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Should this patient with ischemic stroke receive fluoxetine?

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CASE SCENARIO

You admit T.R., a 75-year-old man, to your inpatient rehabilitation unit 10 days following a stroke. He has a past 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 to a social event at the time and detoured immediately to the Emergency Department where he 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 TPA administration. 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. Socially 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 acute hospital course was complicated by aspiration pneumonia requiring intravenous antibiotics and blood sugars ranging from 200-300 requiring insulin coverage in addition to his oral hypoglycemic medications. He experienced a few episodes of orthostasis with light headedness while going sit to stand, but this 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 (ADLs) due to 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 TR on fluoxetine 20mg daily. As part of the conversation, the husband states that TR does not appear depressed to him and that his partner has always been a "man of few words," stoic type.

Should fluoxetine to improve motor function Should this patient be given fluoxetine to improve motor function? Dr. Heidi Schambra will argue that fluoxetine should be administered. Dr 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 (MCA) territory ischemic stroke, appropriately treated with thrombolytics. Although tissue plasminogen activator (tPA) is the only U.S. Food and Drug Administration (FDA)-approved medication 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 stroke patients will thus go on to have deficits that are often 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 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 US. (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 recently shifted 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 pharmacological 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 non-approved indication when it is justified by scientific evidence. When considering a medication's off-label use, we must consider whether there is rigorous scientific data for efficacy and safety when used for the new indication. What is the evidence for fluoxetine's use in post-stroke recovery?

The 2011 Fluoxetine for Motor Recovery after Acute Ischemic Stroke (FLAME) study was a randomized, placebo-controlled, double-blind, multi-center phase II trial evaluating 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 daily fluoxetine 20 mg 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 (UEFM) 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 modified Rankin Scores (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, collecting evidence from 4059 patients, also found positive evidence for selective serotonin reuptake inhibitor (SSRIs) improving functional outcomes in stroke patients. (6) Fluoxetine is believed to have neurotrophic and neuroprotective mechanisms of action (reviewed in Mead 2012.) (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 may also 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 under-diagnosis due to concomitant cognitive and language deficits. (8) The patient's strong family history for depression is also risk factor for depression after stroke. (9) Post-stroke 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 higher mortality rate. (9-11) While depression prophylaxis is not standard practice following stroke, a recent meta-analysis pooled from 776 stroke patients found that SSRIs reduced the odds of developing post-stroke depression in previously non-depressed 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% vs. 29%, $P = .002$). Although depression prevention 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 over 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. Co-administration of fluoxetine was shown to attenuate the antiplatelet effects of clopidogrel by approximately 25. (14) While concerning, this study was carried out in a very small group (n=8) of healthy young controls given a single co-administration 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 anti-platelet effects.

Finally, a recent cohort study in a group of over 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 anti- platelet and -coagulant medications, patients on SSRIs had a significantly increased risk of 1.31 for recurrent ischemic stroke and nonsignificantly increased risk of 1.23 for recurrent hemorrhagic stroke. While these rates are concerning, one must be careful about inferring causality from correlation. Depression alone is associated with increased risk of stroke (16)

and stroke recurrence. (17) and may be a confounder. This study also does not account for different medications, doses, or durations of use within a class. To definitively establish causality between exposure and adverse outcomes, large randomized controlled trials must be performed.

Fortunately, there are currently 3 large multicenter randomized controlled trials (FOCUS, AFFINITY, and EFFECTS) underway that share a core protocol investigating fluoxetine given for 6 months post-stroke. (7) The effects of fluoxetine on disability reduction and depression prevention will be assessed out to one year post-stroke. Because these studies are expected to collectively enroll 6000 participants, we can expect definitive answers about fluoxetine's long-term efficacy and safety profile in ischemic and hemorrhagic stroke populations. These trials should be completed by 2018.

In the meantime, we must base our judgment on the available clinical data. Overall there is good evidence that our patient may benefit from fluoxetine. The risks of fluoxetine in this patient appear to be low. The patient's medical and neurological profile aligns with the inclusion criteria and patient characteristics of the FLAME trial. In terms of the management, I would educate the patient and his husband about the potential benefits and risks of using the fluoxetine off-label. If amenable, I would begin the patient on fluoxetine 10 mg qd with an increase to 20 mg qd in 5-7 days. The patient should remain on fluoxetine 20 mg qd for 3 months, barring major or unendurable side effects.

The safety profile of fluoxetine is well known. Like any medication, its use should be monitored for side effects (Eli Lilly, a. C. (2015). FDA Package Insert. medlibrary.org). Possible adverse reactions include serotonin syndrome, anaphylaxis, lowered seizure threshold, hyponatremia, QTc prolongation, and Torsade de Pointes. Recent or concurrent use of a MAO-I, pimozide, or thioridazine is a contraindication. Less significant but more common side effects are insomnia, anxiety, rash, diarrhea, nausea, anorexia, dry mouth, and sexual dysfunction. Given the long half-life of fluoxetine, abrupt cessation is less likely to cause serotonin withdrawal syndrome. Given his hemorrhagic conversion, I would obtain a head CT before and one week following the initiation of fluoxetine, and monitor for changes in neurological status. I would also obtain an electrocardiogram before and after every adjustment in fluoxetine dose; clinical monitoring for arrhythmias and aggressive management of hypokalemia and hypomagnesemia are also necessary. Sodium should be tracked initially. Evidence of any serious or intolerable side effects warrants drug cessation.

In sum, I would encourage the use of fluoxetine in this patient. The FLAME study was a high-quality clinical trial which supports the use of fluoxetine for motor recovery. While there remain concerns about SSRI use in stroke, definitive evidence for increased risk is lacking. At this time, the potential benefits of fluoxetine appear to outweigh its potential risks.

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