Failure of First SSRI for Depression — What is the Next Step?

Hagai Maoz, MD

Shalvata Mental Health Center, Hod Hasharon, Israel

Abstract: Failure in treating major depression with SSRI is common in clinical psychiatry. To date, there is no specific guideline how to deal with such a failure. This review is aimed at trying to answer the important question of the next step. Since there are no such guidelines, this decision should be made according to the clinical response for the first SSRI, the tolerability to the drug and the clinical practice of the physician.

Major depressive disorder accounts for 4.4% of total overall global disease burden. The prevalence of major depression in the United States is 5.4 to 8.9% (1), and its lifetime prevalence of major depression is estimated between 15 and 20 percent (1). The goal of treatment in major depression is remission, the absence of symptoms. Response is typically defined as a clinically meaningful reduction in symptoms (e.g., a reduction of at least 50% in baseline symptom level). However, response that falls short of remission is suboptimal because it is associated with continued disabling symptoms, negative effects on other axis I and axis III disorders, higher rates of relapse and recurrence, poorer work productivity, more impaired psychosocial functioning, higher levels of health care use, and potentially higher risk for suicide. Remission, on the other hand, is associated with return of normal psychosocial function, higher rates of sustained remission, and lower rates of relapse, lower risk of suicide and alcohol/drug abuse, and lack of disabling symptoms (2).

Remission rates from research-based, 8-week, randomized, placebo-controlled efficacy trials range from 25% to 40% (2), and 12-week efficacy trials with subjects suffering from chronic depression reveal even more modest remission rates of 22% to 30% (2).

SSRIs and other newer antidepressant drugs with greater safety margin constitute first-line medications for moderate-to-severe depression, particularly for outpatients and for patients treated by primary care physicians (2). The acute treatment phase usually lasts 6 to 10 weeks. Thirty to 50% of patients have substantial residual symptoms after adequate first-line treatment with SSRI (1). If there has been no improvement after four weeks of treatment, the ultimate response is almost certainly going to be inadequate (1).

Nonresponse to medication requires a treatment change. Raising the dosage of the current drug given would have been a logical possibility for patients with inadequate response, but no clearcut plasma concentration-clinical effectiveness relationship in patients with depression has been shown, nor has any threshold which defines toxic concentrations (3). Switching to an antidepressant from a different pharmacologic class minimizes polypharmacy and reduces the risk of adverse drug interactions and side effects. The disadvantage of switching agents may be the lost of partial response from the initial drug and a delay in the onset of antidepressant action from the second. Augmentation with a different antidepressant, mood stabilizer or thyroid hormone is another possibility.

The Geneva Outpatient Depression Study (GODS) was aimed to create an algorithm for treating major depression after not reaching remission with the first SSRI. In this study, data regarding 131 patients after a failure to achieve remission with SSRI was analyzed. The most unforeseen and fascinating

Address for Correspondence: Hagai Maoz, MD, Shalvata Mental Health Center, Hod Hasharon, Israel.
E-mail: hagaima@clalit.org.il
outcome of this study was the large dropout rate (65.6%) that made it impossible to construct such an algorithm (4).

Switching to a Different Agent

To date, there are no clear recommendations for the next step after a failure of the first treatment trial with SSRI. The main study trying to answer that question is the Sequenced Treatment Alternatives to Relative Depression (STAR*D) trial that is being conducted in primary and psychiatric care settings (5). The level 2 of the trial examined switching treatment with citalopram to a different agent. The researchers randomly assigned 727 adult outpatients with nonpsychotic depression who had no remission or could not tolerate the SSRI citalopram. There were four switch options (monotherapy with sustained-release bupropion, sertraline, extended-release venlafaxine, or cognitive therapy). The remission rates did not differ significantly among the three antidepressant switch strategies (21.3% with bupropion sustained-release, 18.1% with sertraline, and 24.4% with venlafaxine extended release). The conclusion was that after unsuccessful treatment with an SSRI, approximately one in four patients had a remission after switching to another antidepressant. None of the medication showed superiority over the others (7).

