Special Issues in the Management of Depression in Older Patients

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Major depressive disorder is frequently undiagnosed and untreated in older patients. Grief, pain, sleep issues, concurrent medications, altered physiology, and the presence of comorbid medical and psychiatric conditions can complicate the management of depression in older patients. Remission should be the goal of therapy in treating depression in the elderly, just as it is in younger patients, to maximize the impact of treatment on quality of life. Managing depression in older patients can be done effectively with the antidepressant therapies currently available, including selective serotonin reuptake inhibitors (SSRIs), venlafaxine, and mirtazapine. Comorbid medical conditions, which are common among older patients, can have a significant impact on depression and vice versa. Antidepressant therapy with SSRIs has demonstrated efficacy and tolerability in patients at high risk for cardiovascular events and stroke and in those with vascular dementia or Alzheimer’s disease. Care should be taken to choose antidepressants with no or minimal effects on glucose levels in patients with diabetes. In addition, venlafaxine has demonstrated beneficial effects on the relief of the pain of diabetic neuropathy. Venlafaxine, mirtazapine, and the SSRIs have demonstrated efficacy and tolerability in older patients, while tricyclic antidepressants have also demonstrated efficacy; however, tolerability can be a problem. Depression is not a natural part of the aging process, as some still believe. The review of current data indicates that the goal of management can and should be full remission. Further, the use of newer agents is safe and effective in this population, as long as one considers the pharmacokinetics and pharmacodynamic properties and inherent biological differences in the elderly population when selecting appropriate therapy.

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Clinical Implications

- High morbidity and mortality are consequences of underrecognized or undertreated depression in older adults who are particularly prone to completed suicide or self-neglect. Therefore, remission should be the ultimate goal of therapy in the treatment of older patients, just as it is for younger patients.
- Complicating factors, for example, grief, pain, sleep issues, concurrent medications, altered physiology, and the presence of comorbid medical and psychiatric conditions, should be considered when managing depression in older patient.
- Antidepressant therapies, including selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine, are effective in the management of depression in older patients. Electroconvulsive therapy is a useful intervention in medication-resistant, medication-intolerant, or severely suicidal patients.

Limitations

- This is a narrative review.
- Few trials have examined the long-term efficacy and safety of antidepressant therapies in older patients with depression.
- More data are needed on the effects of antidepressant therapies on comorbid medical conditions such as cardiovascular disease, stroke, diabetes, and Alzheimer’s disease.

Key Words: elderly, older, antidepressant therapy, remission, selective serotonin reuptake inhibitors, serotonin norepinephrine reuptake inhibitors, cardiovascular disease, stroke, diabetes, Alzheimer’s disease, vascular dementia
In North America, the health care of people aged 65 years and over continues to emerge as an important issue. In Canada, Statistics Canada predicts that this group will grow from 12.69% in 2001 to 18.85% of the population in 2021 (1). US population estimates show similar trends, with an increase from 6.8% in 1940 to 12.6% in 2002 to an estimated 16.5% in 2020 (2).

Although common, depression either is frequently not identified among older patients (2) or is attributed to the normal aging process. In general practice, physicians were aware of depression in only 51% of depressed elderly patients (3). Recognition among nursing home residents was even lower, with staff recognizing only 37% to 45% of cases diagnosed by psychiatrists (4).

The prevalence of major depressive disorder (MDD) in older individuals (65 to 100 years) in the community is estimated at 4.4% in women and 2.7% in men (5). Studies conducted in 1988 suggest that current and lifetime prevalence of MDD in later life is significantly lower than at other ages. However, these studies did not go into detail regarding living conditions and other issues for the subjects (6,7). The rate of depression is higher in elderly people living alone, in those who require assistance with the activities of daily living, and in urban vs rural residents (8,9). Several studies have found rates of depression of 13.5% to 14.4% among older individuals receiving home care (10), nursing home residents (4), and general hospital inpatients (11). In addition, minor depression (16.8%) and significant depressive symptomatology (44.2%) were very common in a survey of nursing home residents (4).

MDD and depressive symptoms have been reported to increase the risk of mortality among elderly subjects by 1.5 to 2.0 times that of subjects without depression (12–15).

