Numerous studies failed to translate promising experimental data into clinically effective neuroprotective or neurorestorative therapies for acute ischemic stroke since the introduction of recombinant-tissue plasminogen activator in 1996. Amid gloomy pessimism, the results of the fluoxetine for motor recovery after acute ischemic stroke (FLAME) trial in 2011 ignited hope and restored optimism. FLAME was a double-blind, placebo-controlled trial examining the effects of treatment with the selective serotonin reuptake inhibitor (SSRI), fluoxetine, in patients 5 to 10 days after an acute ischemic stroke. Motor improvement to 90 days poststroke, measured as a change in Fugl-Meyer Motor Scale score, was significantly greater in the fluoxetine-treated patients who also had less disability at day 90, defined as modified Rankin Scale score \( \leq 2 \). Despite some criticisms regarding the limitations of the study and the generalization of its conclusions, the message from FLAME was tempting and appealing. Only a few of acute stroke patients can access and benefit from the currently available reperfusion therapies because of the limited therapeutic time window, whereas the potential neurorestorative effects of fluoxetine and its longer window for intervention poststroke could help many stroke patients. This led many to wonder if SSRIs should be routinely prescribed to acute stroke patients. After all, SSRIs are one of the most commonly prescribed classes of medications today.

The mechanism(s) underlying SSRIs’ putative neurorestorative effects are not fully elucidated. FLAME suggests that the effects of fluoxetine on poststroke recovery may be independent of its antidepressant effects. Dr Marshall and others have lingering doubts and question how much of the effect was because of the antidepressant action of fluoxetine as opposed to the true enhancement of neuroplasticity. This is clearly a valid question, but does it merit concern. Does the lack of a well-defined mechanism of action justify the argument for not using a therapy despite some evidence of efficacy from a randomized, controlled, and overall well-conducted study? Poststroke depression is one of the most frequent complications of stroke, with a prevalence ranging from 20% up to 60%. The long-term adverse psychological, social, and economical consequences of depression, regardless of its cause, do not need to be restated. Furthermore, the secondary effects of depression, including alterations of weight and appetite, disturbed sleep, loss of energy, and psychomotor retardation, can hinder patients’ ability to actively participate in rehabilitation poststroke. SSRIs, including fluoxetine, are clearly effective in ameliorating depression, and on this basis alone their use could be justified in up to 60% of stroke patients. We tend to agree with Dr Chollet that there is clearly a need for more evidence to support the routine use of SSRIs to promote motor recovery after stroke and to probe their mechanism(s) of action. Although the overall risk versus potential benefit supports their use in a large number of stroke patients, particularly those with depressive symptoms, it remains uncertain whether their routine use is justified in nondepressed patients given the associated costs. In our patient who takes a proton-pump inhibitor and likely has a gastroesophageal reflux disease, some might be cautious about prescribing SSRIs without a definite indication. Scattered reports link the use of SSRIs to the development or worsening of gastroesophageal reflux disease-like symptoms. However, strong evidence supporting this association is lacking. In fact, emerging evidence suggests that SSRIs could be beneficial in treating gastroesophageal reflux disease, especially when related to hypersensitive esophagus and functional heartburn. Regardless, we advocate a thorough discussion with the patient regarding the rationale for proposing treatment with SSRI and its potential benefits versus risks.

Although the data supporting the benefits of early intensive rehabilitation or SSRI use in nonmotor deficits, such as aphasia, is lacking, we also agree that intensive rehabilitation and mobilization should be encouraged as early as possible after stroke onset, once it is deemed medically safe by the treating physicians. Although the rate and extent of recovery after stroke depend on several interconnected factors, such as stroke severity, age, and comorbidities, the A Very Early Rehabilitation Trial (AVERT) study showed that mobilization within the first 24 hours of stroke and at regular intervals is safe, feasible, and fast-track return to walking unassisted increasing the likelihood of milder stroke patients being discharged to home and is independently...
associated with good functional outcomes at 3 and 12 months. Early mobilization is also advocated to prevent poststroke complications such as contractures and deep vein thrombosis.

To summarize, we do support initiation of rehabilitation and mobilization as early as possible after stroke and think that the use of SSRIs is probably indicated in a large number of stroke patients merely based on their antidepressant effects. We advocate thoroughly evaluating our patients for poststroke mood disorders and discussing the rationale for SSRI use on a patient-by-patient basis as more data regarding their neurorestorative effects continue to emerge.

Disclosures
None.

References

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Poststroke Treatment With Selective Serotonin Reuptake Inhibitors: A Journey From Sadness to Motor Recovery
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