Modafinil Add-On in the Treatment of Bipolar Depression

Modafinil is a novel compound first approved as a wakefulness-promoting agent in narcolepsy and later found safe and effective in several controlled studies of attention deficit hyperactivity disorder (ADHD). The biochemical mechanism of modafinil is different from that of the usual pharmacological treatments of ADHD, such as amphetamine, which release dopamine. While there are no studies showing modafinil superior to amphetamine or methylphenidate in ADHD or narcolepsy, modafinil seems to have low abuse potential in animal and human studies and is thus more convenient both for the individual clinician and for the health care delivery system. Additional uses for modafinil based on its stimulant properties have been explored in several additional diagnoses.

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Bipolar depression is a high-priority research area because of data showing that bipolar patients spend a large portion of their lives in clinically significant depressions and that current treatments are inadequate for the management of these bipolar depressions. A recent study by Sachs et al. (1) in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) found that treatment with sertraline or bupropion as an add-on to a mood stabilizer had no benefit in the treatment of bipolar depression. In this issue of the *Journal,* Frye et al. now report on a multicenter study of modafinil in bipolar depression. The study randomly assigned 85 patients with bipolar disorder and clinically significant depression despite ongoing treatment with mood stabilizers. Forty-four percent of the patients who were designated to receive modafinil add-on responded within the 6 weeks of the study, and only 23% of those receiving placebo add-on responded, a significant difference.

Previous studies have not found modafinil effective in unipolar depression (2). It is tempting to think that this may reflect a higher prevalence of psychomotor retardation in bipolar depression, which is therefore more responsive to modafinil. However, measures of fatigue and sleepiness did not differ after modafinil and placebo treatment in the study by Frye and associates.

Manic switch was not more common with modafinil than with placebo. However, the mean daily dose of modafinil was only 174 mg (maximum, 200 mg), and studies in narcolepsy and ADHD have sometimes used much higher doses. Patients with past histories of stimulant-induced mania were excluded from the Frye et al. study. The risk of mania in clinical use of modafinil for bipolar depression should be evaluated on the basis of the patient's past history, especially if dose titration above 200 mg is necessary.

Over one-half of the patients in the study were also taking an antidepressant. While the Sachs et al. study suggested that some antidepressants do little to help bipolar depression (1), other antidepressants not included in the Sachs et al. study *have* been shown to be effective in bipolar depression, especially antidepressants with more noradrenaline-reuptake-inhibiting properties (3). Therapeutic effects of antidepressants in bipolar depression develop over time, and it is unclear in the article by Frye et al. how

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many patients receiving antidepressants had been taking these drugs for a long period of time or if they started taking them only 2 weeks before the study.

The response rate of patients in the present study on modafinil was 44%, which the authors point out is similar to response rates in several previous studies of antidepressant treatment of bipolar depression (4). More than half of the patients of Frye et al. were already taking antidepressants and a mood stabilizer. The response rate of about 23% was not different for those receiving antidepressants plus placebo and those receiving placebo only. This could suggest that the present patient group represented antidepressant failures, but the rate is similar to the response rate of about 23% in the study by Sachs et al. (1) for bipolar depressed patients treated with placebo or bupropion or paroxetine. Clearly, there are many differences between patient groups meeting criteria for the diagnosis of bipolar depression.

The present study was double-blind, but all participants, both doctors and patients, knew that it was a study of a new medicine with stimulant-like properties. It is likely that appropriate patients referred to this study were felt by themselves and their physicians to need a stimulant-like compound, perhaps because of fatigue, listlessness, or psychomotor retardation. Patients with prominent agitation or insomnia would be less likely to be referred to or consent to participate in a study where they might receive a stimulant. This could be partially responsible for the positive results.

Often small investigator-initiated studies of new compounds find positive results but larger studies fail to confirm them. It is fairly standard to comment after a small positive study that it should be confirmed in a much larger study. This may not be a universal rule, because in a larger study the investigators might lose the motivation to choose an appropriate subgroup that could be responsive to the compound being tested. It is biologically plausible that modafinil might be useful in some cases of bipolar depression, and the present results in 85 patients support this possibility. A study of perhaps 300 patients might stress the recruitment capacities of the participating centers and lead them to be less discriminating in their choice of patients. This strategy might not lead to definitive further knowledge on the usefulness of modafinil for some bipolar depressed patients.

Does the present study mean that modafinil is the treatment of choice for all bipolar patients with depression? We should avoid assuming that a statistical benefit of one treatment for bipolar depression as a diagnostic entity is relevant for every patient with this heterogeneous condition. The patients in the present study were all taking mood stabilizers. Starting a mood stabilizer would be the first choice for any patient not being so treated. Many of the patients of Frye et al. were taking one mood stabilizer, and Young et al. (5) have shown that adding a second mood stabilizer can often be effective in patients who are having a depressive relapse of bipolar disorder while taking one mood stabilizer. Given that modafinil is an expensive treatment, there well may be bipolar depressed patients for whom appropriate treatment would be a reuptake inhibitor that is also effective on noradrenaline, such as venlafaxine (3).

There have been some preclinical studies of potential wakefulness-inducing treatments that work biochemically by inhibiting the histamine H_3 receptor in the brain. However, modafinil has behavioral effects even in mice whose H_3 receptor is genetically knocked out (6). It is possible that modafinil is working on the hypocretin system (7), a unique peptide neurotransmitter system that is abnormal in narcolepsy but is unlikely to be a key player in the biochemical mechanism of bipolar depression. Therefore, one could think of modafinil as a nonspecific or symptomatic treatment of bipolar depression. Recent studies have found treatments as diverse as ketamine (8), an anesthetic that antagonizes *N*-methyl-D-aspartic acid receptors, on the one hand, and exercise (9), on the other hand, to be useful in depression. It may be that a symptomatic rather than a hypothesis-bound mode of thinking is the best way for a clinician to help a patient with bipolar depression.

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