This review updates what is known about the treatment of depression to full remission in the older population, focusing on randomized clinical trials available from January 2000 through April 2003.

Issues in the Management of Depression in Older Patients

A study of the natural history of late-life depression found that long-term outcomes are poor (16). Over the 6 years of follow-up, the average symptom severity of patients with depression remained above the 85th percentile of the population average. Symptoms were short-lived in only 14%, remission was achieved in 23%, an unfavourable but fluctuating course existed in 44%, and a severe chronic course in 32%. Individuals with subthreshold disorders had the best outcome, followed by those with MDD, dysthmic disorder, and double depression. However, the prognosis of subthreshold disorders was unfavourable in most cases (16).

Depressive symptoms are frequently complicated by other factors, such as grief, pain, sleep, medication, poor energy owing to medical illness, or dementia. These factors lead to the underdetection of depression and to its undertreatment. Evidence suggests that only about 10% to 38% of elderly patients with depression receive antidepressants (3,5,10). Antidepressant use was lower among elderly suffering from depression in the community (4.2%), compared with those in institutions (36.0%), in a Canadian study published in 1999 (17). In surveys of medication use among older individuals, antidepressants were being used by only 2.2% to 4.1% of those who lived in the community and by 3.6% to 16.5% of those in institutions (17,18). When antidepressants were used, one-third to two-thirds of older patients received dosages that were lower than those recommended for treatment of depression (10,18).

The management of older patients with depression must also consider the presence of comorbid medical and psychiatric conditions. These may contribute to depressive illness, but depressive disorders are not a consequence of aging (19). Studies have found a relatively high rate of comorbid anxiety disorders in elderly individuals with depression, with rates between 23% and 48%. In elderly subjects, this is associated with more severe depressive illness (20,21). In addition, elderly patients with depression are likely at a high risk of developing progressive dementia. Even when maintained on a regimen of full-dosage antidepressant medication, elderly patients with psychotic depression are at greater risk of relapse or recurrence than their counterparts without psychosis. They also have a higher risk of recurrence following discontinuation of therapy. However, it has been shown that the vast majority of elderly patients who experienced a recurrence responded to reinstated treatment (22,23). These findings suggest the importance of long-term therapy in these patients (maintenance pharmacotherapy for at least 2 years) (24). Older individuals with cognitive impairment at baseline do not necessarily reach normal levels of performance, particularly in memory and executive functions, after treatment of late-life depression (25).

Pharmacokinetic Considerations

The use of antidepressants in older patients can be complicated by several factors. Older individuals use multiple medications (2 or more prescription drugs) 3 times more frequently than younger persons, increasing the potential for interactions (26). Age-related alterations in physiology can result in variable plasma drug concentrations, which may increase the number of adverse events, and the elderly may be more sensitive to adverse events (19,27). Aging is associated with several neuroendocrine changes, including alterations in monoamine oxidases, noradrenergic neurons, dopaminergic neurons and concentrations, cholinergic neurons and...
receptors, adrenocorticotropic hormone concentration and function, and serotonin receptors and concentrations (28).

Recommended initial dosages are lower for the elderly for all antidepressants, and increases should be slow and individualized (19,27). The pharmacokinetics of some of the selective serotonin reuptake inhibitors (SSRIs) may be altered in older patients, and it is recommended that dosages be adjusted in these patients (27). Lower dosages should be used for citalopram and for paroxetine (29,30). Medical conditions can affect drug elimination, which is decreased in patients with hepatic (citalopram, fluoxetine, fluvoxamine, sertraline) or renal (paroxetine) impairment (29,30).

Suicide Risk

The risk of suicide demonstrates the need for early geriatric psychiatric assessments and vigorous treatment protocols. Among elderly depression patients who had committed suicide, 80% of patients had no psychiatric referral, 87% were untreated, and of the 13% who were taking antidepressant medication, none were on newer and safer agents (31). Suicidal feelings are high among individuals aged 85 years or over with mental disorders, with 30% believing “life was not worth living” and 10% having thought of taking their own life (32). Among women who felt life was not worth living, the 3-year mortality rate was 3 times that of women without these feelings (43% vs 14%, respectively). Correlates of suicide include perceived poor health, poor sleep quality, and lack of a confidant. There is also a strong association with deliberate self-poisoning using benzodiazepine in the elderly (33,34).

