Bipolar depression represents a critical unmet need in our field. Recent research concerning the longitudinal course of bipolar disorder has consistently shown that mood problems are more chronic and persisting than was once believed, and that bipolar patients are significantly depressed for the majority of the duration of their illness.1,2 However, clinical trials for the treatment of bipolar depression are relatively few compared with those of acute mania.3 Currently, nine drugs are approved in the US for the treatment of acute mania,4,5 while only two – the fluoxetine plus olanzapine combination and quetiapine monotherapy – are approved for use in acute bipolar depression (see Table 1).6 Long-term use of these agents is limited by their well-known adverse effects on bodyweight and metabolic profile.7 To date, there are few other effective options for bipolar depression. Traditional mood stabilisers, such as lithium and valproic acid, are less effective for the treatment of bipolar depression compared with mania, and treatment studies of lamotrigine in acute bipolar depression have yielded mixed results. Two clearly effective options for the treatment of acute bipolar depression are approved by the US Food and Drug Administration: the olanzapine/fluoxetine combination and quetiapine. However, metabolic adverse effects may limit their long-term use. Modafinil is a psychostimulant with a novel mechanism of action that is approved in the US for the treatment of excessive somnolence associated with narcolepsy, obstructive sleep apnoea syndrome, and shiftwork sleep disorder. Modafinil has shown promise as a pharmacological adjunct to lithium or valproic acid in one six-week randomised, placebo-controlled, multicentre trial of bipolar depressed patients without apparent increase in risk of mood switching. Adjunctive use of modafinil is endorsed as a second-line pharmacological option in one very recently updated clinical practice guideline for treatment of bipolar depression. However, results from replication studies are unavailable, and long-term effectiveness studies in bipolar depression are lacking. Given the limited options available for the treatment of bipolar depression, adjunctive modafinil may be considered if other approved options are exhausted or are unfeasible. Monitoring modafinil-treated bipolar patients for drug-drug interactions, mood switching, and abuse during follow-up is warranted, although preliminary evidence suggests a low propensity for these complications.

Modafinil as an Adjunctive Treatment for Bipolar Depression

William V Bobo and Richard C Shelton

1. Assistant Professor of Psychiatry; 2. James G Blakemore Research Professor of Psychiatry, and Professor of Pharmacology, Vanderbilt University School of Medicine

Abstract

Bipolar depression represents a critical unmet need in our field. Traditional mood stabilisers, such as lithium and valproic acid, are less effective for the treatment of bipolar depression compared with mania, and treatment studies of lamotrigine in acute bipolar depression have yielded mixed results. Two clearly effective options for the treatment of acute bipolar depression are approved by the US Food and Drug Administration: the olanzapine/fluoxetine combination and quetiapine. However, metabolic adverse effects may limit their long-term use. Modafinil is a psychostimulant with a novel mechanism of action that is approved in the US for the treatment of excessive somnolence associated with narcolepsy, obstructive sleep apnoea syndrome, and shiftwork sleep disorder. Modafinil has shown promise as a pharmacological adjunct to lithium or valproic acid in one six-week randomised, placebo-controlled, multicentre trial of bipolar depressed patients without apparent increase in risk of mood switching. Adjunctive use of modafinil is endorsed as a second-line pharmacological option in one very recently updated clinical practice guideline for treatment of bipolar depression. However, results from replication studies are unavailable, and long-term effectiveness studies in bipolar depression are lacking. Given the limited options available for the treatment of bipolar depression, adjunctive modafinil may be considered if other approved options are exhausted or are unfeasible. Monitoring modafinil-treated bipolar patients for drug-drug interactions, mood switching, and abuse during follow-up is warranted, although preliminary evidence suggests a low propensity for these complications.