In clinical practice, it is popular to switch after the failure of SSRI to a different drug that targets dopamine, norepinephrine, or a combination of serotonin, norepinephrine and dopamine. There is some suggestive evidence that the dual uptake inhibitors are associated with a slight higher remission rate (6). However, STAR*D suggests that this is not necessarily more efficient than switching to a different SSRI.

Ruhe et al. (8) tried to systematically review the evidence for switching pharmacotherapy after a first SSRI. They analyzed eight randomized controlled trials and 23 open studies. Observed response rates after switching to any classes of antidepressants varied between 12–86% and the remission rates were between 7–82%. Reasonably, remission rates were negatively correlated to the number of previous treatments. Conclusions were that after a first SSRI, any switch within or between classes of antidepressants appear legitimate without clear preference to one of the groups.

Augmentation

Another approach is the use of combination of two antidepressants from different classes with complementary mechanisms of action, in order to avoid loss of partial response to the first medication. This approach may increase the risk of drug interactions and new side effects, as well as the cost of treatment. On the other hand, augmenting antidepressant medication with another agent may enhance the antidepressant efficacy and thus it is possible to avoid transition from treatment with SSRI to another medication.

In the STAR*D trial these augmented treatments were compared among patients who did not have remission or who had intolerance to citalopram. The trial examined 1,439 patients, 565 of whom were randomly assigned to receive augmentation with sustained-release bupropion or buspirone. Remission rates were slightly higher for bupropion, but the difference was not statistically significant (29.7% of patients achieved remission with citalopram plus bupropion sustained-release, and 30.2% achieved remission with citalopram plus buspirone). The remission rates in this trial were similar to those found in most previous uncontrolled trials of augmentation of SSRIs.

Lithium is a popular first-line augmenting agent (1). Thyroid supplements have been advocated even in the absence of clinical hypothyroidism for the purpose of enhancing antidepressant action. The level 3 of the STAR*D trial compared augmentation with lithium (mean dose 859.8 mg/d and mean blood level 0.6 mEq/liter) and T3 (mean dose 45.2 µg/d). The remission rates were not different statistically (after a mean of 9.6 weeks the remission rates were 15.9% with lithium augmentation and 24.7% with T3 augmentation), but there was evidence that the lithium therapy was less tolerable than the T3 augmentation. Thus, the authors suggested that there was a slight advantage for T3 over lithium for patients who have experienced several failed medication trials (6). It is worth mentioning an interesting finding in a different study conducted at Hadassah Hospital Hebrew University of Jerusalem.
in Israel. In this study, 25 patients who did not respond to SSRI were treated with augmentation therapy of T3 (25–50 µg/d). There was a good response in female patients (10/16), but no response in male patients (0/9), suggesting that augmentation with T3 might be more effective in women than in men (9).

The STAR*D may suggest that in general, augmentation is somewhat better than switching, due to slightly higher remission rates (18.1–24.4% remission after switching to a different agent, and 29.7–30.2% when augmenting with bupropion or buspirone). However, these two trial groups of the STAR*D study involved largely distinct groups of patients who had different outcomes with citalopram treatment, making it impossible to compare the two strategies (5). Even though the study was not designed to compare these two approaches, it appears that in general, it is better off augmenting than switching. Clearly, if a patient has partially responded to an SSRI, augmentation makes more sense. On the contrary, if there has been no response or if a patient has not tolerated the initial SSRI, switching is more reasonable.

Concluding the data reviewed in this article, there are no specific guidelines for pharmacological treatment after failure in treating with SSRI. As long as there is a lack in such guidelines, it seems logical to make this decision according to the clinical response for the first SSRI, the tolerability to the drug, the clinical practice of the physician. Factors to be considered when deciding on switching or augmentation treatment include efficacy, tolerability, burden of side effects, interaction among drugs, dosing convenience, and cost.

References