Management of Depression in Older Patients

Remission is the Goal of Therapy

Like younger patients with depression, older patients should be treated to remission rather than simply response. Remission maximizes the impact of treatment on quality of life domains (35). In 100 older patients with recurrent MDD, those who achieved remission with antidepressant treatment showed significantly ($P < 0.001$) greater improvement than either partial responders or nonresponders on both emotional and physical quality of life measures.

Several factors should be included in an ideal elderly depression treatment program. When treating older patients, a strong doctor–patient relationship is essential, and interventions should include environmental, social, recreational, supportive, and spiritual programs, as well as psychoeducational programs that include the patient’s family. Antidepressant medications at appropriate dosages and durations are the mainstay of therapy as in younger patients, and ECT is recommended for severe cases.

Antidepressant Therapy

Evidence suggests that older patients will benefit from antidepressant therapy as much as younger adults but that improvements may occur more slowly (36). Remission rates during acute-phase therapy were 78.4% in 116 elderly patients (mean age 67.9 years) and 69.6% in 214 midlife patients (mean age 38.5 years). The midlife patients had faster reductions of Hamilton Depression Rating Scale (HDRS) scores. Relapse rates were higher among the elderly patients (15.5% vs 6.7% of the midlife patients), but ultimately, more of the late-life patients (66.2% vs 57.0% of the midlife patients) recovered fully.

A recent metaanalysis suggested that most antidepressants evaluated in older people are effective, with relatively small numbers needed to treat (NNT), which are similar to those reported in younger patients. However, the analysis for fluoxetine indicated relatively high NNT. The confidence intervals (CIs) were extremely wide for many trials, suggesting inadequate sample sizes (37). A Cochrane database review included 17 trials of antidepressant use in older patients with depression (38). The standardized effect sizes were comparable for tricyclic antidepressants (TCAs) (OR 0.32; 95%CI, 0.21 to 0.47), SSRIs (OR 0.51; 95%CI, 0.36 to 0.72), and monamine oxidase inhibitors (MAOIs) (OR 0.17; 95%CI, 0.07 to 0.39). At least 6 weeks of treatment were recommended to achieve optimal therapeutic effect.

In the recent efficacy trials shown in Table 1, most of the studies demonstrated equivalent efficacy between various SSRIs and TCAs. Three trials compared an SSRI and a TCA: there were no differences in remission rates between the groups, with the exception of a significantly higher remission rate with nortriptyline, compared with citalopram (39–41). There were no significant differences in remission rates with venlafaxine and nortriptyline (71% vs 70%, respectively). Among the SSRIs, no differences in remission rates were seen in comparisons between sertraline and fluoxetine and between paroxetine and fluoxetine (42,43). Remission rates were 45% to 60% with these agents. Similar results were seen in a comparison of mirtazapine and paroxetine, with remission rates of 38% and 29%, respectively (44). However, time to response was faster with mirtazapine (26 and 40 days, respectively; $P = 0.016$). Bupropion has also demonstrated efficacy and safety in older patients, comparable with paroxetine (45).

In a metaanalysis of 8 double-blind, randomized controlled trials (RCTs) of venlafaxine, SSRIs, or placebo, no significant age-by-treatment interactions were detected (Figure 1) (46). Regardless of age, onset of remission was more rapid during venlafaxine therapy, with remission rates significantly higher than during SSRI therapy (remission rates at week 8: venlafaxine, 40% to 55% vs SSRI, 31% to 37%; $P < 0.05$). In the subgroup of patients aged 65 years or over, remission rates...
Table 1 Remission rates in clinical trials in older patients (Intent to treat, LOCF except where noted)

