Improving Recovery After Stroke
A Role for Antidepressant Medications?
Harold P. Adams, Jr, MD; Robert G. Robinson, MD

Although stroke is a leading cause of death in the United States and around the world, many people fear this disease because of its nonfatal neurological impairments that lead to disability or dependency. Considerable research has focused on lessening the neurological effects of the acute brain injury. To date, success is limited. Despite these research efforts, only intravenous thrombolysis and endovascular interventions are accepted as effective in limiting the acute effects of ischemic stroke. Although these therapies are efficacious, only 3% to 5% of patients with stroke are receiving reperfusion-based therapies due to the very short time windows for treatment.1 No medical or surgical intervention is useful in improving outcomes after intracerebral hemorrhage.

Annually, approximately 400 000 Americans need rehabilitation to help with recovery after stroke.2 Given the magnitude of the problem, effective new therapies are needed to augment the process of recovery. These therapies could be given as adjuncts to conventional rehabilitation to these patients who have potentially disabling residual neurological impairments. Because many more patients could be treated, an effective therapy that maximizes neurological recovery might have a much bigger societal impact than emergency reperfusion therapy alone.3,4 Unfortunately, relatively few clinical studies have tested interventions that might augment recovery. The basic science understandings of the process of recovery after stroke have advanced.5-10 It is now clear that the adult brain has a real capacity for physiological and anatomic modifications that lead to motor and cognitive recovery.11 This complex process is mediated by multiple mechanisms including enhanced regional metabolism and resolution of diaschisis. Cellular changes after stroke include proliferation of neural and glial cell precursors, activation of astrocytes and inflammatory cells, migration of blood vessels, increased axonal sprouting, increased branching of dendrites, and development of new synapses.12-14 Neurogenesis after stroke also includes production of progenitor cells in the subventricular zone, hippocampus, and other brain regions that migrate into areas of infarction. In experimental models, the maximal effects are seen within the first 2 to 3 weeks after stroke and may extend for 3 to 6 months.5

Potential interventions to enhance restorative processes include administration of growth factors, use of marrow stromal cells or erythropoietin, robotic assistance, brain stimulation, and intrasfenal stem cell transplantation.15-18 Some of these interventions likely will be expensive and may require special expertise, resources, and technology that could limit their use. Another approach would be the adjunctive use of pharmacological therapies.19 Clinical studies of the potentially positive impact of medications have begun to emerge.20,21 Laboratory studies of medications that increase brain concentrations of brain amines (serotonin, dopamine, etc), including amphetamines, demonstrate a positive impact on outcomes.22 However, clinical trials have found conflicting results and some of these medications may not be optimal for treatment of patients with recent stroke.23

Another promising approach is the use of antidepressants, particularly in management of patients who are not depressed. Depression is a common consequence of ischemic stroke; it occurs in approximately 25% to 30% of patients and it peaks within the first 3 to 6 months.24 When adjusting for age, severity of stroke, and other covariables, depression has major negative effects on cognitive and motor recovery and is associated with increased mortality and an increased risk of recurrent vascular events.24,25 However, there have been concerns about the safety of the antidepressants when given to elderly patients. In particular, the risk of bleeding may be increased because of potential interactions with antiplatelet agents. Some observational studies have reported an increased risk of either hemorrhagic or ischemic stroke among older patients taking antidepressant medications, whereas others have not found these associations.26-31 In addition, the use of antidepressants in preventing depression after stroke also has been debated. For example, a small randomized trial reported that early administration of sertraline reduced the incidence of depression (16.7% [8 of 48] versus 21.6% [11 of 51] for placebo, P=0.59).32 However, the nonsignificant results may be explained in part by the limited number of patients in the study. Based on a meta-analysis of randomized trials, Fournier et al33 concluded that the medications were effective in treating severe depression but of uncertain efficacy in less severely depressed patients. In a rebuttal, Isaccson and Adler34 noted that the scales used in the trials...
included in the meta-analysis were not sufficiently sensitive to detect treatment effects and, thus, the conclusions could not be sustained. This observation is supported by the findings of Hackett et al.\(^3\) In addition, a Cochrane systematic review found that antidepressant medications are effective in treating depression after stroke.\(^3\) Another meta-analysis performed by Yi et al\(^7\) found that fluoxetine is beneficial for prevention of poststroke depression although it did not reduce the severity of the depressive symptoms. Based on the available data, current American Heart Association guidelines recommend regular screening for depression for stroke and if depression is detected, antidepressants are advised.\(^3\) Given these recommendations, enrolling depressed patients into a randomized placebo-controlled trial testing the use of antidepressants in improving neurological outcomes would be problematic.

