear pharmacokinetics (93) can be problematic for some geriatric patients. The side effects of paroxetine are similar to those of other SSRIs: nausea, diarrhea, insomnia, dry mouth, nervousness, sedation, and sexual dysfunction.

Paroxetine strongly inhibits the isoenzyme P450 3A4 and can potentiate the psychomotor effects of triazolam, alprazolam, and diazepam; the manufacturer recommends substantial reduction in dosage if these benzodiazepines are combined with nefazodone. Other potential drug interactions include nonsedating antihistamines (terfenadine, astemizole, loratadine), calcium channel blockers (nifedipine, diltiazem, verapamil), steroids, macrolide antibiotics (erythromycin), and quinidine, all metabolized by the same isoenzyme (77). Nefazodone does not seem to inhibit the P450 1A2 isoenzyme and is a very weak inhibitor of P450 2D6. The manufacturer does not recommend combining nefazodone with MAOIs.

**Nefazodone.** Nefazodone is a relatively new antidepressant that not only blocks serotonin reuptake but also blocks 5-HT1 receptors and, to a lesser extent, the 5-HT2C receptors. There are no published studies of nefazodone in the elderly at this time; most of the information available, therefore, has to be derived from studies on younger populations. The following information is derived from Bristol-Myers Squibb’s submission of a new drug application to the Federal Drug Agency (96). Nefazodone has a short elimination half-life, minimal anticholinergic activity, no apparent arrhythmogenic effect, and less toxicity than TCAs in overdose. Nefazodone does have some mild α-adrenergic effects that can lead to a lowering of blood pressure. Most commonly reported side effects include dry mouth (7.5%), somnolence (5.8%), dizziness (5.6%), lightheadedness (4.2%), constipation (3.3%), blurred vision (3.2%), and postural hypotension (2.6%). Nefazodone does not appear to cause problems of sexual dysfunction encountered with TCAs and SSRIs and seems to provide early positive effects on sleep. A pharmacokinetics study of nefazodone (97) shows that the same dose of nefazodone gives a greater area under the curve and greater systemic exposure in the elderly compared with younger subjects. The same study also reports nonlinear pharmacokinetics. In younger patients, nefazodone was found to be as efficacious as imipramine (98).

Our clinical experience to date suggests starting with 50 mg twice daily in the elderly, expecting the therapeutic geriatric dose to be between 200 mg/day and 400 mg/day.

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**Venlafaxine.** Venlafaxine is a new antidepressant that blocks the reuptake of noradrenaline and serotonin and weakly inhibits dopamine reuptake. It has a short elimination half-life of a few hours and an active metabolite that has a longer but still reasonable half-life. Like many of the newer antidepressants, it presents a more favourable side effect profile than the tricyclics, particularly with regard to anticholinergic, antihistaminic, and α-adrenergic side effects, and is less toxic in overdose (99).

An 8-week, randomized, double-blind comparison of the efficacy and safety of venlafaxine (mean dose 112 mg) with fluoxetine (20 mg) in 314 outpatients with major depression
included a few patients over the age of 65. Efficacy was comparable, and the side effects of venlafaxine included nausea, headache, dry mouth, insomnia, sweating, anxiety, tiredness, palpitation, and tremor. Overall, both drugs were well tolerated, venlafaxine causing more nausea (28%) and anticholinergic-type side effects (15%) than fluoxetine (100%). Clerc and others (101) compared venlafaxine and fluoxetine in 68 inpatients suffering from severe major depression and melancholia over 6 weeks: total scores for MADRS and HDRS were significantly lower in the venlafaxine group at weeks 4 and 6, and overall tolerance was similar, with the same side effect profile as reported previously.

Clinical experience to date indicates quite a bit of variability in what constitutes a therapeutic dose in the elderly, ranging from as little as 37.5 mg/day to the maximum recommended dose of 375 mg/day. In a 12-month, open-label clinical trial of venlafaxine in 58 depressed patients aged 65 or older, the mean dose was 114 mg/day (SD 59 mg), and 2 patients experienced elevated blood pressures that were judged to be probably drug-related (102). There is a well-documented dose-dependent increase in blood pressure with venlafaxine: in the studies, 13% of those taking over 300 mg/day had a small but significant increase in blood pressure (103). Clinicians should watch for possible increases in blood pressure and pulse, particularly for geriatric patients who have concurrent hypertension or cardiovascular disease. In addition to the side effects reported earlier, somnolence, dizziness, and abnormal ejaculation can occur.

Venlafaxine weakly inhibits the isoenzymes 2D6, 1A2, 2C19, and 3A, and therefore drug interactions are less likely than with SSRIs (77). It appears, however, that cimetidine does increase venlafaxine serum levels. Combinations with MAOIs are not recommended.