<table>
<thead>
<tr>
<th>Study details</th>
<th>(Age in years)</th>
<th>Treatment and dosage, mg</th>
<th>Number completed/enrolled (%)</th>
<th>Onset</th>
<th>Response, % Decrease ≥ 50% on HDRS</th>
<th>Remission, %</th>
<th>Cognition</th>
<th>Adverse events</th>
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<tbody>
<tr>
<td>Bondareff and others (39)</td>
<td>(≥ 60)</td>
<td>SER 50–150; NOR 25–100</td>
<td>74/105 (70.5)</td>
<td>70/105 (66.7)</td>
<td>NR</td>
<td>HDRS24 ≤ 7</td>
<td>52.9&lt;sup&gt;a&lt;/sup&gt;</td>
<td>MMSE, SLT, DSST</td>
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<td></td>
<td>12 weeks; HDRS24 = 24.8; stable comorbidity eligible</td>
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<td>41.3, ns&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>Navarro and others (40)</td>
<td>(≥ 60)</td>
<td>CIT 30–40; NOR 50–100</td>
<td>24/29 (82.8)</td>
<td>25/28 (89.3)</td>
<td>HDRS vs baseline onset at 4 weeks</td>
<td>HDRS ≤ 7</td>
<td>NR</td>
<td>69.0, 89.3&lt;sup&gt;b&lt;/sup&gt;</td>
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<td>12 weeks; HDRS&lt;sub&gt;17&lt;/sub&gt; = 6.8; single-blind, stable comorbidity eligible</td>
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<td>Gasto and others (112)</td>
<td>(≥ 65)</td>
<td>VEN 225–300; NOR 50–100</td>
<td>29/31 (93.5)</td>
<td>28/30 (93.3)</td>
<td>NR</td>
<td>HDRS&lt;sub&gt;17&lt;/sub&gt;</td>
<td>71.0</td>
<td>70.0, ns</td>
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<td>6 months; HDRS&lt;sub&gt;17&lt;/sub&gt; = 26.5, single-blind, stable comorbidity eligible</td>
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<td>Entsuah and others (46)</td>
<td>(≥ 65)</td>
<td>VEN; SSRIs&lt;sup&gt;c&lt;/sup&gt;; PBO (55–64)</td>
<td>—/38</td>
<td>—/36</td>
<td>Remission significant vs PBO</td>
<td>HDRS21 ≤ 10</td>
<td>NR</td>
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<td>Pooled data; 6–12 weeks; HDRS&lt;sub&gt;21&lt;/sub&gt; = 26; comorbidity NR</td>
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<td>Newhouse and others (42)</td>
<td>(≥ 60)</td>
<td>SER 50–100; FLX 20–40</td>
<td>80/117 (68.0)</td>
<td>80/119 (67.0)</td>
<td>CGI vs baseline at 2 weeks</td>
<td>HDRS&lt;sub&gt;24&lt;/sub&gt; ≤ 10</td>
<td>45</td>
<td>46, ns</td>
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<td>12 weeks; HDRS24 = 25.1; no clinically significant medical problems</td>
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<td>Cassano and others (43)</td>
<td>(≥ 65)</td>
<td>PRX 20–40; FLX 20–60</td>
<td>73/123 (59.4)</td>
<td>74/119 (62.2)</td>
<td>HDRS vs baseline</td>
<td>CGI-I 1 or 2</td>
<td>HDRS&lt;sub&gt;21&lt;/sub&gt; &lt; 10</td>
<td>60</td>
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<td>1 year; HDRS&lt;sub&gt;21&lt;/sub&gt; = 24; stable comorbidity eligible</td>
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<td>Schatzberg and others (39)</td>
<td>(≥ 65)</td>
<td>MIR 15–45; PRX 10–40</td>
<td>99/128 (77.3)</td>
<td>87/126 (69.0)</td>
<td>Response 26 days</td>
<td>HDRS&lt;sub&gt;17&lt;/sub&gt; ≤ 7</td>
<td>38</td>
<td>29, ns</td>
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<td>8 weeks; HDRS&lt;sub&gt;17&lt;/sub&gt; = 22.3; stable comorbidity eligible</td>
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<td>**Asterisks indicate significant differences between treatments: * P ≤ 0.05; ** P ≤ 0.01; ns = not significant (P &gt; 0.05).</td>
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<td>SSRIs included FLX, FLV, PRX.</td>
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CGI = Clinical Global Impression Scale; CIT = citalopram; DES = desipramine; DSST = Digit Symbol Substitution Test; FLV = fluvoxamine; FLX = fluoxetine; HDRS = Hamilton Depression Rating Scale; IMP = imipramine; LOCF = last observation carried forward; LOE = loss of efficacy; MIR = mirtazapine; MMSE = Mini-Mental State Exam; NOR = nortriptyline; NR = not reported; PBO, placebo; PRX = paroxetine; SE = side effect; SER = sertraline; SLT = Shopping List Task; SSRI = selective serotonin reuptake inhibitor; VEN = venlafaxine
with venlafaxine were almost 30% higher than with SSRIs; however, the number of patients in this group was too small to show statistical significance.

