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Point/Counterpoint

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Should This Patient With Ischemic Stroke Receive Fluoxetine?

CASE SCENARIO

You admit T.R., a 75-year-old man, to your inpatient rehabilitation unit 10 days after a stroke. He has a medical history of hypertension and type II diabetes. On the day of his admission to the neurology service, he experienced a sudden onset of severe left-sided weakness with a facial droop and slurring of speech. His husband was driving them both to a social event at the time and detoured immediately to the emergency department, where the patient received tissue plasminogen activator (tPA) for a large, right middle cerebral artery thrombosis seen on magnetic resonance imaging. There was no hemorrhage noted on the initial scan, but a very small area of peri-infarct hemorrhage was noted after the administration of tPA. The tPA resulted in a modest improvement in weakness.

Family history was significant for a mother and sister both successfully treated for severe, idiopathic depression with oral medications. Social history reveals that T.R. is a retired accountant who lives in a ground-story home with his husband of 30 years, who is also retired and is in good health. The patient's acute hospital course was complicated by aspiration pneumonia that required intravenous antibiotics and blood sugars ranging from 200 to 300 that required insulin coverage in addition to his oral hypoglycemic medications. He experienced a few episodes of orthostasis with lightheadedness while going from sitting to standing, but this lightheadedness resolved with adjustment of blood pressure medications.

On admission to your rehabilitation unit, T.R. is a quiet, elderly man who speaks only when asked a question but offers no spontaneous information. He demonstrates a moderate left hemiparesis with manual muscle testing scores of 3+ in most upper and lower extremity muscle groups. He also has sensory extinction on the left and mild visual neglect. On the first day, he required moderate assistance with most activities of daily living because of poor trunk balance and neglect. He walked 15 feet with rolling platform walker with moderate assistance for advancing the left leg, left-sided neglect, and poor balance. Medications on admission to rehabilitation included glyburide, hydrochlorothiazide, losartan, lisinopril, clopidogrel, aspirin, as-needed acetaminophen for shoulder pain, oral cephalexin, and subcutaneous unfractionated heparin.

The husband spent time searching the Internet for stroke treatments and approaches you about starting T.R. on fluoxetine 20 mg daily. As part of the conversation, the husband states that T.R. does not appear depressed to him and that his partner has always been a "man of few words," a stoic type.

Should this patient be given fluoxetine to improve motor function? Dr Heidi Schambra will argue that fluoxetine should be administered. Dr Brian Im argues that fluoxetine should not be administered at this time.

Heidi Schambra, MD, Responds

I would prescribe this patient fluoxetine. His is a case of a large right middle cerebral artery territory ischemic stroke, appropriately treated with thrombolytics. Although tissue plasminogen activator (tPA) is the only medication approved by the U.S. Food and Drug Administration (FDA) for the treatment of ischemic stroke, the vast majority of patients with ischemic stroke *do not* receive tPA—estimated as high as 98% nationally [1]—and its administration rarely results in total reversal of deficits. A large proportion of patients who experience stroke will thus go on to have deficits that often are severe and chronic. The patient could achieve up to 70% of his total possible recovery in the coming 3 months [2], but a 70% improvement from a

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baseline of moderate or severe impairment still translates to significant limitations. It is thus not surprising that stroke is the leading cause of serious long-term disability in the United States [3]. It is my belief that impairment after stroke is a modifiable outcome. We in neurorehabilitation can do better than just hope for endogenous biological recovery to "do its best." Given ever-diminishing lengths of stay in acute rehabilitation, attention has shifted recently to the role of recovery adjuvants—interventions that alone do not induce plasticity but amplify the activity-dependent plasticity driven by training. Fluoxetine is one of the only pharmacologic agents that has been shown to impact recovery after stroke and may serve this role.

As physicians, we may lawfully prescribe FDA-approved drugs for a nonapproved indication when it is justified by scientific evidence. When considering a medication's off-label use, we must consider whether there are rigorous scientific data for efficacy and safety when used for the new indication. What is the evidence for fluoxetine's use in poststroke recovery?

