Modafinil: Not just for sleep disorders?

Off-label use of this stimulant might improve mood disorders, ADHD, and other conditions

Ms. B, a middle-aged mother of 3, is being monitored for bipolar disorder. She has a history of stimulant abuse but has been in remission for 5 years. She complains of excessive daytime sleepiness. Most days she wakes at 7 AM, but sleeps on several occasions during the day. She also complains of fatigue and lack of motivation.

She is being treated with lithium, venlafaxine, and zolpidem and reports good adherence. Basic laboratory work and serum lithium levels are within acceptable ranges. Her symptoms do not improve when venlafaxine is titrated from 225 mg/d to 300 mg/d. She also reports previously failed trials with bupropion and fluoxetine.

We decide to try a psychostimulant as an augmenting agent. Because of her past stimulant abuse, we add modafinil, 100 mg/d and increase to 200 mg/d. Ms. B reports improvement in her daytime sleepiness and fatigue and—except for a mild headache—tolerates the medication well.

Modafinil is being investigated for potential roles in managing inattention, excess sleepiness, fatigue, and cognitive dysfunction associated with:

- mood disorders (major depression and bipolar depression)
- attention-deficit/hyperactivity disorder (ADHD)
- schizophrenia
- cocaine dependence.

This article discusses how the drug promotes wakefulness, how it might improve cognitive function, and what the evidence reveals about off-label indications.

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Mechanism such as amphetamines and methylphenidate, Modafinil does not bind to norepinephrine, serotonin, dopamine, or benzodiazepine receptors. It might target specific hypothalamic regions such as the tuberomammillary nucleus and orexin neurons, which are peptide neurotransmitters that promote wakefulness.

Preclinical studies found that modafinil increases neuronal activation in the hypothalamus. Because several cell groups in the hypothalamus project diffusely to the cerebral cortex and mediate arousal and attention, it has been suggested that modafinil might improve cognitive function. Clinical trials found that modafinil has beneficial effects on:

- working memory, recognition memory, and sustained attention in healthy humans
- prefrontal-dependent cognitive functions in schizophrenia, major depression, and adult ADHD.

**Evidence for approved indications**

Modafinil is indicated to improve wakefulness in patients who have excessive sleepiness associated with narcolepsy, obstructive sleep apnea, or shift work sleep disorder. It was approved for reducing excessive sleepiness in narcoleptic patients after two 9-week placebo-controlled clinical trials. The drug significantly reduced sleepiness and improved overall disease status as measured by the Clinical Global Impression of Change (CGI-C) scale.

Modafinil also significantly improved sleep latency and CGI-C scores in 2 clinical trials of patients with obstructive sleep apnea/hypopnea. Approximately 80% of patients in these studies were using their continuous positive airway pressure devices.

In patients with shift work sleep disorder, a 12-week placebo-controlled clinical trial found that modafinil significantly improved sleep latency and CGI-C scores.

**Dosage and side effects.** For patients with narcolepsy or obstructive sleep apnea, the recommended dose is 200 mg given in the morning. For patients prescribed modafinil for work-time wakefulness, the dose is 200 mg 1 hour before their work shift. Lower doses are recommended for patients who are elderly or have hepatic impairment. Those with severe hepatic impairment typically are prescribed 100 mg/d. Modafinil is rapidly absorbed and is metabolized primarily by

### Table 1

**Modafinil’s pharmacokinetics**

<table>
<thead>
<tr>
<th>Action</th>
<th>Description</th>
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<tr>
<td>Absorbed rapidly, with peak plasma concentrations at 2 to 4 hours</td>
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<td>Apparent steady states reached after 2 to 4 days of dosing</td>
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<td>Half-life: 15 hours</td>
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<td>Major route of elimination (~90%) is metabolism, primarily by the liver</td>
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### Table 2

