Clinical and Practical **Psychopharmacology**

Fluoxetine for Stroke:
A Mixed Bag of Outcomes

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Each month in his online column, Dr Andrade considers theoretical and practical ideas in clinical psychopharmacology with a view to update the knowledge and skills of medical practitioners who treat patients with psychiatric conditions.

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ABSTRACT

Stroke is the leading neurologic cause of burden operationalized in terms of disability-adjusted life-years. After stroke, motor deficits, cognitive deficits, and depression cause loss of independence, disability, decreased functioning, and reduced quality of life; these persist into the long term. There are theoretical grounds to consider that, through neuroplasticity and other mechanisms, such impairments can be prevented or attenuated by the early introduction of a selective serotonin reuptake inhibitor such as fluoxetine. However, a recent meta-analysis of 13 randomized controlled trials (RCTs; pooled N = 4,145) found that fluoxetine neither improved independence nor reduced disability; whereas fluoxetine did reduce the risk of poststroke depression, it did not improve other outcomes, such as motor and cognitive outcomes, but, rather, was associated with many adverse outcomes. Two very large RCTs were subsequently published. The findings of these RCTs, in combination with the findings of the meta-analysis, suggest that, if fluoxetine is started within 2 weeks of ischemic or hemorrhagic stroke and is administered in a dose of 20 mg/d for 3–6 months, there is a 3%–4% reduced risk of new onset depression; however, there is no improvement in the likelihood of achieving independence or of reduction of disability. The risk of several adverse outcomes is increased; these include falls (by 2%), bone fractures (by 1%–2%), seizures (by 1%), and hyponatremia (by 1%). Fluoxetine is also associated with the theoretical risk of adverse drug interactions in stroke patients. In summary, there does not appear to be a role for the routine use of fluoxetine in poststroke pharmacologic care.

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During 2016, across the world, neurologic disorders were the leading cause of burden operationalized as disability-adjusted life-years (DALYs) and the second leading cause of deaths; stroke was the single largest contributor to the burden of disease, accounting for 42% of the neurologic disorder DALYs.[1] The burden associated with stroke is greater in countries with poorer resources. Because stroke is a disorder the risk of which increases with age, and because the global population is aging because of improved life expectancy, the burden of stroke is likely to increase.[2]

Important long-term poststroke disabilities include motor deficits, cognitive deficits, and depression; these impair function and reduce quality of life.[3,4] In this context, there are theoretical grounds to hypothesize that a selective serotonin reuptake inhibitor (SSRI), such as fluoxetine, may improve not just mood but also cognitive, motor, and functional outcomes after stroke.[5]

Fluoxetine for Stroke: Benefits Beyond Antidepressant Effects

Fluoxetine was the first SSRI to be marketed in the US.[6] Over a decade ago, Yi et al[7] described a systematic review and meta-analysis of 6 randomized controlled trials (RCTs; pooled N = 385) that examined whether fluoxetine is safe and effective in the prevention of depression after stroke. The authors[7] found that fluoxetine did substantially reduce the odds of poststroke depression (odds ratio [OR], 0.25; 95% confidence interval [CI], 0.11–0.56). Importantly, they found that, in addition, fluoxetine was associated with significantly greater recovery of neurologic functioning as well as with improvement in independence in activities of daily living. Fluoxetine was not associated with an increased risk of adverse events.

Mechanisms of Benefits With Fluoxetine

What could be the mechanisms through which fluoxetine might improve neurologic and psychiatric outcomes after stroke? For starters, because fluoxetine is an antidepressant drug, and because antidepressant drugs prevent as well as treat depression, it is conceivable that the same mechanisms that prevent relapse or recurrence of depression in patients with mood disorders may operate to prevent new-onset depression in patients after stroke.

As a nonspecific mechanism, by preventing or treating poststroke depression, fluoxetine may attenuate depression-associated health risk behaviors such as nonadherence to medical recommendations related to diet, exercise, and medication use. As a specific mechanism, antidepressants stimulate neuroplasticity, and neuroplasticity has been suggested to drive antidepressant action.[8] The neuroplasticity response is most evident in the hippocampus. Because the hippocampus is the seat of learning and memory in the brain,[9] stimulation of hippocampal neuroplasticity may also

carry cognitive benefits poststroke. As an additional mechanism, the administration of fluoxetine in animal models of ischemic stroke has been shown to protect against inflammatory neurotoxicity[10]; such benefits may operate in humans, as well. SSRIs have also been shown to increase vascular endothelial growth factor levels[11]; the promotion of angiogenesis may provide the vascular support necessary for the neuroplasticity changes.