Few data are available on antidepressant therapy in the very old patient. In a small placebo-controlled trial in very old patients (aged 80 years or over) in long-term care facilities, paroxetine was not significantly better than placebo but was associated with 2 cases of delirium (47).

Recent data on the prevention of relapse or recurrence in older patients demonstrates the efficacy of ongoing antidepressant therapy (48,49). Results are similar to those in younger patients, where ongoing SSRI or venlafaxine therapy are associated with reductions in relapse rates of about 30% to 50% (50–54). In a small, open, follow-up study in older patients, paroxetine and nortriptyline demonstrated similar efficacy in relapse prevention and time to relapse (49).

Long-term treatment with citalopram effectively reduced recurrence after sustained response in a double-blind, placebo-controlled trial in older patients. At 48 weeks, about one-half as many patients in the citalopram group had a recurrence (32%), compared with the placebo group (67%; \( P < 0.0001 \)) (48).

**Psychotherapy**

Evidence in elderly patients indicates that the combination of both antidepressant and psychotherapy was more effective than either therapy alone, the combination was more effective than the TCA but similar to the CBT only (55). Maintenance therapy with interpersonal psychotherapy (IPT) alone or in combination with paroxetine, has been shown to protect against recurrence of MDD in elderly patients (56). In an older study, combined treatment with nortriptyline and IPT was superior to IPT and placebo and showed a trend to superior efficacy over nortriptyline monotherapy (\( P = 0.06 \)) (58). Recurrence rates over 3 years were as follows: nortriptyline and IPT, 20% (95%CI, 4% to 36%); nortriptyline and medication clinic visits, 43% (95%CI, 25% to 61%); IPT and placebo, 64% (95%CI, 45% to 83%); and placebo and medication clinic visits, 90% (95%CI, 79% to 100%).

The combination of psychotherapy and medication has also been shown to maintain social adjustment better than either treatment alone and to improve both the duration and quality of wellness (57).

**Augmentation Strategies**

Lithium has demonstrated some benefits when used as augmentation to antidepressants in older patients. In a study in 50 elderly patients, relapse rates were significantly greater in patients taking antidepressants alone, compared with those taking additional low-dosage lithium after both 6 months (17% vs 0%, respectively) and 2 years (33% vs 4%, respectively) of treatment (59). A review of lithium augmentation in patients with depression reported a response rate of at least 50% after 1 to 2 weeks (60). However, it is recommended that
special care be taken when treating elderly patients, because of a higher risk of adverse effects.

Electroconvulsive Therapy (ECT)
Although patients who receive ECT tend to be older than those who do not (61,62), there are few good studies of the use of ECT in the elderly population. ECT was reported to be effective in elderly patients in an older, open, nonrandomized trial (63). Open follow-up of 52 consecutive older patients treated with ECT reported clinical improvement in 79%, with a 38% incidence of adverse reactions (64). In a prospective follow-up study of 239 elderly patients, ECT was associated with a shorter time to remission. Safety has been generally acceptable, with only minor complications during ECT among older patients with preexisting cardiovascular disease (65); falls are reported with increasing frequency as the number of treatments increases (62).

