

Recent Developments in Antidepressant Therapy in Special Populations

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Abstract

Major depressive disorder (MDD) in the elderly, children, and patients with unstable angina or acute myocardial infarction (MI) is a serious disorder. In elderly patients, where major depression is often overlooked and may have a significant impact on the quality of life, the goal of therapy is full remission. Selective serotonin reuptake inhibitors (SSRIs) have the most favorable combination of efficacy and side-effect profile for the elderly with MDD, regardless of the presence of medical comorbidities. Although the dual agent venlafaxine has been proposed as an alternative agent for older patients who are either nonresponders or partial responders to SSRIs, the frail elderly may be particularly vulnerable to its side effects. Most elderly patients have a relapse of depression when antidepressants are stopped; depression subsides when antidepressants are resumed. Because recent evidence suggests that the dosage of an antidepressant that achieves remission in the elderly does not always protect against recurrence, in addition to long-term maintenance, consideration should be given to increased dosage. Patients with major depression and either unstable angina or acute MI should be identified and considered for antidepressant treatment. Findings from the recent Sertraline Anti-Depressant Heart Attack Randomized Trial suggest that SSRIs may have antiplatelet and endothelium-protective properties that may benefit patients with depression and comorbid coronary artery disease and ischemic stroke. Concern regarding the safety of SSRIs in children has prompted new studies. Evidence suggests that the risks of SSRIs, except for fluoxetine, might outweigh benefits in the treatment of depression in children and adolescents.

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Antidepressant Therapy in the Elderly With Major Depression

Major depressive disorder (MDD) in the elderly is an important public health problem that will continue to challenge managed care as the aging population grows. In addition to worsening mood and diminishing feelings of self-worth, MDD impairs physical, social, and cognitive functioning. MDD is also associated with increased rates of mortality and suicide in the elderly.^{1,2} Overall, clinically significant depression affects up to 14% of the elderly population; between 2% and 4% of the elderly have MDD and approximately 10% have minor depression.³⁻⁵ Clinically significant depression, which is often long term or recurrent, is untreated in at least 60% of the elderly⁴ and is associated with increased utilization of medical services. However, approximately 36% of all nursing home residents receive antidepressants.⁶

The class of antidepressants most widely prescribed among the elderly is the selective serotonin reuptake inhibitors (SSRIs) (eg, citalopram, fluoxetine, paroxetine, and sertraline). Compared with the older tricyclic antidepressants, SSRIs are equally effective but cause significantly less orthostatic, cognitive, cardiovascular, and anticholinergic side effects. The SSRIs are categorized as "newer" antidepressants, along with dual-action serotonin-norepinephrine reuptake inhibitors (eg, mirtazapine and venlafaxine), reversible inhibitors of monoamine oxidase A, and norepinephrine reuptake inhibitors. A structured review⁷ of 27 trials involving these newer antidepressants in depressed elderly patients (with mostly MDD) found that approximately 50% of subjects receiving them had at least a 50% improvement in depressive symptoms compared with an average placebo response rate of 30%.

Efficacy. Most recent trials comparing the efficacy of different SSRIs for MDD in the elderly have shown these agents to be equivalent in efficacy. For example, sertraline was shown to have efficacy comparable with flu-

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oxetine for MDD in a 12-week, double-blind, randomized trial.⁸ A more recent large, double-blind, placebo-controlled trial showed sertraline to be effective and well tolerated by older adults with MDD. Also, the efficacy of sertraline appeared greater in patients with more severe depressive symptoms.⁹ In another recent study, mirtazapine and paroxetine resulted in similar rates of remission.¹⁰ A comparison of the dual agent venlafaxine and nortriptyline found no significant differences in remission rates of treated patients.¹¹ A single-blind study suggested that nortriptyline confers a significantly higher remission rate compared with citalopram.¹²

Treating to Full Remittance. The goal of treatment of MDD in the elderly should be remission rather than simple response.¹³ Among 100 elderly (aged 60-88 years) patients with recurrent MDD who were randomized to receive bupropion or paroxetine for 6 weeks, improvements in quality of life were achieved with either agent. However, remitters showed significantly ($P < .001$) greater improvement than both partial responders and nonresponders on various measures.¹⁴