Last but not least, SSRIs inhibit platelet aggregation and reduce the risk of ischemic events through this and other mechanisms,[12,13] potentially reducing the risk of deterioration due to future stroke events.

Meta-Analysis: Fluoxetine for Recovery From Stroke[14]

Patients with stroke commonly have motor deficits, and these compromise quality of life and result in disability and loss of independence that persist into the very long term.[3,4] If fluoxetine truly improves neurologic and functional outcomes, as suggested by the meta-analysis by Yi et al,[7] then stroke could open a new frontier for the use of the drug.[5] A large number of RCTs have now investigated this possibility. These RCTs were examined in a systematic review and meta-analysis by Mead et al.[14]

These authors[14] searched electronic databases, reference lists, and other sources and identified 13 RCTs (pooled N = 4,145) of fluoxetine monotherapy for patients with stroke. Almost all RCTs dosed fluoxetine at 20 mg/d with treatment most commonly initiated within the first 2 weeks after stroke. One study administered fluoxetine as a single dose; most of the others administered the drug for 2–3 months. The comparison group was a placebo-treated arm in 9 RCTs and standard care in the rest. Five RCTs had been conducted in China, and most of the rest, in European countries. The data were examined in fixed effect meta-analyses so that small RCTs would not disproportionately bias outcomes as happens in random effects models.

Primary Outcome Results From the Meta-Analysis[14]

Independence and disability were coprimary outcomes. Independence was predefined as a poststroke modified Rankin Scale score of 0–2. In the 3 RCTs (N = 3,249) that reported independence, there was no significant difference between fluoxetine and control groups in the proportion of patients independent after treatment (36.6% vs 36.7%; risk ratio [RR], 1.00; 95% CI, 0.91–1.09). Disability, as operationalized in individual RCTs, also did not differ significantly between fluoxetine and control groups (7 RCTs; N = 3,404; standardized mean difference [SMD], 0.05; 95% CI, −0.02 to 0.12). There was considerable heterogeneity in both meta-analyses.

In random effects sensitivity analyses, the result for independence remained nonsignificant, but the result for disability showed a small effect size that favored fluoxetine, indicating the biasing effects of the small RCTs. Additionally, when one very large RCT[15] was excluded from the fixed effect meta-analysis, for both primary outcomes the meta-analysis results significantly favored fluoxetine over control treatment. However, the analysis favoring fluoxetine for independence was based on just 2 RCTs with 142 patients, and the analysis for disability was based on 6 RCTs, of which the 3 RCTs that significantly favored fluoxetine were all from China, a part of the world that has been associated with studies with untrustworthy results.[16]

Secondary Outcome Results From the Meta-Analysis[14]

In secondary analyses, on the positive side, fluoxetine was associated with better improvement in neurologic deficit scores (8 RCTs; N = 803; SMD, −0.28; 95% CI, −0.42 to −0.14), with lower depression scores (6 RCTs; N = 3,113; SMD, −0.16; 95% CI, −0.23 to −0.09), and with fewer diagnoses of depression (2 RCTs; N = 3,194; RR, 0.77; 95% CI, 0.65–0.90). Heterogeneity was high in all analyses. On the negative side, fluoxetine was associated with a higher risk of seizures (7 RCTs; N = 3,815; 3.9% vs 2.6%; RR, 1.49; 95% CI, 1.05–2.11); the higher risk of gastrointestinal adverse effects narrowly missed statistical significance (7 RCTs; N = 688; RR, 1.38; 95% CI, 0.99–1.94); heterogeneity was low to absent. The results were broadly similar in the sensitivity random effects meta-analyses.

In other secondary analyses, there was no significant difference in outcomes between fluoxetine and control arms for motor score (5 RCTs; N = 3,079; SMD, 0.06; 95% CI, −0.02 to 0.13), cognition (2 RCTs; N = 2,834; SMD, −0.04; 95% CI, −0.11 to 0.03), and death (11 RCTs; N = 3,824; RR, 1.00; 95% CI, 0.79–1.26). There was also no significant difference between fluoxetine and control groups for serious bleeding (2 RCTs; N = 3,477; RR, 1.10; 95% CI, 0.72–1.62) and dropout before the end of the first follow-up (11 RCTs; N = 3,972; RR, 0.92; 95% CI, 0.61–1.40). Disability at follow-up, 6 months beyond the end of the treatment period, was reported in only 2 trials (N = 2,924); there was no advantage for fluoxetine (SMD, −0.11; 95% CI, −0.17 to 0.40).