Cognitive Effects of Antidepressant Therapy
Both aging and depression itself have been associated with impairments in cognitive functioning. Older patients with depression have demonstrated impaired executive functioning, compared with younger patients with depression or healthy elderly individuals without depression (66). Both older and younger individuals with depression perform significantly worse on measures of selective and sustained attention.

Several studies have demonstrated improvements in various measures of cognitive functioning among older patients treated with antidepressants. In a study specifically designed to assess the cognitive effects of venlafaxine, open therapy was associated with significant improvements in cognitive measures (67). The SSRIs sertraline, paroxetine, and fluoxetine have demonstrated significant improvements in cognitive functioning; however, sertraline and paroxetine demonstrated an advantage over fluoxetine on some measures of memory function (Table 1) (42,43). In contrast, a small study in very old (aged 80 years and over) patients found a risk of adverse cognitive effects with paroxetine: 2 patients developed delirium, and others were more likely to experience decreases in Mini-Mental State Exam (MMSE) scores (47).

Compared with nortriptyline, sertraline offered an advantage in measures of cognitive function, memory, and quality of life (39). In fact, nortriptyline had mildly negative effects on cognitive measures, which may reflect the vulnerability of older patients to the central anticholinergic activity of TCAs. The detrimental effects of TCAs on cognition have been well documented in several reviews (68,69). In patients with MDD and existing cognitive impairment, open treatment with sertraline was associated with minor improvements in cognition among responders and mild deterioration among nonresponders (70).

Managing Depression in Older Patients With Comorbid Conditions
Older patients often have significant medical comorbidity, and evidence suggests a significant association with depressive symptoms (71,72). Depression can have an important impact on the outcome of medical conditions and vice versa. Among community-dwelling older persons, the presence of a medical condition was associated with higher depressive symptom scores, which increased with increasing number of comorbid medical conditions (71).

A Cochrane database review of antidepressants in medically ill patients over age 16 years included 18 studies covering 838 patients with a range of physical diseases (cancer; 2; diabetes, 1; head injury, 1; heart, 1; HIV, 5; lung, 1; multiple sclerosis, 1; renal, 1; stroke, 3; mixed, 2) (73). Patients treated with antidepressants were significantly more likely to improve than those given placebo (13 studies; OR 0.37; 95%CI, 0.27 to 0.51) or no treatment (1 study; OR 3.45; 95%CI, 1.10 to 11.1). The NNT with antidepressants to produce 1 recovery from depression was 4.2 (95%CI, 3.2 to 6.4), while the number needed to harm (NNH) to produce 1 dropout for adverse effects was 9.8 (95%CI, 5.4 to 42.9).

Cardiovascular
The level of depressive symptoms during admission for myocardial infarction (MI) is closely linked to long-term survival (74–76). Patients with depression after acute MI were at significantly increased risk of cardiac events at 1 year (31.2% yearly), compared with those without depression (23.9% yearly) (OR 1.41; 95%CI, 1.03 to 1.92; P = 0.03) (77). Similarly, depression was associated with an increased risk of major cardiac events in patients with unstable angina (78). Several studies have also demonstrated that depression is independently associated with a substantial increase in the risk of heart failure, particularly among women (79,80). In addition, patients with heart failure have a much higher rate of depression (36.5%) than patients without (25.5%) (72).

Evidence suggests an association between the use of TCAs and the risk of MI. A cohort study with 4.5 years of follow-up reported an adjusted relative risk of MI of 2.2 (95%CI, 1.2 to 3.8) in users of TCAs and 0.8 (95%CI, 0.2 to 3.5) in users of SSRIs, compared with subjects who did not use antidepressants (81). However, in a naturalistic study, the abnormalities in conduction and orthostatic hypotension associated with TCA treatment were reported, but cases of first-degree atrioventricular block, prolonged QTc interval, and orthostatic hypotension were also observed in the SSRI-treated patients (82).
Several studies have found sertraline to be effective in patients with MDD after MI and in those with hypertension and other cardiovascular morbidity (83, 84). In a small study, no significant changes in heart rate, blood pressure, cardiac conduction, coagulation measures, or left ventricular ejection fraction were observed (83). Bleeding time increased in 12 patients, decreased in 4 patients, and was unchanged in 2 patients. Paroxetine has also demonstrated good efficacy and tolerability in patients with MDD and documented ischemic heart disease (85, 86).

