EDITORIAL

Exploring new frontiers in neuropsychopharmacology: SSRIs for stroke

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Selective serotonin reuptake inhibitors (SSRIs) are approved treatments for a variety of indications: depression, obsessive–compulsive disorder, generalized anxiety disorder, panic disorder, social anxiety disorder, post-traumatic stress disorder, premenstrual dysphoric disorder, and others.[1] SSRIs are experimental or off-label treatments for a variety of conditions ranging from premature ejaculation[2] to alcoholism.[3] A new frontier now appears to be opening for the use of SSRIs: stroke, a condition which commonly results in physical and cognitive impairments, functional dependence, caregiver burden, and poor quality of life. Importantly, the data for this indication have emerged from clinical trials that were independent of the pharmaceutical industry. What have been the findings?

FLUOXETINE AND STROKE

A meta-analysis[4] of data from six randomized controlled trials (RCTs) with a pooled sample size of 385 patients suggested that in patients with recent stroke, fluoxetine may reduce the incidence of post-stroke depression [odds ratio (OR) 0.25; 95% confidence interval (CI) 0.11–0.56], promote the recovery of neurological functioning [weighted mean difference (WMD) 4.72; 95% CI 1.13–8.31], and improve independence in activities of daily living (WMD 8.04, 95% CI 2.68–3.40).

One of the fluoxetine RCTs[5] provided interesting follow-up data. In the original study, 104 stroke patients were treated for 12 weeks with fluoxetine (up to 40 mg/day), nortriptyline (up to 100 mg/day), or placebo. At a 9-month follow-up,[6] a third of patients were observed to have dropped out of each of the antidepressant arms relative to 14% dropout with placebo. A completer analysis performed on the combined antidepressant versus placebo groups showed that after adjusting for confounding variables such as age, intensity of rehabilitation therapy, baseline stroke severity, and baseline Hamilton Depression Rating Scale (HAM-D) score, patients who had received 3 months of treatment with antidepressant medication showed significantly greater improvement in modified Rankin Scale scores than those who had received placebo. Outcomes with fluoxetine and nortriptyline were similar, with each being superior to placebo. Activities of daily living, assessed using the Functional Independence Measure, showed a trend ($P=0.09$) for superiority of antidepressant drugs over placebo. Outcomes in patients who received antidepressants for 6 months did not differ significantly from those in patients who received treatment for 3 months; however, these analyses were probably underpowered. A limitation of this completer analysis is that about half of the patients who did not complete the study dropped out because of medical deterioration or adverse effects; thus, an intent-to-treat analysis would almost certainly have found limited benefits with drugs.[6]

Significantly, at a 9-year follow-up, 36 out of 53 (68%) patients who received full dose antidepressants were alive in contrast with only 10 out of 28 (36%) placebo-treated patients. After controlling for confounding variables such as age and coexisting diabetes, this long-term benefit of just 12 weeks of post-stroke antidepressant therapy was found to remain significant in patients who were depressed as well as in those who were not depressed at baseline.[7]

Earlier this year, another fluoxetine RCT showed that in patients ($n=118$) with stroke and moderate to severe hemiplegia or hemiparesis, fluoxetine (20 mg/day, started 5–10 days after stroke) combined with physiotherapy was associated with significantly better 3-month motor outcomes than placebo combined with physiotherapy. Gastrointestinal disturbances were commoner with fluoxetine than with placebo (25% vs. 11%, respectively);

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otherwise, common adverse effects differed little between groups.[8]

One RCT found that fluoxetine, however, does not benefit the specific symptom of post-stroke fatigue.[9]

ESCITALOPRAM AND STROKE

Escitalopram has also been found to benefit patients with stroke. One long-term study randomized nondepressed patients who had suffered either ischemic or hemorrhagic stroke during the previous 3 months to receive 1 year of double-blind treatment with escitalopram (10 mg/day; 5 mg/day in those aged 65 years and above) or placebo, with a third, non-blind, manual-driven, problem-solving therapy arm. The results were published in several papers.[10-12] In one analysis of 1-year treatment data, there were 59 patients treated with escitalopram, 58 with placebo, and 59 with problem-solving therapy.[10] After adjusting for a history of mood disorders, new-onset major and minor depression (DSM-IV) were found to be less common with escitalopram than with placebo [9% vs. 22%, respectively; hazard ratio (HR) 4.5; 95% CI 2.4–8.2]. Major and minor depression were also less common with problem-solving therapy than with placebo (12% vs. 22%, respectively; HR 2.2; 95% CI 1.4–3.5). The advantage for escitalopram and problem-solving therapy remained after adjusting for other confounding variables (e.g. age, sex, treatment site, and severity of impairment) as well. In an intent-to-treat analysis which assumed that depression would develop in all 27 patients who did not start randomized treatment, escitalopram remained superior to placebo (HR 2.2; 95% CI 1.2–3.9), but problem-solving therapy was no better than placebo (HR 1.1; 95% CI 0.8–1.5). There were no significant differences between the three groups in adverse events, including all-cause hospitalizations, nausea, and other adverse effects known to be associated with escitalopram.[10]

In a subgroup analysis of data from a single center in this study,[11] there were 43 patients treated with escitalopram, 45 with placebo, and 41 with problem-solving therapy. Patients were assessed using the repeatable battery for the assessment of neuropsychological status (RBANS), the Trail-Making test, the Controlled Oral Word Association test, the Wechsler Adult Intelligence Scale-III Similarities test, and the Stroop test. Escitalopram was associated with a significant advantage on the RBANS total score and the RBANS immediate memory and delayed recall scores, but not on the other neuropsychological measures. The RBANS advantage for escitalopram persisted even after adjusting for its antidepressant action. There were no significant differences in adverse events across groups.[11]

Curiously, in a third paper from this study, the incidence of post-stroke depression was significantly higher in the escitalopram group 6 months after discontinuation of escitalopram than in the problem-solving or placebo groups.[12] Whether or not this is a chance finding requires to be studied in future research.