Keywords

Modafinil, bipolar disorder, bipolar depression, adjunctive therapy

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Correspondence: William V Bobo, 1500 21st Ave South, Suite 2200, Village at Vanderbilt, Nashville, TN 37212, US. E: william.v.bobo@vanderbilt.edu

Bipolar depression is a psychiatric disorder characterized by at least two episodes of hypomania or mania, often accompanied by depressive episodes. Bipolar depression is often underdiagnosed and undertreated, with many patients experiencing symptoms for years before a correct diagnosis is made. The treatment of bipolar depression is challenging, as mood stabilizers alone may not be sufficient for symptom control. In such cases, adjunctive therapies, such as cognitive-behavioral therapy, psychosocial interventions, and antipsychotics, may be considered. Modafinil is a psychostimulant with a novel mechanism of action that is approved in the US for the treatment of excessive somnolence associated with narcolepsy, obstructive sleep apnoea syndrome, and shiftwork sleep disorder. Modafinil has shown promise as a pharmacological adjunct to mood stabilizers for the treatment of bipolar depression (reviewed below). At least one very recently published guideline recommends its use as a second-line option for bipolar depression as a pharmacological
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Table 1: Approved Treatments for Bipolar Disorder in the US

<table>
<thead>
<tr>
<th></th>
<th>Mania/Mixed Episodes</th>
<th>Depression Maintenance</th>
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<tbody>
<tr>
<td>Lithium</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td></td>
<td></td>
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<tr>
<td>Carbamazepine (extended rel.)</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>X</td>
<td></td>
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<tr>
<td>Valproic acid</td>
<td>X</td>
<td></td>
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<tr>
<td>Antipsychotics (typical)</td>
<td></td>
<td></td>
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<tr>
<td>Chlorpromazine</td>
<td>X</td>
<td></td>
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<tr>
<td>Antipsychotics (atypical)</td>
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<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>X</td>
<td>X</td>
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<tr>
<td>Asenapine</td>
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<tr>
<td>Olanzapine</td>
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<td>Quetiapine</td>
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<td>X</td>
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<td>Ziprasidone</td>
<td>X</td>
<td></td>
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<tr>
<td>Drug combinations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Olanzapine/floxetine</td>
<td>X</td>
<td></td>
</tr>
</tbody>
</table>

X = indication approved by the US Food and Drug Administration (FDA).
a. Valproic acid extended-release (ER) formulation is FDA-approved for both mania and mixed episodes. The conventional formulation of valproic acid is approved for mania. b. FDA-approved for mania only. c. FDA-approved as an adjunctive treatment with lithium or valproic acid. d. Risperidone long-acting injectable formulation is FDA-approved for maintenance treatment as a monotherapy and as an adjunct to lithium or valproic acid.

Figure 1: Clinical Response and Remission Rates (Adjunctive Modafinil versus Placebo) in Bipolar Depression

The intention-to-treat (ITT) data set consisted of subjects who received at least one dose of modafinil (MOD) or placebo (PLC) and had at least one post-randomisation follow-up visit (MOD, n=41; PLC, n=44). Clinical response was defined as >50% reduction in Inventory of Depressive Symptoms- Clinician Rated (IDS-C) score from baseline. Remission was defined as a final IDS-C score <13. a. Clinical response: MOD versus PLC, χ²=4.31, p=0.04; remission: MOD versus PLC, χ²=4.55, p=0.03. Data from Frye et al., 2007.

Modafinil – Mechanism of Action and Pharmacological Effects

Modafinil interacts with a wide variety of neurotransmitter systems, but the precise mechanism of action regarding its wake-promoting and putative antidepressive effects is unknown. Modafinil inhibits dopamine and norepinephrine transporters (DAT and NET, respectively), leading to increased extracellular levels of dopamine (DA) and norepinephrine (NE), effects shared by some antidepressant medications. There are no established direct interactions at any specific neureceptor sites. That said, modafinil has been shown to increase levels of serotonin, dopamine, glutamate, orexin, and histamine in the central nervous system (CNS), and to decrease central gamma-aminobutyric acid (GABA) neurotransmission. These effects appear to occur through an indirect mechanism. The wakefulness-promoting activity of modafinil appears to depend, at least to some degree, on dopamine activation.

In addition, modafinil’s activating effects on orexin and histamine pathways, and weak DA release secondary to reduced GABA transmission, have also been proposed as underlying mechanisms for the drug’s wakefulness- and vigilance-promoting effects.