Antidepressant Therapy in Elderly With Depression and Medical Illness. More aggressive antidepressant drug therapy may be warranted in some elderly patients with depression and medical comorbidities. Approximately 25% of patients aged 65 years and older with long-term medical illness have significant coexisting depression; about 15% have MDD.¹⁵ Elderly patients with both long-term medical illness and depression have greater overall impairment in quality of life¹⁶ and may fail to adhere to treatment up to 3 times more often than nondepressed patients.¹⁷

Only a few recent studies have demonstrated the safety and efficacy of SSRIs among elderly patients with medical comorbidities. An analysis of the pooled results for the sertraline treatment group drawn from 2 prospective, randomized, double-blind studies involving either sertraline versus fluoxetine¹⁸ or sertraline versus nortriptyline⁸ provided preliminary evidence that sertra-

line is a safe, well-tolerated, and effective antidepressant in elderly patients suffering from hypertension and other forms of vascular comorbidity.¹⁹ A more recent, randomized, double-blind, placebo-controlled trial involving more than 750 patients aged 60 years and older with MDD showed sertraline to be superior to placebo in reducing depressive symptoms, regardless of the presence of comorbid medical illness, on all 3 primary outcome measures of the study. The drug was safe and well tolerated by patients with or without medical illness.²⁰ Interestingly, the degree of improvement correlated with patient cardiac, cerebral, or peripheral vascular pathology. This finding is consistent with that of another study comparing buspirone and imipramine where patients with cardiovascular illness were likely to have higher antidepressant response rates.²¹ A recent analysis of the Cochrane database showed that the use of antidepressant medications in medically comorbid depressed patients was associated with 3 times the recovery rate of patients taking placebo.²² Another recent study suggested that long-term maintenance with antidepressant treatment did not adversely affect elderly patients with a high degree of cerebrovascular risk.²³ In all, these findings offer reassurance to clinicians of the safety, tolerability, and efficacy of sertraline and other SSRIs.

Partially Responsive, Nonresponsive, and Frail Patients. Because many elderly patients with depression are either nonresponsive or partially responsive to SSRIs, there continues to be interest in alternative agents. A review of 3 double-blind comparisons and 4 open-label studies²⁴ involving the use of the dual-action serotonin norepinephrine reuptake inhibitor venlafaxine in older patients concluded that venlafaxine was safe and effective in elderly patients with MDD. Subsequently, an expert consensus panel on the treatment of depression in the elderly proposed venlafaxine as both an alternative first-line antidepressant for severe depression and an agent for SSRI nonresponders.²⁵ However, in the largest study examined by the review, nearly 30% of subjects taking venlafaxine withdrew because of adverse events.²⁶ Furthermore,

evidence from a recent trial suggested that the frail elderly may be especially vulnerable to the side effects of venlafaxine. The 10-week randomized, double-blind study, which compared the efficacy and tolerability of venlafaxine and sertraline in the treatment of depression among nursing home residents, found that venlafaxine was less well tolerated and, possibly, less safe than sertraline.²⁶ Thus, some medications that appear safe among the community elderly may be less safe among the frail elderly. Consistent with this, in a small placebo-controlled trial in very old patients with non-major depression in long-term care facilities, paroxetine (which was not significantly better than placebo) was associated with 2 cases of delirium.²⁷

Prophylaxis Against Recurrence. Elderly patients in remission from MDD have a high rate of recurrence after discontinuation of antidepressant medication. Several recent studies provide evidence regarding optimal length of treatment and antidepressant dosage for prophylaxis against recurrence. Fava et al²⁸ found that fluoxetine-treated patients who relapsed after switching to placebo would most likely respond to reinitiating fluoxetine. A recent well-designed 48-week, randomized, controlled trial provided good evidence that maintenance therapy with the SSRI citalopram is more effective than placebo in reducing recurrence of unipolar major depression in the elderly. At 48 weeks, 32% of citalopram-treated patients had relapsed compared with 67% of the placebo group ($P < .0001$).²⁹ A small, open-label study in older patients showed that maintenance with either paroxetine or nortriptyline demonstrated similar efficacy in relapse prevention and time to relapse.³⁰