Trials to assess impact of treating depression on cardiovascular risk are in their infancy. A recent randomized trial studying the impact of CBT (and SSRIs when indicated) on both major and minor depression post-MI was unable to detect an impact on event-free survival (87).

**Stroke**

MDD has also been shown to be an independent predictor of stroke, approximately doubling the risk after other known risk factors are controlled (88, 89). During a 13-year prospective follow-up of 1703 individuals, those with a history of depressive disorder were 2.6 times more likely to report stroke than those without (88). Depression was associated with poor long-term functional outcome after stroke and vice versa (90). Worsening of depression between 3 and 15 months follow-up had an independent negative effect on dependent living up to 15 months after ischemic stroke (91). In a study of patients with stroke admitted to an inpatient program, those with current depressive symptoms used rehabilitation services less efficiently (92).

A recent review conducted to determine the feasibility and effectiveness of antidepressant treatment for poststroke depression in elderly patients found that TCAs would be contraindicated in 83% of patients, while SSRIs would only be contraindicated in 11% of patients (93). In the studies reviewed, rates of discontinuation and study completion were similar, and all the treatments appeared to be at least modestly effective in the short term. In a study in 104 poststroke patients with or without depression, nortriptyline produced a significantly higher response rate than fluoxetine or placebo in improving depression, anxiety symptoms, and recovery of activities of daily living as measured by the Functional Independence Measure (94). The antidepressants had no effect on recovery of cognitive or social functioning.

However, as is the case in cardiovascular patients, no trial has yet examined whether treating depression in patients at risk for stroke will improve long-term survival.

**Diabetes**

A recent metaanalysis found that the rate of depression among individuals with diabetes was twice that of individuals without diabetes (OR = 2.0; 95%CI, 1.8 to 2.2) (95). In addition, patients with type 1 diabetes and a lifetime history of MDD have shown significantly worse glycemic control than patients with no history of psychiatric illness ($P < 0.05$) (96). In a metaanalysis of 24 studies, hyperglycemia was significantly associated with depression (97).

A review of treatment of depression in patients with comorbid diabetes mellitus included 6 studies of fluoxetine for up to 12 months that demonstrated reductions in weight (up to 9.3 kg), in fasting plasma glucose (FPG) (up to 45 mg/dL or 2.5 mmol/L), and in glycosylated hemoglobin (HbA1c) (up to 2.5%) (98). Sertraline also has demonstrated beneficial effects on glycemic control, while the TCA nortriptyline, which produces increased synaptic catechols, has led to worsening of glucose control. In the United Kingdom Prospective Diabetes Study (UKPDS), every 1% reduction in HbA1c was associated with reductions in risk of 21% for any endpoint related to diabetes, of 21% for diabetes-related deaths, and of 14% for myocardial infarction (all $P < 0.0001$) (99).

In patients with diabetic neuropathy and without depression, dual-action antidepressants appear more effective at lower dosages than do SSRIs, perhaps owing to the fact that catecholamines and serotonin may both be implicated in pain pathways (98). The TCAs, particularly amitriptyline and desipramine, while having significant adverse effects in the elderly, have demonstrated success in double-blind studies (100–102). In a double-blind, placebo-controlled trial, venlafaxine achieved higher response rates, defined as a ≥ 50% reduction in pain intensity on the visual analogue scale, than placebo (56% vs 34%; $P < 0.02$). Significant pain relief was apparent as early as week 2 (103). In addition, in a comparative crossover study in 40 patients, venlafaxine relieved pain in polyneuropathy as effectively as imipramine (104). Reductions in pain scores at week 4 were greater with venlafaxine (20%) and imipramine (23%) than placebo (0%), but there was no statistical difference between the 2 active treatments.

**Dementia and Alzheimer’s Disease (AD)**

A recent cross-sectional study found that the prevalence of depressive symptoms was 31.4% in patients with vascular dementia, 19.9% in patients with AD, and 13.2% in cognitively normal elderly individuals (105). In addition, depressive symptoms among patients with vascular dementia were more persistent and refractory to drug treatment (106). Depressive symptoms in patients with AD appear to have higher rates of spontaneous resolution than those in patients with vascular dementia, where depression appears more persistent and refractory to drug treatment (106).

