Should Every Patient With Stroke Be on Selective Serotonin Reuptake Inhibitors?

No

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Attempts to enhance the rehabilitation and recovery process is an admirable goal that is showing more promise in recent years. The investigation of brain reorganization and repair is currently one of the most active and exciting fields in neuroscience. We as standard-bearers of stroke treatment, however, must resist unbridled enthusiasm and exercise caution in the clinical setting. With regard to whether the patient before us should be given fluoxetine for the purpose of enhancing recovery of his motor and language deficits, I must vote an emphatic and decisive “No.” Giving fluoxetine to this patient at this time is not justified by our current state of knowledge.

We have tantalizing evidence of potential benefit of selective serotonin reuptake inhibitors in stroke. A recently published clinical trial, Fluoxetine for motor recovery after acute ischemic stroke (FLAME), was well designed and well executed, containing the elements required to maximize likelihood of reaching a secure conclusion: double blinding, randomization, and adequate statistical power. Among 118 patients with acute stroke with severe hemiparesis, those given 20 mg fluoxetine orally daily starting 5 to 10 days after stroke onset showed greater gains in Fugl-Meyer motor score at 90 days compared with the placebo group. Not unexpectedly, given the actual current indication for selective serotonin reuptake inhibitors, the incidence of poststroke depression was substantially lower in the fluoxetine group.

Although the results of this trial were statistically significant, questions remain regarding clinical readiness, which are directly applicable to the patient before us: (1) How much of the effect was due to the antidepressant action of fluoxetine as opposed to true enhancement of neuroplasticity? The trial results are reported to be significant after adjusting for depression, but there may still be an important interaction with mood, unquestionably a mediator of recovery. (2) Is there solid evidence for mechanism? Although selective serotonin reuptake inhibitors may act by suppressing poststroke hyperexcitability in the unaffected hemisphere, there is no direct preclinical evidence of this effect nor explanation of how this action might alter the recovery process at the cellular level. (3) Are the findings relevant to nonmotor deficits? Our patient has a significant aphasia, which may be a more important determinant of recovery than his motor deficit and was not addressed by this trial. (4) How generalizable are the results to patients with milder stroke deficits? The patient has a Fugl-Meyer motor score of 35, >1.5 SD higher than the average Fugl-Meyer motor score in the trial. Mild-to-moderate hemiparetic patients tend to recover well spontaneously; how much additional gain can be expected in this case? (5) Does the timing of administration matter? Patients in the FLAME trial were started at a mean of 8.9 days. Administration at 3 days could produce different results. (6) What happens when the patient stops the medication? Beyond outcomes at 90 days, we are responsible for our patients’ long-term well-being. (7) What about side effects of the drug? Nausea, insomnia, and epileptic seizures have been reported.

We are also asked to consider promoting physical and speech therapy within the first 48 to 72 hours. Even less is known about whether very early intensive physical and speech therapy is beneficial. Although an enhanced neuroplasticity window appears to open early after stroke, intervening in the first 72 hours when blood pressure fluctuations, edema, and medical comorbidities are present may make this early time period detrimental rather than beneficial. Some Phase III clinical trials in which early physical therapy has shown harm rather than benefit. In short, we have far too limited data to promote fluoxetine or very early therapy this patient. One must be sure of one’s actions before opting to apply results of a single clinical trial to our patients, particularly when clinical criteria do not match well.

Translating Clinical Trials to Clinical Practice

The question of generalizability from any trial is important for the individual practitioner. The field of stroke recovery is rife with case series and small clinical trials in which beneficial results are not replicated by other studies. Even knowing this, a recent study of practices among 4 rehabilitation centers in Switzerland showed that use of pharmacological agents to enhance rehabilitation occurred in 34.3% of
patients despite an absence of clinical indication. Interestingly, use was not determined by demographic or clinical characteristics of patients, but rather by the center where the physicians practiced, suggesting that arbitrary standards may emerge organically based on a culture at a given institution. Furthermore, even when a practice becomes broadly accepted, “reversals” in medicine are not uncommon. Recently in the New England Journal of Medicine, of 124 studies that made some claim with respect to a medical practice, 16 (13%) were reversals. This implies that for a period of time during which a given practice was considered effective, an error, or even harm to patients, was being perpetrated by unknowing treating physicians.

I therefore urge caution. We must resist the temptation to jump on the bandwagon of enthusiasm of selective serotonin reuptake inhibitors and act responsibly. We must await confirmation that the use of fluoxetine is broadly applicable for poststroke recovery, especially among patients who do not fit the highly controlled criteria of a clinical trial. Let us not be guilty of perpetrating errors on our patients because of an incompletely informed understanding.

Disclosures

None.

References


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