In analyses of 9 outcomes in studies at low risk of bias, only depression scores and gastrointestinal adverse effects significantly differentiated the fluoxetine from control groups; fluoxetine was associated with a small reduction in depression scores (SMD, −0.11) and with a doubled risk of gastrointestinal adverse effects (RR, 2.19). These results are of only academic interest because there were only 2–3 RCTs in 7 of the analyses and 4 RCTs in the remaining 2 analyses.

New Data

The FOCUS trial[15] strongly dominated the results of the meta-analysis by Mead et al[14]; its weight was 99% in the 3-RCT analysis for the independence outcome and > 83% in the 7-RCT analysis for the disability outcome. So, the meta-analysis results were really mostly about FOCUS rather than about all the RCTs that had been identified. This is a situation that is not ideal in meta-analysis. Reassuringly, 2 large new RCTs have been published, both with findings that support those of FOCUS.[15]

The new RCTs were AFFINITY[17] and EFFECTS.[18] FOCUS, AFFINITY, and EFFECTS were similar in many

ways. All were multicenter trials, conducted in patients with all types of stroke. FOCUS was conducted in 103 centers in the UK; AFFINITY in 43 centers in Australia, New Zealand, and Vietnam; and EFFECTS in 35 centers in Sweden. Whereas FOCUS recruited 3,127 patients, AFFINITY and EFFECTS recruited 1,280 and 1,500 patients, respectively. In all 3 trials, patients were recruited 2–15 days after stroke, and fluoxetine was administered in the dose of 20 mg/d for 6 months; medication adherence was good.

In all 3 trials, the primary outcome, the distribution of modified Rankin Scale categories, was similar in the fluoxetine and placebo groups; the adjusted common OR was 0.95, 0.94, and 0.94 in FOCUS, AFFINITY, and EFFECTS, respectively. FOCUS (by 3.8%) and EFFECTS (by 3.6%) but not AFFINITY found a significantly lower risk of poststroke depression with fluoxetine. In all 3 trials, with the exception of mood, fluoxetine was no better than placebo on any domain in the Stroke Impact Scale. All 3 trials found an increased risk of bone fractures with fluoxetine: by 1.4%, 2.0%, and 2.3% in FOCUS, AFFINITY, and EFFECTS, respectively. AFFINITY additionally found a 2.0% higher risk of falls and a 1.2% higher risk of seizures, and EFFECTS additionally found a 1.3% higher risk of hyponatremia.

The findings of these RCTs are important because the RCTs were very large, well designed, well conducted, and well analyzed; because they recruited elderly men and women of different ethnicities and with all types of stroke; because fluoxetine was given an adequate trial (20 mg/d for 6 months); and because many clinically important outcomes were assessed. It is very unlikely that a new RCT in the field will change anything.[19]

Take-Home Message

When fluoxetine is started within 2 weeks of ischemic or hemorrhagic stroke and is administered in a dose of 20 mg/d for 6 months, there is a 3%–4% reduced risk of new onset depression; fluoxetine, however, does not improve the odds of achieving independence, nor does it reduce measures of disability. Disturbingly, fluoxetine increases the risk of several adverse outcomes, including falls (by 2%), bone fractures (by 1%–2%), seizures (by 1%), and hyponatremia (by 1%). These findings do not encourage the routine use of fluoxetine in poststroke pharmacologic care. Besides fluoxetine, sertraline, paroxetine, citalopram, and escitalopram have also been trialed in patients with acute stroke; the general conclusion appears to be that there is currently no indication for the routine prescription of SSRIs to promote stroke recovery.[20] At best, an SSRI may be trialed in combination with neurorehabilitation because this is one area that has not been systematically studied.[19]

Parting Notes

Patients may receive drugs such as aspirin or clopidogrel after ischemic stroke. If SSRIs are prescribed to elderly patients receiving these drugs, the risk of bleeding is increased, especially at gastrointestinal sites.[12,13] An additional concern is that fluoxetine and fluvoxamine inhibit cytochrome P450 2C19 and can therefore interfere with the activation of and the benefits with clopidogrel.[21]

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