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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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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Dr. Plante reports no competing interests.

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Dr. Frye Replies

TO THE EDITOR: In his letter to the Editor, Dr. Plante suggests that our conclusion, which indicates that adjunctive modafinil "did not pose an added risk of mood destabilization," may be premature, since we did not address the potential confound that a greater percentage of modafinil subjects were treated with adjunctive sedative hypnotic medications, such as clonazepam, lorazepam, or zolpidem. Additionally, he presents an important overview of the risk of mania associated with antidepressants and sleep deprivation and highlights specifically our exclusion criteria of a baseline pattern of sleep <6 hours.

The only study criteria related to medication status was depression that was inadequately responsive to a mood stabilizer, plus or minus additional antidepressant therapy. The mean number of psychotropic medications at the time of randomization was not significantly different for subjects receiving modafinil (3.5) and placebo (2.9). Subjects were receiving a mood stabilizer, but the mood stabilizer was often in conjunction with an antidepressant (modafinil group: 61%; placebo group: 55%), a second mood stabilizer, or sedative hypnotics in various combinations.

Treatment-emergent hypomania (defined as a Young Mania Rating Scale score >13) did not differ between the modafinil subjects (6/41 [14.6%]) and placebo subjects (5/44 [11.4%]). Additional antidepressant treatment did not contribute to the rate of treatment-emergent hypomania between groups. We conducted this post hoc analysis given that the majority of subjects in the study were receiving antidepressants and had clear liability of manic risk. While sedative hypnotics may protect against manic induction, this has not been well documented for substance-induced switches, and only a minority of patients were receiving sedative hypnotics in our study. Nonetheless, of the six subjects who became hypomanic or manic while receiving modafinil, three were treated with sedative hypnotics and three were not treated with sedative hypnotics.

Although the literature on modafinil in adult bipolar disorder is small and primarily retrospective, these preliminary studies, which involved more than 40 patients, have reported no manic switches (1–3). Menza et al. (1) reported three bipolar depressed patients who responded to modafinil; two of these patients were undergoing modafinil and antidepressant therapy without concurrent mood stabilization. Fernandes et al. (2) presented a case report on two euthymic bipolar patients who were receiving a mood stabilizer/antidepressant combination without additional sedative hypnotic treatment. The study conducted by Nasr et al. (3) reported a total of 191 patients with mood disorders (bipolar I disorder: N=31; bipolar II disorder: N=33; unipolar depression: N=118; other: N=9). The majority of patients continued to receive the medication for 2 months or longer, 60 patients continued to receive the medication for at least 1 year, and 45 patients continued to receive the medication for at least 2 years. The reason for drop out (N=86) prior to the 2-month mark was because of lack of efficacy (40%), cost (37%), or adverse event (23%), mostly related to sleep. No patient in any group demonstrated a switch into mania/hypomania while receiving modafinil. Finally, a large placebo-controlled trial of modafinil (with active drug: N=158) in major depression was conducted and reported no cases of treatment-emergent mania (4).

Dr. Plante emphasizes several important, critical clinical points. Sleep deprivation, whether in our experimental design (our exclusion criteria related to baseline reduced sleep) or in less monitored clinical situations, can precipitate, potentiate, and perpetuate manic symptoms. We agree that careful clinical monitoring is required for patients when modafinil is prescribed. Furthermore, we also emphasize the importance of a careful assessment of current sleep pattern, historical sleep pattern, and characterization of depressive episode prior to non-mood stabilizing treatment. Reduced sleep in the context of depression could be a sign of bipolar-mixed depression (i.e., syndromal depression with manic/hypomanic symptoms, such as reduced need for sleep and racing thoughts), which has been associated with an increased risk of switching while taking antidepressants (5). Mixed depression may warrant treatment with a mood stabilizer or an atypical antipsychotic as opposed to a conventional antidepressant or an experimental agent such as modafinil.

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