Modafinil Augmentation of Antidepressant Treatment in Depression

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Background: Despite a relative lack of controlled data, stimulants are often used to augment antidepressant treatment in patients who have had only a partial response to first-line therapy. Modafinil is a novel psychostimulant that has shown efficacy in, and was recently marketed for, treating excessive daytime sleepiness associated with narcolepsy. The mechanism of action of modafinil is unknown, but, unlike other stimulants, the drug is highly selective for the central nervous system, has little effect on dopaminergic activity in the striatum, and appears to have a lower abuse potential.

Method: In this retrospective case series, we describe 7 patients with DSM-IV depression (4 with major depression and 3 with bipolar depression) for whom we used modafinil to augment a partial or nonresponse to an antidepressant. The Hamilton Rating Scale for Depression was administered as part of routine clinical practice prior to treatment and at each subsequent visit.

Results: At doses of 100 to 200 mg/day, all 7 patients achieved full or partial remission, generally within 1 to 2 weeks. All patients had some residual tiredness or fatigue prior to starting modafinil, and this symptom was particularly responsive to augmentation. Side effects were minimal and did not lead to discontinuation of the drug in any of the patients.

Conclusion: Modafinil appears to be a drug with promise as an augmenter of antidepressants, especially in patients with residual tiredness or fatigue. It is a particularly attractive alternative to other stimulants because of its low abuse potential and Schedule IV status.

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Despite the advances in antidepressant therapy over the past decades, nonresponse and partial response to antidepressant medications remain difficult problems. Approximately one half of all patients beginning a trial of an antidepressant fail to respond, and one third who complete a trial of an antidepressant fail to respond.[1] Recently, there has been a renewed interest in the psychostimulants as augmenters for patients with partial response or nonresponse to antidepressants. A number of reports now suggest that methylphenidate and amphetamine are useful as augmentation of selective serotonin reuptake inhibitors, monoamine oxidase inhibitors, and tricyclic antidepressants.[2–6] However, in addition to the lack of controlled data supporting efficacy, the use of stimulants has always been limited by the risk of abuse associated with these drugs, the need for multiple daily dosing, and their Schedule II classification, which precludes the ordering of multiple refills.

The current article describes the use of modafinil as an augmentation strategy. Modafinil (2-([diphenylmethyl) sulfinyl]acetamide) is a novel psychostimulant drug that has shown efficacy in, and was recently marketed for, treating excessive daytime sleepiness associated with narcolepsy. It has wake-promoting actions like the sympathomimetic agents including amphetamine and methylphenidate, although the pharmacologic profile is not identical to that of the sympathomimetic amines.[7–9] Unlike amphetamines and methylphenidate, modafinil exhibits only weak affinity for the dopamine uptake carrier site, and does not stimulate striatal dopamine release in rodents.[10–12] Modafinil induces c-*fos* expression mainly in the anterior hypothalamic nucleus and adjacent areas, while amphetamine and methylphenidate induce c-*fos* in the striatum and whole cortex.[13] It does not bind to any known adrenergic, dopamine, γ-aminobutyric acid (GABA), or serotonin receptors,[10] but some evidence does suggest that modafinil may work by reducing GABA release.[14]

Although modafinil may produce euphoric effects and is reinforcing at high doses in monkeys, the subjective effects of modafinil are markedly different from those of amphetamine and methylphenidate, suggesting that at clinically useful doses modafinil does not have the same abuse liability as those drugs.[15,16] Gold and Balster[15] found that the drug was 250-fold less potent than amphet-

Table 1. Case History Details of Patients Who Responded to Modafinil[a]

Patient	Age, y	Sex	Diagnoses	Fatigue	Prior Medication	Concurrent Medication	Dose of Modafinil mg/d	HAM-D Score		Time to Initial Effect,wk
								Pre-Modafinil	Post-Modafinil	
1	68	F	Major depression	Yes	Unknown tricyclic antidepressant, electroconvulsive therapy	Citalopram, bupropion	200	18	5	1
2	34	F	Bipolar II disorder (depressed), panic disorder	Yes	Fluoxetine	Bupropion, trazodone	100	31	7	2
3	63	F	Major depression	Yes	Fluoxetine	Citalopram	200	10	4	2
4	33	F	Major depression, obsessive-compulsive disorder	Yes	…	Citalopram	200	13	4	3
5	56	M	Bipolar disorder (depressed)	Yes	Fluoxetine, olanzapine, gabapentin, lithium	Bupropion, divalproex, lamotrigine	200	17	2	1
6	37	M	Major depression, panic disorder	Yes	Fluoxetine, sertraline, nortriptyline	Nefazodone, paroxetine	200	28	16	1
7	42	F	Bipolar disorder (depressed)	Yes	Lithium	Venlafaxine	200	21	13	1