The prophylactic effect of fluoxetine and escitalopram in stroke[4,10] is, of course, apparent in relapsing disorders such as unipolar recurrent depression; but it has also been described, for example, in patients receiving interferon therapy for chronic hepatitis, in whom the risk of psychiatric adverse effects is reduced.[13]

In a speculative vein, one wonders whether the mood and cognitive benefits with escitalopram[10,11] are limited to patients with recent stroke or may be experienced by healthy elderly persons as well. The subject may merit investigation.

ADVERSE OUTCOMES

Some data suggest that prior SSRI use may be associated with adverse outcomes in stroke patients.[14,15] These data, however, were obtained from observational studies in which patients with greater loading for poor prognosis factors could have been more likely to have needed SSRIs. Of note, in one of these studies,[15] initiation of SSRIs after stroke improved survival.

Available data suggest that SSRIs, which are known to increase bleeding at various sites,[16] do not increase the risk of hemorrhagic stroke.[17-19]

MECHANISMS

What may be the mechanism of action of SSRIs for the benefits described in stroke patients? There are at least four possibilities.

1. Patients who are depressed exhibit unhealthy behaviors such as nonadherence to medical recommendations regarding diet, exercise, and medication use. By treating[20] or preventing[4,10] depression, SSRIs can reduce the risk of unhealthy behaviors and hence improve a wide range of health outcomes.
2. SSRIs inhibit platelet aggregation and reduce the risk of ischemic events through a variety of mechanisms.[16,21] Some data exist to demonstrate benefits in patients with cardiovascular disease. For example, in a meta-analysis of six RCTs of patients with comorbid ischemic heart disease (IHD) and depression, SSRI treatment was associated with a modest antidepressant effect and lower IHD readmission rates and mortality rates.[22] Similar mechanisms and benefits may operate in patients with stroke as well.
3. SSRIs stimulate neuroplasticity, and this has been suggested as a final common pathway of antidepressant action.[23] Although the neuroplasticity response has

largely been described in the hippocampus, it is conceivable that beneficial changes occur in other parts of the brain as well, promoting recovery of functioning in stroke. In this context, in animal models of ischemic stroke, acute administration of fluoxetine[24] has been shown to protect against inflammatory neurotoxicity while chronic administration of fluoxetine[25] has been shown to improve hippocampal neurogenesis and attenuate spatial memory impairments. Gross motor improvement, however, was not observed in one animal study.[26]

4. SSRIs (but not tricyclic antidepressants) have also been shown to increase the levels of vascular endothelial growth factor, a growth factor which promotes angiogenesis.[27] This may assist the recovery of neurons that are ischemic but not dead, and may also provide the vascular support for the neuroplasticity changes.

CONCLUDING NOTES

SSRIs may play an important therapeutic and prophylactic role in improving neuropsychiatric outcomes in patients who have experienced a recent stroke; benefits include a lower risk of new-onset depression, better motor recovery, fewer cognitive deficits, improved levels of functioning, and reduced long-term mortality. Now that the SSRIs have moved out of patent, it is unlikely that the pharmaceutical industry will conduct regulatory clinical trials in patients with stroke. One hopes that the subject will attract independent investigator-initiated research.

Most of the research has been conducted with fluoxetine and escitalopram; however, there is no logical reason to suppose that other SSRIs would not have similar effects. Although there is little literature on the use of non-SSRI drugs in patients with stroke, it must be acknowledged that the benefits need not necessarily be associated with SSRIs alone. Just as antipsychotics as a class may increase the risk of stroke in the elderly and in patients with dementia,[28,29] so also may antidepressant drugs as a class improve outcomes in patients with stroke. However, whereas benefits with nortriptyline have already been described in this paper, mianserin (60 mg/day) was found to be no better than placebo in its 1-year effect on functional outcomes.[30]

A word of caution

After ischemic stroke, patients may receive drugs such as aspirin or clopidogrel; these can interact with SSRIs to increase the risk of bleeding disorders, especially at gastrointestinal sites; the risk is small, but real.[16] Clinicians must therefore be aware of the risk if they prescribe SSRIs to improve mood, cognitive, motor, and other outcomes after stroke. Separately, fluoxetine and fluvoxamine inhibit Cytochrome P450 2C19, and thereby interfere with the activation of clopidogrel.[31] This could diminish the benefits of clopidogrel, which is a prodrug often prescribed to reduce the risk of future ischemic events in patients who suffer stroke or IHD events. The RCT data, however, show that SSRIs are generally well tolerated in patients with stroke.[8,10,11]

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