Paroxetine and imipramine demonstrated equivalent efficacy in the treatment of depression in elderly patients with
coexisting dementia at 8 weeks (107). There was a trend toward better tolerability with paroxetine, compared with imipramine, in terms of anticholinergic adverse events (6.1% and 13.1%, respectively) and serious nonfatal adverse events (4.0% and 8.1%, respectively).

Response to the SSRIs in patients with AD has been mixed (108–110). A small study in 31 nursing home patients with late-stage AD demonstrated no significant benefits of sertraline over placebo (108). However, more patients had at least a partial response to 12 weeks of sertraline (9 of 12), compared with placebo (2 of 10), in a study in outpatients with AD (109). Fluoxetine demonstrated higher remission rates, compared with placebo, in a study in 41 patients with AD (47% and 33%, respectively) (110). Positive results were reported with mirtazapine in a case report of 3 patients (111).

**Antidepressant Safety and Tolerability in Older Patients**

In a recent metaanalysis, adverse-effect data from clinical trials in older patients suggested a modest, but consistent, superiority of venlafaxine and SSRIs over TCAs (37). Based on efficacy and tolerability or safety data, this metaanalysis supported the preferential use of venlafaxine and SSRIs, with the possible exception of fluoxetine, in the treatment of depression in older people.

In the recent efficacy trials shown in Table 1, most of the agents were generally well tolerated, with little difference between treatment groups in discontinuations owing to adverse events. TCAs were associated with more cholinergic side effects, including dry mouth, constipation, and impaired accommodation, compared with SSRIs and venlafaxine (39,40,112). Overall side effect rates for the SSRIs sertraline, paroxetine, and fluoxetine were similar and usually included nausea (42–44). Fluoxetine was associated with a greater incidence of severe adverse events and of central nervous system–related side effects, compared with paroxetine (43). The most common side effects with mirtazapine included dry mouth and weight gain (44). Pooled data from 8 RCTs in older patients demonstrated the safety of citalopram, with only increased sweating occurring more often than with placebo (113). SSRI and venlafaxine use have been independently associated with the presence of hyponatremia in elderly psychiatric inpatients (114).

Older patients frequently take multiple medications, which makes the potential for drug interactions with antidepressant medications a concern (26). The drug interaction potential of antidepressant therapy is generally higher with older compounds (such as TCAs and MAOIs), which are associated with clinically significant interactions with many medications frequently prescribed to elderly patients (115). New antidepressants have a more selective mechanism of action and a lower potential for pharmacodynamic drug interactions.

**Summary**

Managing depression in older patients can be done effectively with the antidepressant therapies currently available. Older patients with depression should be treated to remission, just as are their younger counterparts. Residual symptoms of depression are associated with a lower quality of life. In addition, there are concerns unique to older patients. Older patients have altered physiology that can impact the concentrations of antidepressant medications and make these individuals more sensitive to side effects.

Depression in older patients can have a significant impact on comorbid medical conditions, which are common among the elderly. Rates of cardiovascular events and strokes are higher in patients with depression, compared with those without. Antidepressant therapy with SSRIs has demonstrated efficacy and tolerability in patients at high risk for cardiovascular events and stroke. Diabetes is also common among older patients, and increased rates of hyperglycemia have been associated with depression. Although fluoxetine has more data supporting beneficial effects on glucose levels, other SSRIs and venlafaxine may also be useful in patients with diabetes and depression. In addition, venlafaxine has demonstrated beneficial effects on the relief of the pain of diabetic neuropathy. Early results in the treatment of depression in patients with vascular dementia or Alzheimer’s disease suggest SSRI therapy may have beneficial effects.

Overall, venlafaxine, mirtazapine, and the SSRI antidepressants have demonstrated efficacy and tolerability in older patients with MDD. TCAs have also demonstrated efficacy; however, tolerability, particularly cholinergic side effects, can be a problem.

**References**


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