STAR*D: Have We Learned the Right Lessons?

TO THE EDITOR: The investigators of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial are to be congratulated for the comprehensiveness and generalizability of the antidepressant treatment trials that they have conducted. They have confirmed findings from other studies (1), which have reported that a significant minority (approximately 33%) of depressed patients have a form of depression that does not remit, even with multiple combinations of antidepressant treatments (2). In light of these findings, it is not clear whether the right lessons have been learned from the STAR*D trials (3). The investigators of the STAR*D study, as well as the APA Practice Guideline, advocate remission as the major goal of antidepressant treatment, especially for treatment-resistant patients (3, 4). It is not clear, however, that this recommendation is in the best interest of our patients.

There is ample evidence to show that patients who continue to experience residual symptoms of depression are at higher risk for multiple adverse outcomes (5, 6). Such findings are used to justify the push for remission. The correlation of adverse outcomes with residual symptoms, however, does not prove causation. Persistence of depressive symptoms in spite of optimal treatment may be an indicator rather than a cause of a form of depression that is not likely to respond to treatments currently available. The idea that there are some patients with a form of depression that is not responsive to available treatments is consistent with our current nosology, which groups together many different types of depression.

Advocating for "more complex regimens" (3) even earlier in the treatment algorithm may cause more harm than good. Very few studies have assessed either the safety or the effectiveness (3) of complex polypharmacy trials. Polypharmacy increases the likelihood of side effects, drug interactions, cost increases, and noncompliance. Polypharmacy, nonetheless, is becoming more commonly used in routine clinical practice (7), presumably in part because of the setting of remission as the goal of treatment. Focusing too much on symptom remission in treatment-resistant patients may aggravate an already difficult-to-manage illness. Patients may feel even more discouraged if they do not respond to complex treatment trials. Such discouragement may lead to noncompliance with treatment. The STAR*D trials reported substantial rates of attrition despite the extra staffing, attention, patient education, and free care usually associated with clinical trials (3).

What should be the goals of antidepressant treatment? One goal should be to achieve the greatest symptomatic relief possible, with the recognition and acknowledgment that this may not mean remission for a significant minority of depressed patients. For these patients, in particular, more attainable goals may be to improve their quality of life and psychosocial functioning in spite of persisting depressive symptoms.

There are ways to help patients manage their persistent illness more effectively. Disease-management programs for chronic and remitting/relapsing illnesses are available that help patients focus on improving their psychosocial functioning and quality of life in the face of persisting symptoms (1). Pharmacologic treatment and disease management are not mutually exclusive. Ongoing medication and psychosocial treatment trials should be pursued concurrently in order to engender hope, since some patients may benefit over time or take longer to achieve remission. Clinicians should also feel comfortable, however, to address with patients the reality that they are suffering from a chronic illness. We can do a great deal of good by facilitating more effective coping strategies rather than promising something that we cannot deliver.

References

1. Keitner GI, Ryan CE, Solomon DA: Realistic expectations and a disease management model for depressed patients with persistent symptoms. J Clin Psychiatry 2006; 67:1412–1421
2. Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, Niederehe G, Thase ME, Lavori PW, Lebowitz BD, McGrath PJ, Rosenbaum JF: Acute and longer-term outcome in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006; 163:1905–1917
3. Rush AJ: STAR*D: what have we learned? Am J Psychiatry 2007; 164:201–203
4. American Psychiatric Association: Practice Guideline for the Treatment of Patients With Major Depressive Disorder (revision). Am J Psychiatry 2000; 157(April suppl):1–45
5. Judd LL: The clinical course of unipolar major depressive disorders. Arch Gen Psychiatry 1997; 54:989–991
6. Miller IW, Keitner GI, Schatzberg AF, Klein DN, Thase ME, Rush AJ, Markowitz JC, Schlager DS, Kornstein SG, Davis SM, Harrison WM, Keller MB: The treatment of chronic depression, part 3: psychosocial functioning before and after treatment with sertraline or imipramine. J Clin Psychiatry 1998; 59:608–619
7. Kekes NA, Burrows GD, Copolov DL, Newton R, Paoletti N, Schweitzer I, Tiller J: Beyond the evidence: is there a place for antidepressant combinations in the pharmacotherapy of depression? Med J Aust 2007; 186:142–144

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Dr. Rush Replies

Drs. Keitner, Solomon, and Ryan raise three important issues: 1) the limitations of current treatments in not producing sustained remission in a substantial number of depressed patients; 2) the undisputed importance of improving psychosocial function and quality of life for all depressed patients; and 3) the potential downside of medication combinations or other "complex treatment regimens."