Moclobemide. Moclobemide is a reversible and selective inhibitor of monoamine oxidase of the isoenzyme A, is well tolerated in the elderly, and has a favourable side effect profile compared with TCAs. It appears to be safe in overdosage (104). A number of small clinical trials looked at the efficacy of moclobemide in geriatric populations. Pancheri and others (105), in a double-blind study of 183 elderly patients with major depression and cognitive decline: HDRS scores dropped from 23.4 ± 5.4 to 12.9 (52% response rate, significantly more than for patients treated with placebo), and Mini-Mental State Examination (MMSE) scores improved, but no more than for the placebo group (24). In the same study, an additional 511 patients had dementia and depressive symptoms (476 had DSM-III major depression): the moclobemide group showed significantly greater improvement in depressive symptomatology (HDRS dropped from 24.5 ± 5.3 to 11.9) and on MMSE (P < 0.05) than the placebo group. Overall, moclobemide was well tolerated, with dizziness, tiredness, and nausea slightly more frequent in the moclobemide group (24).

Initial geriatric doses of 100 to 150 mg twice a day are usually well tolerated in the elderly with gradual titration to the maximum recommended dose of 600 mg/day. No dietary precautions are necessary except perhaps avoiding large quantities of aged cheese (> 200 g) and “Marmite” (> 70 g). The manufacturer recommends taking moclobemide after meals to minimize the possibility of a tyramine reaction. Clinicians should advise their patients to avoid wine and cheese parties where they might consume large quantities of aged cheese. The most common side effects of moclobemide are headaches, insomnia, dizziness, nausea, and sedation.

Cimetidine inhibits the metabolism of moclobemide, and dosage should be reduced by 50% if combined. Serious side effects occurred when moclobemide was combined with clomipramine, and the manufacturer recommends avoiding combinations with TCAs. There are possible interactions with meperidine, dextromethorphan, and medications containing phenylephrine or other sympathomimetics such as OTC cold remedies and weight-reducing agents. Studies with metoprolol produced a slight decrease of blood pressure when moclobemide was added, and there may be a slight increase in extrapyramidal symptoms when combined with antipsychotics.

Conclusion

The use of antidepressants in geriatric populations is more likely to be complicated by poorly tolerated side effects and drug interactions than in younger patients. The newer antidepressants, however, seem to have a more favourable side effect profile for most of our geriatric patients. The expanded number of available antidepressants has allowed clinicians to treat many patients who could not tolerate TCAs or MAOIs in old age, resulting in the successful resolution of their
depressive symptoms. This review should help clinicians use currently available antidepressants to the best advantage of their geriatric patients.

Clinical Implications

- The majority of elderly patients suffering from major depression can be treated successfully with the judicious selection and careful use of currently available antidepressant treatments.
- Newer antidepressants appear to have a more favourable side effect profile for geriatric patients, particularly in regard to cardiovascular and cognitive side effects.
- All classes of antidepressants, particularly the SSRIs, have been associated with potential interactions with drugs that the elderly commonly take. A careful review of concurrent treatment, considering potential drug interactions, is an essential part of treatment selection in the elderly.

Limitations

- There are few published studies on the use of newer antidepressants in treating depressed elderly patients.
- Geriatric patients who are very old, medically ill, and those who take multiple concurrent medications are usually excluded from geriatric studies, which limits generalization to typical geriatric populations.
- The author based her recommendations on clinical experience gathered over the last 17 years with elderly patients treated in the geriatric psychiatry acute care services of a specialty psychiatry hospital. The readers may deal with a different mix of geriatric patients in their practice.

References


Résultats : Grâce à la commercialisation de nouveaux antidépresseurs, les médecins disposent d’un plus large éventail de médicaments, qui sont en général plus sûrs, pour lutter contre la dépression. Bien que ces médicaments semblent posséder un profil d’effets secondaires plus favorable chez les patients âgés, le présent examen est limité par le peu d’études publiées sur le recours à ces nouveaux antidépresseurs chez les personnes âgées.

Conclusion : La dépression est un problème psychiatrique fréquent au cours de la vieillesse, mais on réussit habituellement à la traiter. Bien que le recours aux antidépresseurs dans les populations gériatriques risque d’être compliqué par des effets secondaires et des interactions médicamenteuses moins bien tolérés que par les patients plus jeunes, cet examen devrait aider les cliniciens à utiliser les médicaments actuellement offerts au mieux des intérêts de leurs patients gériatriques.

Réséumé

Objectif : Présenter un guide clinique de sélection d’un traitement pharmacologique sûr et efficace à l’intention des patients gériatriques déprimés.


Conclusion : La dépression est un problème psychiatrique fréquent au cours de la vieillesse, mais on réussit habituellement à la traiter. Bien que le recours aux antidépresseurs dans les populations gériatriques risque d’être compliqué par des effets secondaires et des interactions médicamenteuses moins bien tolérés que par les patients plus jeunes, cet examen devrait aider les cliniciens à utiliser les médicaments actuellement offerts au mieux des intérêts de leurs patients gériatriques.