[a]Abbreviation: HAM-D = Hamilton Rating Scale for Depression (24-item).

amine and 15-fold less potent than ephedrine in producing cocaine-like discriminative stimulus effects in rats. Single oral doses of modafinil did not cause elation or euphoria in healthy volunteers[16] or substance abusers,[17] whereas both amphetamine and methylphenidate cause euphoria and are identified as stimulants. Because of this lower abuse potential, modafinil is a Schedule IV prescription, allowing multiple refills, and pharmacists are allowed to accept phone prescriptions. Modafinil has a limited side effect profile with only weak peripheral sympathomimetic activity and minimal effects on hemodynamics.[18] With an effective elimination half-life of 15 hours, modafinil is prescribed for once-a-day dosing.[19]

This report, the first to describe the use of modafinil in patients with depression, is a review of 7 patients who were given modafinil to augment a nonresponse or partial response to antidepressants.

METHOD

Seven patients seen at the Robert Wood Johnson Medical School Psychopharmacology Clinic (Piscataway, N.J.) who had been successfully given modafinil to augment antidepressant treatment during routine clinical treatment were included in this sample. The charts of these patients were retrospectively reviewed after obtaining institutional review board approval. The patients selected all had initial diagnoses of either major depression or bipolar disorder/depressed type by DSM-IV[20] criteria and had a Hamilton Rating Scale for Depression (HAM-D, 24-item)[21] administered prior to beginning modafinil and at each subsequent visit as part of routine clinical care.

RESULTS

Seven patients were identified, including 5 women and 2 men, whose ages ranged from 33 to 68 years. The pre-modafinil HAM-D mean score was 19.7 (range, 10–31) and the mean post-modafinil score was 7.6 (range, 2–16). Five of the 7 patients achieved at least a 50% decrease in their HAM-D score. Dosing of modafinil was from 100 to 200 mg/day. Table 1 lists the patients' diagnoses, prior treatment histories, antidepressant used concurrently with modafinil, the dose of modafinil, pre- and post-modafinil HAM-D scores, and the time to response. Three illustrative cases, of the 7 seen, are described.

Case 1

Ms. A, a 68-year-old woman, presented with a history of a recurrent major depression. Her first depressive episode was at age 19 years and was successfully treated with electroconvulsive therapy. In 1973, a depressive episode was treated with an unknown tricyclic antidepressant, but never totally resolved. Her husband commented that for the past 5 years, she had been continuously and severely depressed. At the time of initial evaluation, her symptoms included decreased appetite, sleep, energy, concentration, memory, and interest, as well as intermittent self-deprecatory thoughts and social withdrawal. There were no psychotic symptoms or features of anxiety disorders. Her family psychiatric history is notable for a daughter's completed suicide. Bupropion (sustained release) was titrated to 100 mg q.i.d. over 12 weeks with only a partial response, at which time citalopram, 20 mg q.d., was added. After 5 weeks on the combined bupropion/citalopram regimen, the

patient remained depressed and prominently fatigued with a HAM-D score of 18. Modafinil, 200 mg each morning, was added, and the patient showed progressive improvement, with the HAM-D score dropping to 5 within 6 weeks. She noted the initial onset of improvement within 1 week of starting modafinil. The patient has complained of no side effects attributable to modafinil and remains well at 10-week follow-up.

Case 2

Ms. B, a 34-year-old woman, first presented to our clinic with a 19-year history of bipolar II disorder, characterized by multiple depressive episodes and occasional hypomania. On initial examination, she had a full range of neurovegetative symptoms, including decreased sleep, energy, concentration, memory, interest, and libido, as well as guilt and passive suicidal ideation. She further admitted to panic attacks without agoraphobia. She denied psychotic symptoms or drug and alcohol abuse. Her past medical history is pertinent for sarcoidosis (with 48% lung capacity) and treated hypothyroidism. Steroids improved her breathing, but resulted in weight gain, hypertension, and mood swings and thus were discontinued. She had partial responses to adequate trials of fluoxetine and the subsequent combination of bupropion and trazodone, but the depression then worsened, with prominent symptoms of fatigue and decreased productivity. Her HAM-D score was 31 on the bupropion/trazodone regimen when modafinil was initiated at 100 mg each morning. Within 2 weeks, she saw clear improvement, and 1 month later, her mood was euthymic, with increased productivity, decreased fatigue, and decreased anxiety. Her HAM-D score was now 7, and she stated that her husband and friends all noted a dramatic change. The husband went so far as to state, "She is back to her real self, back to normal." No hypomanic features have emerged, and she remains well at 3-month follow-up.