Remission of depression is associated with improved outcomes with rehabilitation, which implies that the administration of antidepressant medications might potentially augment recovery.\(^3\) Recent data show that antidepressant medications also might be useful in fostering recovery in nondepressed patients.\(^4\) Because antidepressant medications are widely and safely used, they would be strong candidates to be used as adjunctive agents in the subacute phase of stroke. The selective serotonin reuptake inhibitors are of particular interest because of their safety profile in patients with heart disease and stroke.\(^5,6\) Laboratory research also supports the use of selective serotonin reuptake inhibitors as a tactic to maximize recovery after stroke.\(^7\)

Several clinical studies, testing different agents, have evaluated the potential use of the selective serotonin reuptake inhibitor medications in several settings after stroke. When compared with a control group that received placebo, Dam et al\(^8\) found that fluoxetine (20 mg/day) facilitated motor recovery among patients receiving physical therapy. Fruehwald et al\(^9\) initiated fluoxetine therapy (20 mg/day) within 2 weeks after stroke to 24 patients and continued treatment for 12 weeks; they found sustained benefits from treatment at 18 months when compared with a group of patients treated with a placebo. In a study using functional MRI, Pariete et al\(^10\) reported that a single dose of fluoxetine (20 mg) led to hyperactivation of the ipsilesional insular and lateral motor cortex at 5 hours when compared with placebo; they also found that fluoxetine improved finger-tapping speed as well as strength of the paretic arm. In a crossover study of 8 patients with chronic stroke, Zittel et al\(^11\) reported that a single (40 mg) dose of citalopram improved motor performance on a peg board when compared with the responses among patients receiving placebo. In another study, Acler et al\(^12\) gave citalopram (10 mg/day) for 1 month to 10 patients with stroke and reported greater improvements in the National Institutes of Health Stroke Scale when compared with 10 patients treated with placebo. Bilge et al\(^13\) treated patients with poststroke depression with citalopram (20 mg/day) for 6 months and found improvements in the scores of the Scandinavian Stroke Scale, modified Rankin Scale, and Barthel Index at 12 months; the results paralleled improvement in the depression. Another trial found that paroxetine improved motor outcomes after stroke.\(^14\) A crossover study that included functional MRI reported that reboxetine increased grip strength and finger dexterity and was associated with a reduction in cortical hyperactivity.\(^15\)

The 2 largest studies were conducted by Chollet et al\(^16\) and our group.\(^17\) In the former study, 57 patients were treated with fluoxetine (20 mg/day) and 56 patients received placebo for 3 months beginning within 10 days of stroke. All patients needed rehabilitation and the mean baseline National Institutes of Health Stroke Scale scores were approximately 13 in both groups. At 3 months, improvements in the Fugl-Meyer motor scores were significantly higher with fluoxetine (34 points; 95% CI, 29.7–38.4) than with placebo (24 points; 95% CI, 19.9–28.7). Similarly, modified Rankin Scale scores of 0 to 2 were achieved in 26% of fluoxetine-treated patients and 9% of control subjects. In a 3-arm trial that enrolled patients within 3 months of stroke and treated for 3 months, we compared 32 patients treated with fluoxetine (40 mg/day), 22 patients treated with nortriptyline (100 mg/day), or 29 patients administered placebo. After controlling for age, depression, rehabilitation intensity, and baseline severity of stroke, improvements in the modified Rankin Scale were significantly greater at 12 months with treatment (t(156)=3.17, \(P=0.002\)).\(^18\) Furthermore, follow-up of this group found that 70% of the patients treated with antidepressants had survived 7 years compared with 36% of those given placebo (\(P=0.001\)).\(^19\) In another multicenter, randomized, placebo-controlled trial, we demonstrated that escitalopram (10 mg/day) given for 1 year prevents development of poststroke depression and was associated with improved short- and long-term memory recovery, even after controlling for age, sex, and baseline cognitive function.\(^20,21\) These findings are buttressed by the results of the project of Simis and Nitin\(^22\) who reported that citalopram was associated with improved memory and attention.

Although these studies are relatively small, they demonstrate the potentially positive impact of the adjunctive use of selective serotonin reuptake inhibitor medications in treatment of nondepressed patients with recent stroke.\(^3\) Interest in the potential efficacy of antidepressants in improving outcomes after stroke, especially in nondepressed patients, is considerable. The selective serotonin reuptake inhibitors appear to augment motor and cognitive recovery. The medications seem to be relatively safe in patients with stroke.\(^23,24,25\) Because the prices of the medications are relatively inexpensive (for example, US $4 per month for fluoxetine), the cost-effectiveness of these agents could be considerable. Although the preliminary data are promising, they are not definitive. A recommendation for widespread use of antidepressants in the management of patients with recent stroke is premature. Larger trials are needed to test the use of antidepressants in a broad range of patients with recent stroke. If these trials replicate the results of the recent studies, the overall impact of adjunctive antidepressant therapy could represent a major advance in the care of persons surviving stroke.

**Disclosures**

Dr. Adams is a consultant (member of adjudication panel) for Merck <$10,000; a consultant (member of safety panel) for Medtronic <$10,000; and has received grant support from the National Insti-
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References


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