The 2011 Fluoxetine for Motor Recovery after Acute Ischemic Stroke (FLAME) study was a randomized, placebo-controlled, double-blind, multicenter phase 2 trial whose investigators evaluated the effects of fluoxetine on motor recovery [4]. One-hundred eighteen ischemic stroke patients with moderate-to-severe motor impairment and no active depression were enrolled in the first week after their stroke. For 3 months, they received fluoxetine 20 mg daily or a placebo, in addition to conventional rehabilitation therapy. At 3 months, the fluoxetine group had a 10-point greater improvement on the upper-extremity Fugl-Meyer scale than the placebo group (P =.002), exceeding the minimal clinically important difference for impairment reduction [5]. In addition, 26% of patients in the fluoxetine group achieved functional independence on the modified Rankin Score (mRS), compared with 9% in the placebo group (P = .015). Importantly, these improvements in motor outcomes remained even after statistical adjustment for fluoxetine's expected antidepressant effects.

A recent Cochrane review, which collected evidence from 4059 patients, also found evidence that selective serotonin reuptake inhibitors (SSRIs) improved functional outcomes in stroke patients [6]. Fluoxetine is believed to have neurotrophic and neuroprotective mechanisms of action (reviewed in Mead 2012 [6]) [7]. These collective findings point to an advantageous influence of fluoxetine when paired with rehabilitation in the recovering stroke patient.

Also notable in this case is the patient's withdrawn behavior, which could be his personality baseline but also may be an early sign of depression. After stroke, patients are at high risk for depression, with a prevalence of 30%-60% and high rate of underdiagnosis resulting from concomitant cognitive and language deficits [8]. The patient's strong family history for depression is also a risk factor for depression after stroke [9]. Poststroke depression is associated with reduced engagement in rehabilitative therapy; diminished long-term function, participation, and quality of life; caretaker and societal burden and cost; and greater rate of mortality [9-11]. Although depression prophylaxis is not standard practice after stroke, a recent meta-analysis pooled from 776 stroke patients found that SSRIs reduced the odds of developing poststroke depression in previously nondepressed patients [12]. This effect was also evident in the FLAME trial: in this group of patients who were not depressed at baseline, significantly fewer in the fluoxetine group became depressed than in the placebo group (7% versus 29%, $P = .002$). Although the prevention of depression is not a primary indication for the use of fluoxetine in this patient, this outcome would be a welcome secondary benefit.

What about the risks of using fluoxetine? Three specific issues must be considered before administering fluoxetine in this case: the patient's small hemorrhagic conversion, clopidogrel use, and history of ischemic stroke.

Fluoxetine may reduce platelet adhesion and aggregation. In a meta-analysis of more than 500,000 patients without stroke, SSRIs were associated with a relative risk of 1.48 for intracranial hemorrhage; however, the absolute risk remains quite low: "given an estimated global incidence of 24.6 per 100,000 person-years, 1 additional intracerebral bleeding episode per 10,000 persons treated for 1 year could be expected" [13]. This increased risk of hemorrhage is almost immediately present and doesn't accrue with exposure. Although the lack of symptomatic hemorrhages in the FLAME trial is somewhat reassuring, it is possible that the fluoxetine sample size was too small to reflect population-level incidence.

Contrarily, fluoxetine may reduce the efficacy of clopidogrel. Coadministration of fluoxetine was shown to attenuate the antiplatelet effects of clopidogrel by approximately 25% [14]. Although the results are concerning, this study was carried out in a very small group ($n = 8$) of healthy young control patients given a single coadministration of the medications; validation in a demographically matched, larger sample is merited. If confirmed, it is unclear what functional ramifications this decrease may have on the rate of cerebrovascular events or how this effect may interact with ostensible antiplatelet effects.

Finally, a recent cohort study in a group of more than 16,000 ischemic and hemorrhagic stroke patients found an increased rate of event recurrence in those taking antidepressants [15]. After adjustment for patient demographics, stroke risk factors, and antiplatelet and anticoagulant medications, patients on SSRIs had a significantly increased risk of 1.31% for recurrent ischemic stroke and nonsignificantly increased risk of

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