Increasing the maintenance dosage has been considered as a strategy to manage recurrence of MDD in the elderly. Increasing the dosage of sertraline in a general adult population already receiving the drug reduced the recurrence rate of depression.³¹ Wilson et al³² found evidence that challenges the assumption that the dosage of an antidepressant that achieves remission in an older population protects against recurrence. In a randomized, double-blind, placebo-con-

trolled continuation/maintenance study of 100 weeks duration, sertraline at therapeutic dosages did not provide significant protection against recurrent depression in older patients compared with placebo. The study found that extreme age appears to be associated with an increased risk of recurrence of depression for more than 2 years, which was consistent with a similar finding in another study³³ for 3 years. The authors made 3 specific recommendations for relapse prevention: practitioners should (1) beware of the particular vulnerability of older people with depression and encourage an aggressive and closely observed treatment plan, (2) promote long-term antidepressant maintenance, irrespective of the number of previous episodes, and (3) consider increased dosage.³²

Antidepressants in Children and Adolescents With Major Depression

Safer and More Effective Antidepressants Needed. Safer and more effective antidepressants are needed for depressed children and adolescents. Approximately 2% to 6% of children and adolescents suffer from depression,^{34,35} and suicide ranks third as the most common cause of death in youths between 10 and 19 years of age.³⁶ Tricyclic antidepressants are potentially toxic and are generally regarded as ineffective for children with MDD; there is only marginal evidence for their use in the treatment of the disorder in adolescents.³⁷ SSRIs, because of early evidence suggesting that they might be more effective and better tolerated in young people, have experienced a steady increase in prescription rate. The most supportive published trial of fluoxetine, the only SSRI approved for children, suggested that fluoxetine was superior in both children and adolescents with MDD compared with placebo.³⁸ However, this study suggested that fluoxetine improved only selected measures of clinician-rated improvement and failed to show an increase in rate of remission or recovery.³⁹

SSRIs With Unfavorable Risk-Benefit Profiles. In 2003, results of several recent large, randomized, controlled trials caused new concern regarding the effectiveness and safety of SSRIs in children. As a result, the

United Kingdom's Medicines and Health-Care Products Regulatory Agency issued a general advisory that all antidepressants, except fluoxetine, had unacceptable risk-benefit profiles for the treatment of MDD in children up to the age of 18 years.⁴⁰ Meanwhile, the US Food and Drug Administration recommended that paroxetine not be used in children and adolescents for the treatment of MDD.⁴¹

In view of growing concern about publication bias and the fact that researchers were both withholding unfavorable trial data and underreporting adverse events in trials of SSRIs, Whittington et al⁴² conducted a meta-analysis of the risk-benefit profile of individual SSRIs in children using published and unpublished data from trials conducted before April 2003. The authors identified 5 randomized, controlled trials evaluating SSRI versus placebo in patients between the ages of 5 and 18 years that were published in a peer-reviewed journal or were unpublished and included in a review by the United Kingdom's Committee on Safety of Medicines. The authors concluded that, except for fluoxetine, risks from SSRIs might outweigh benefits in the treatment of depression in children and adolescents. For paroxetine, the authors found a published trial⁴³ and 2 unpublished trials⁴⁴ suggesting that paroxetine does not improve depressive symptoms but appears to be associated with increased risk of serious adverse events, suicidal ideation, and/or suicide attempt. Two trials of sertraline⁴⁵ provided equivocal or weak evidence of its efficacy and suggested it might contribute to increased suicidal ideation. Unpublished trials of citalopram and venlafaxine⁴⁴ showed that these agents had unfavorable risk-benefit profiles. Because the drugs reviewed by the authors had been recommended for use in children on the basis of very restricted published evidence, they concluded that there was an urgent need for evidence-based medicine guideline developers to have greater access to unpublished full-trial reports.⁴²