While modafinil has been shown to inhibit the DAT, the effect of modafinil at this site is much weaker than that of traditional psychostimulants, leading to significant but smaller elevations in DA levels. Weaker catecholaminergic effects and more selective (rather than widespread) cortical and hypothalamic brain activation have also been demonstrated with modafinil compared with psychostimulants. This may confer a number of advantages related to the treatment of bipolar depression symptoms, including improvements in attention, vigilance, subjective energy, and mood state in the absence of adverse cardiovascular effects and reduced addiction liability. These effects are consistent with the known role of both DA and NE in regulating mood and cognition.

Clinical Studies

Studies in Non-Bipolar Subjects

Modafinil has been shown to improve subjective alertness, energy level, and mood state in a wide variety of clinical samples and in healthy volunteers. For example, in a randomised, cross-over comparison of modafinil (400mg daily) and placebo involving 12 healthy subjects, modafinil resulted in significantly greater increases in positive affect as assessed by the Positive and Negative Affect Schedule (PANAS). However, modafinil also resulted in greater increases in subjective anxiety and arousal.

Several studies have investigated the use of modafinil both in monotherapy and as an adjunct to antidepressants for patients with unipolar depression. Preliminary studies suggested that adjunctive modafinil can reduce residual fatigue and sleepiness in antidepressant-treated patients with major depression. Direct effects of adjunctive modafinil on mood were subsequently examined in a randomised, placebo-controlled trial in a sample of patients with major depression who were partially responsive to selective serotonin reuptake inhibitor (SSRI) treatment and had residual, persisting fatigue and sleepiness. Modafinil resulted in significantly greater improvement in depressive symptoms than placebo. An extension study showed that these benefits were sustained over 12 weeks of follow-up for most patients. However, in another multicentre, placebo-controlled add-on study involving unipolar depressed patients who were partially responsive to SSRI treatment, adjunctive modafinil did not result in significant improvement in mood.

Studies in Bipolar Depression

An early case series of modafinil effects in bipolar depression suggested that it may reduce fatigue and promote wakefulness without increasing risk of mood switching; however, patients in this small study had remitted rather than active core depressive symptoms. In addition, there were subsequent isolated reports of rapid emergence of manic and mixed mood-switching in the setting of modafinil treatment. To formally test the hypothesis that modafinil used in conjunction with mood-stabilising medications may result in clinically significant antidepressive effects without increasing risk for manic induction, Frye et al. conducted a multicentre, randomised study of modafinil in patients with bipolar disorder, depressed phase. All subjects (n=85) had Structured Clinical Interview for DSM-IV (SCID)-confirmed diagnoses of bipolar I or II disorder and were on stable regimens of mood stabilisers and/or atypical antipsychotic drugs – with or without concomitant antidepressants.
result in clinically significant antidepressive effects without increasing risk for manic induction, Frye et al. conducted a multicentre, randomised study of modafinil in patients with bipolar disorder, depressed phase.\textsuperscript{31} All subjects (n=85) had Structured Clinical Interview for DSM-IV (SCID)\textsuperscript{14}-confirmed diagnoses of bipolar I or II disorder and were on stable regimens of mood stabilisers and/or atypical antipsychotic drugs – with or without concomitant antidepressants (61% in the modafinil group, 55% in the placebo group). Patients were randomly assigned to receive adjunctive modafinil (n=41, mean dose 174.2mg/day) or placebo (n=44) for six weeks. The primary end-point was change in Inventory of Depressive Symptoms–Clinician Rated (IDS) scale scores.\textsuperscript{32} There was significantly greater improvement in depressive symptoms associated with adjunctive modafinil compared with placebo. In addition, rates of response (defined as >50% reduction in IDS score) and remission (IDS score <12 at end-point) were significantly greater with modafinil than placebo (see Figure 1). Adjunctive modafinil was well tolerated, and there were no significant between-group differences in blood pressure, heart rate, or bodyweight during follow-up. The most common side effect in the study was headache (modafinil, n=4; placebo, n=1). Additional adverse effects reported in modafinil-treated subjects included nausea (n=1), insomnia (n=2), and rapid heart rate (n=1). The most common adverse effects that occurred in other clinical trials, e.g. those occurring in >5% of subjects and more frequently than placebo, included headache, insomnia, palpitations, nervousness, diarrhoea, anxiety, and nausea according to the modafinil package insert.\textsuperscript{33} In the Frye et al. study,\textsuperscript{31} one patient in the modafinil group and four patients in the placebo group developed hypomania. There were two hospitalisations for mania (one in each group) and for depression (one in each group).

