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.

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This letter (doi: 10.1176/appi.ajp.2007.07081375) was accepted for publication in October 2007.

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."

Since STAR*D did not evaluate all available treatments for depression, we cannot conclude that the 33% who did not reach remission after four treatment steps would not have benefited from other medications, psychotherapies, or somatic treatments. Furthermore, even at the fourth treatment step, a small but meaningful (8%–14%) number of participants achieved remission. Thus, the decision to scale back the goals of treatment to less than remission seems unwise until at least four treatment attempts. On the other hand, some patients may well be unable to reach and sustain remission. Clinicians must decide when to no longer pursue remission as the goal of treatment by making further treatment changes. However, patients who partially benefit from medication may further improve their well-being and quality of life when psychosocial interventions or other rehabilitative efforts are put in place (1, 2). On the other hand, given the undisputed advantage of remission, both functionally and prognostically continued efforts may well be worthwhile in selected patients. The decision to switch from remission to improved quality of life should be a collaborative one between patient and doctor. Indeed, efforts to improve function and quality of life, as noted by Dr. Keitner et al., can readily become part of the treatment regimen for all patients (remitted or not) and may be provided along with additional efforts to achieve remission.

Whether "more complex regimens" (i.e., medication combinations) are more burdensome, risky, or effective is an empirical question that deserves study. Many psychiatrists now use combination medications, but few controlled trials have actually evaluated this practice. Some studies (3, 4) do suggest better efficacy and little additional side-effect burden for selected combinations. Whole sale polypharmacy is not to be recommended. Carefully conducted randomized trials pitting monotherapy against drug combinations are needed to directly assess whether both acute and longer-term outcomes can be enhanced without undue patient burden.

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*Dr. Rush's disclosures accompany the original STAR*D articles that appeared in the* Journal.

This letter (doi: 10.1176/appi.ajp.2007.07081375r) was accepted for publication in October 2007.

Treatment-Emergent Hypomania or Mania With Modafinil

TO THE EDITOR: In the August 2007 issue of the *Journal,* Mark A. Frye, M.D., et al. (1) reported that in their placebo-controlled trial of adjunctive modafinil in the treatment of bipolar depression, there was no significant difference in treatment-emergent hypomania or mania between modafinil and placebo groups. In their discussion, they noted that adjunctive modafinil, like adjunctive antidepressant therapy, "did not pose an added risk of mood destabilization" (1, p. 1247). This conclusion may be premature, since the authors did not address the potential confound of the significantly different use of sedative-hypnotic medications (clonazepam, lorazepam, or zolpidem) between the modafinil and placebo groups (19/41=46% versus 7/44=16%, respectively).

The importance of adequate sleep in the maintenance of mood stability of patients with bipolar disorder is well established. Experimental sleep deprivation can induce manic switching in bipolar depressed patients at rates comparable with antidepressant medications, and of note, nocturnal benzodiazepines alone have been reported to successfully manage a proportion of these induced manic episodes (2). Furthermore, it has been hypothesized that sleep reduction associated with the numerous potential causes of mania (drug abuse, withdrawal, transmeridian travel, postpartum states, bereavement, etc.) may be a common pathway through which mania is induced (3). The importance of adequate sleep in patients with bipolar disorder is also reflected in the study's exclusion of subjects with a baseline pattern of <6 hours of sleep (1).

In the case of modafinil, a wake promoting agent, the potential that sleep may be disturbed must be considered when assessing the risk of manic switching. Since subjects exposed to modafinil also used sedative-hypnotic agents at significantly greater rates, it is possible that these sedating agents either masked the symptoms of hypomania/mania or inhibited the process (i.e., sleep reduction) that might cause manic switching (4).

In this instance, a post hoc analysis of the data may be useful to evaluate treatment-emergent hypomania or mania in modafinil-treated subjects who were using or not using sedative-hypnotic medications. Recognizing the limitations of such an analysis, it still might provide some insight into whether sedative-hypnotic use confounded the reported finding of no significant difference in treatment-emergent hypomania or mania between modafinil and placebo in this study.

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