Treatment of Patients With Acute Coronary Syndrome and Major Depression

Depression and Risk of Sudden Death in Acute Coronary Syndrome. Several stud-

ies have shown that the presence of depression in patients with acute coronary syndrome (ACS) (ie, unstable angina or acute myocardial infarction [MI]) confers an approximate 3-fold increased risk of death, depending on the severity of depression. In addition, patients who survive acute MI have impairment in quality of life and functioning commensurate with the degree of depression.^{46,47} The prevalence of MDD in patients with acute MI or ACS is 15% to 23% and even higher when milder forms of depression are considered.⁴⁸ Therefore, there is great interest in the effect of antidepressant treatment on the quality of life and the functioning of patients with acute MI and comorbid depression. However, published evidence that antidepressant drugs are either safe or effective in patients with acute MI has been lacking. Indeed, few patients with recent acute MI or unstable angina and comorbid depression receive antidepressant treatment.⁴⁹

Safety, Tolerability, and Efficacy of SSRIs. The SSRIs, with their favorable safety, tolerability, and efficacy, have been used increasingly to treat depression in the elderly and may prove capable of reducing morbidity and mortality associated with ACS. Several studies have found sertraline to be effective in patients with MDD after acute MI and in patients with hypertension and other cardiovascular morbidity.^{19,20} In a small study by Shapiro et al,⁵⁰ no significant changes in heart rate, blood pressure, cardiac conduction, coagulation measures, or left ventricular ejection fraction (LVEF) were observed.

Interestingly, in the recent large sertraline trial conducted by Sheikh et al,²⁰ the degree of improvement in depressive symptoms in elderly patients correlated with their severity of cardiac, cerebral, or peripheral vascular pathology. In 2 studies in patients with MDD and documented ischemic heart disease, paroxetine has been shown to have favorable efficacy and tolerability.^{51,52}

Persistent or Recurrent Depression in ACS Should Be Treated. The Sertraline Antidepressant Heart Attack Randomized Trial (SADHART), which involved 369 outpatients with MDD who had been hospital-

ized the previous month for ACS (MI, 74%; unstable angina, 26%), provided evidence that sertraline is safe and more effective than placebo in treating recurrent depression in this population.⁵³ The randomized, double-blind, placebo-controlled trial also showed that sertraline treatment was not associated with significant changes in LVEF or any other measures of cardiovascular function. The authors concluded that, even in the absence of evidence that antidepressant treatment reduces risk in ACS, persistent or recurrent depression in ACS should be identified and treated.⁵³

Quality of Life. A separate analysis of the SADHART trial population⁵⁴ found that treatment with sertraline was associated with significantly greater improvement than placebo on most quality-of-life measures. The improvement at 6 months was substantial, but nonspecific, and occurred with both sertraline and placebo for the subgroup of at-risk patients who had experienced depression before hospitalization for ACS. The analysis also found depression after acute MI to be associated with more severe baseline impairments in quality of life and functional status than previously reported in nondepressed post-acute MI patients or in depressed patients without coronary artery disease (CAD).⁵⁴

SSRIs, Platelet Activation, and Increased Risk of Sudden Cardiac Death. One of the factors that may contribute to the increased risk of sudden cardiac death among patients with both ACS and MDD is increased platelet activation.⁵⁵ SSRIs are known to inhibit platelet activity. In a SADHART substudy, treatment with sertraline in depressed post-ACS patients was associated with reductions in platelet endothelial activation, despite widespread coadministration of antiplatelet regimens, including aspirin and clopidogrel. This study suggests that the antiplatelet and endothelium-protective properties of SSRIs might benefit patients with depression and comorbid CAD and ischemic stroke.⁵⁶

Conclusion

In general, of the newer antidepressants, the SSRIs continue to offer the most favor-

able combination of efficacy and side-effect profile for the elderly with MDD, regardless of the presence of medical comorbidities, and should be used to achieve full remission. Modification of dosage and duration of treatment may be appropriate in elderly who are frail or those who are prone to recurrence of MDD. Although antidepressant treatment has not been shown to reduce the risk conferred by MDD in ACS, persistent or recurrent depression with ACS should be identified and treated. Currently, except for fluoxetine, risks from SSRIs outweigh benefits in the treatment of depression in children and adolescents.

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