Case 3

Ms. C, a 63-year-old retired school teacher, presented with a new-onset major depression with symptoms including decrease in energy, interest, subjective mood, appetite, and sleep as well as prominent problems with guilt. There was little associated anxiety, no suicidality, and no symptoms of psychosis. Her initial HAM-D score was 20. A trial of fluoxetine, 20 mg/day, for 6 weeks resulted in increased tiredness and no decrease in the depressive symptoms. A subsequent 6-week trial of citalopram, 20 mg/day, resulted in an improvement in her HAM-D score to 10, but she continued to complain of significant impairment from her tiredness. Modafinil was begun at 200 mg each morning, and within 2 weeks she noted a marked improvement, both in tiredness and the residual symptoms of depression. Her HAM-D score was now 4. She had no side effects attributable to modafinil and remains well at 3-month follow-up.

DISCUSSION

These 7 cases illustrate the benefit we have found from adding modafinil to antidepressant regimens in patients who had a partial or nonresponse to antidepressant treatment. All of these patients had sustained clinically significant improvement in their overall well-being as well as a decrease in their HAM-D scores. Additionally, the patients described a rapid response, usually within 1 to 2 weeks. While their diagnoses and symptomatic presentations differed and did not appear to predict response, all patients did have prominent fatigue that improved with modafinil treatment. The improvement in fatigue did not, however, account for the full response clinically or in the HAM-D scores, since improvements were seen in both physical and cognitive subscales of the HAM-D. None of these patients had symptoms suggestive of adult attention-deficit disorder.

Dosing (100–200 mg/day) in our experience was at the low end for this drug, which carries a recommendation of 200 to 400 mg/day for narcolepsy. These patients tolerated the drug well without significant side effects, difficulties with abuse, or sleep disturbance. Of note is that 3 of these patients had bipolar disorder diagnoses and that there was no emergence of hypomania, agitation, or psychosis.

As in any case series, these results must be viewed with caution. Enthusiasm for a new medication can induce powerful placebo-like effects. Additionally, there could be a significant selection bias since this series of cases was not consecutive. Many of these patients had tried other medications previously, but the history of treatment resistance varied among the patients, so we do not suggest that modafinil would be helpful in most patients with true treatment-resistant depression. While it is also possible that the additional time on the concurrent therapy or the normal fluctuations in the course of the disorder may have resulted in improvement without the addition of modafinil, this explanation is not likely. Six of the 7 patients had been taking adequate antidepressant doses for at least 6 weeks, and the remaining patient had been taking an adequate dose for 4 weeks. Furthermore, those patients who had had augmentation trials had been treated for an adequate time on a sufficient dose.

Additional caution is suggested by the history of positive responses to augmentation in open-label case reports and subsequent failure to demonstrate efficacy in placebo-controlled trials. Modafinil is metabolized by cytochrome P450 1A and 3A4, which it slightly induces,[7] and it may, therefore, decrease levels of other drugs metabolized by these enzyme systems.

Modafinil does seem to offer a number of advantages over methylphenidate and amphetamine. It has a relatively low abuse potential, has few peripheral sympathomimetic effects, is dosed once a day, and, as a Schedule IV drug, may be ordered over the phone and with multiple refills.

In summary, modafinil may be an effective augmenting agent in patients with depression who are partial or nonresponders to antidepressant therapy. This appears to be especially likely in those patients who have residual tiredness or fatigue. Given the advantages of this drug and the robust response of our patients, further controlled trials should be pursued.

Drug names: bupropion (Wellbutrin), citalopram (Celexa), divalproex sodium (Depakote), fluoxetine (Prozac), gabapentin (Neurontin), lamotrigine (Lamictal), methylphenidate (Ritalin), modafinil (Provigil), nefazodone (Serzone), nortriptyline (Pamelor and others), olanzapine (Zyprexa), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).

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