\textbf{Discussion and Conclusions}

Existing options for the long-term treatment of bipolar depression are far from ideal. An ideal agent would have a number of required features, including efficacy in both acute- and maintenance-phase treatment, lack of addictive properties, limited drug–drug interactions, and good tolerability, including low risk of mood switching and cycle acceleration.

With respect to clinical efficacy and safety, the positive results of the study by Frye et al.\textsuperscript{31} are encouraging, especially in view of the sound study design and very low manic switch rate associated with modafinil. However, results from replication studies are unavailable, and long-term effectiveness studies in bipolar depression are lacking. In addition, this study had a short duration of follow-up (six weeks) and tested a relatively low mean dose of modafinil (174.2mg/day). Although absence of manic mood switching has been reported in one small retrospective chart review involving 191 patients, 39 of whom had a bipolar disorder diagnosis,\textsuperscript{34} propensity for manic or hypomanic mood switching may increase with longer follow-up and with use of higher modafinil doses. Further studies are needed, including studies in bipolar depressed patients who have failed a therapeutic trial or other approved options.

Modafinil is thought to be relatively safe with regard to abuse liability, particularly compared with classic psychostimulants. This was based on the belief that the drug’s DA-enhancing effects were largely restricted to cortex,\textsuperscript{35} and not the nucleus accumbens.\textsuperscript{36} However, DA-enhancing effects in the nucleus accumbens have been demonstrated in a very recent positron-emission tomography (PET) study of healthy male volunteers.\textsuperscript{37} Although animal studies have indeed suggested a lack of addictive potential,\textsuperscript{38,39} at least some potential for abuse has been demonstrated in humans.\textsuperscript{40,41} Further clinical experience and systematic investigation will shed light on this important issue; in particular, data on abuse liability in bipolar patients are lacking.

Although amide hydrolysis is believed to be the major route of metabolism, modafinil has been shown to interact with a number of hepatic cytochrome P450 (CYP) isoenzymes, including dose-dependent induction of the CYP3A4 isoenzyme.\textsuperscript{42,43} These effects suggest that a number of potential drug–drug interactions between modafinil and other psychotropic medications used in the treatment of bipolar disorder and other conditions may take place.\textsuperscript{44,45,46} However, to date, clinically significant interactions with such agents have not been conclusively shown. It should be pointed out that modafinil may reduce the effectiveness of oral contraceptives by increasing their rate of metabolic clearance\textsuperscript{47} – an important clinical consideration given the reproductive safety concerns with some mood stabilisers.\textsuperscript{48} Thus, use of concomitant or alternative methods of contraception is recommended during active modafinil treatment and for one month following modafinil discontinuation.\textsuperscript{49}

Could modafinil have other potential benefits in the treatment of bipolar depression? Modafinil has been linked to cognitive-enhancing effects, including beneficial effects on attention, memory, and executive functioning, in healthy volunteers and non-bipolar clinical samples.\textsuperscript{50,51} As is the case with schizophrenia, cognitive dysfunction is emerging as an important core feature of bipolar disorder that robustly predicts functional incapacity associated with the diagnosis.\textsuperscript{52,53} The field awaits studies of modafinil effects on attention, memory, and executive function deficits in bipolar patients. Impairments in these cognitive domains have been shown to persist across all bipolar mood states, including euthymia.\textsuperscript{54}

In the meantime, given the limited options available for the treatment of bipolar depression and the high degree of persisting fatigue and daytime drowsiness associated with it, modafinil may be considered if other approved options are exhausted or are unfeasible. Based on our review, available evidence indicates that modafinil may be an effective, well-tolerated and safe option during short-term treatment. Long-term effectiveness, safety/tolerability, and potential for interactions with other medications are unknown at present. As such, monitoring modafinil-treated bipolar patients for drug–drug interactions, mood switching, and abuse during follow-up is warranted.\textsuperscript{55}

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