Improving Recovery After Stroke
A Role for Antidepressant Medications?

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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 available at http://stroke.ahajournals.org DOI: 10.1161/STROKEAHA.111.640524

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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.\textsuperscript{35} In addition, a Cochrane systemic review found that antidepressant medications are effective in treating depression after stroke.\textsuperscript{36} Another meta-analysis performed by Yi et al\textsuperscript{37} 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.\textsuperscript{38}

Given these recommendations, enrolled 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.\textsuperscript{39–41} Recent data show that antidepressant medications also might be useful in fostering recovery in nondepressed patients.\textsuperscript{41,42} 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.\textsuperscript{43,44} Laboratory research also supports the use of selective serotonin reuptake inhibitors as a tactic to maximize recovery after stroke.\textsuperscript{45–47}

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\textsuperscript{48} found that fluoxetine (20 mg/day) facilitated motor recovery among patients receiving physical therapy. Fruehwald et al\textsuperscript{49} 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\textsuperscript{50} reported that a single dose of fluoxetine (20 mg) led to hyperactivation of the ipsilesional insular and lateral motor\textsuperscript{51} 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\textsuperscript{52} 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\textsuperscript{53} 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\textsuperscript{54} 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.\textsuperscript{54} 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.\textsuperscript{51}

The 2 largest studies were conducted by Chollet et al\textsuperscript{44} and our group.\textsuperscript{55} 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).\textsuperscript{52} 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).\textsuperscript{52} 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.\textsuperscript{43,55} These findings are buttressed by the results of the project of Simis and Nitrin\textsuperscript{56} 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.\textsuperscript{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.\textsuperscript{43,44,55} 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-
tutes of Neurological Disorders and Stroke >$10,000. Dr Robinson is a consultant for Avanir <$10,000 and an expert witness <$10,000.

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