**Selected drug-drug interactions with modafinil**

<table>
<thead>
<tr>
<th>Action of modafinil</th>
<th>Potential drug interactions</th>
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<tbody>
<tr>
<td>Increases elimination of CYP 3A4 substrates</td>
<td>Carbamazepine, phenytoin may decrease modafinil levels Azole antifungals, protease inhibitors, and erythromycin may increase modafinil levels</td>
</tr>
<tr>
<td>Inhibits CYP 2C19 enzyme</td>
<td>Modafinil may increase levels of citalopram, diazepam, and sertraline</td>
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<tr>
<td>Decreases absorption of ethinyl estradiol</td>
<td>Modafinil can decrease effectiveness of oral contraceptives</td>
</tr>
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**Source:** Reference 11

### Clinical Point

Unlike conventional stimulants, modafinil has minimal risk for abuse or dependence.
the liver (Table 1). A summary of potential drug-drug interactions appears in Table 2.11

In pivotal trials, adverse events that occurred more frequently with modafinil than with placebo and in >5% of the study population included headache, nausea, nervousness, rhinitis, diarrhea, back pain, insomnia, dizziness, and dyspepsia. Headache was most commonly reported; in most patients, it resolved soon after they started taking modafinil. Post-marketing reports have included cases of psychosis, mania, and suspected serious skin reactions, including Stevens-Johnson syndrome.11 Modafinil lacks euphoric properties and has minimal potential for abuse.12

**Evidence for off-label uses**

**Major depressive disorder (MDD).**

The fatigue and excessive sleepiness often seen with MDD often persist after other depressive symptoms have remitted with antidepressant treatment.13 Patients with these symptoms might benefit from modafinil’s stimulating properties. Conventional stimulants such as methylphenidate have been used to improve neurovegetative symptoms of depression, but modafinil offers several advantages:

- decreased adverse CNS effects
- fewer drug-drug interactions
- minimal risk for dependence or abuse.

Two double-blind, placebo-controlled studies evaluated adjunctive modafinil treatment for patients whose MDD did not remit or partially responded to selective serotonin reuptake inhibitor therapy. In one, modafinil, 100 to 400 mg/d, produced significant decreases in Epworth Sleepiness Scale scores at 1 week and Fatigue Severity Scale scores at 2 weeks, but modafinil’s overall effects were not significantly greater than those of placebo in either study (Table 3).14,15

A 6-week open-label study of 25 depressed patients with residual fatigue and sleepiness showed that adjunctive

<table>
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<th>Table 3</th>
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<tr>
<td><strong>Can modafinil help patients with mood disorders?</strong></td>
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<tr>
<td><strong>Author</strong></td>
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<tr>
<td><strong>Major depressive disorder</strong></td>
</tr>
<tr>
<td>Fava et al, 200514</td>
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<tr>
<td>DeBattista et al, 200315</td>
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<tr>
<td>Konuk et al, 200616</td>
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<tr>
<td><strong>Bipolar depression</strong></td>
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<td>Frye et al, 200712</td>
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</table>

HAM-D: Hamilton Rating Scale for Depression; IDS: Inventory for Depressive Symptoms; SSRI: selective serotonin reuptake inhibitor
Modafinil, 100 to 200 mg/d, significantly improved these symptoms, as well as Hamilton Rating Scale for Depression (HAM-D) score, as early as week 2. Seventy-six percent of patients responded to treatment, defined as a >50% reduction in HAM-D scores.16 Several open-label studies and case reports have evaluated adjunctive modafinil use in patients with:

- depression characterized by ongoing lethargy or apathy17
- depression with atypical features18
- seasonal affective disorder19
- partial response to antidepressants20,21

Modafinil improved depressive symptoms, overall clinical condition, fatigue, and excessive sleepiness, but these findings need to be confirmed by larger, randomized controlled trials.

Bipolar depression. A 6-week, double-blind, placebo-controlled trial randomly assigned 85 patients with bipolar depression to adjunctive modafinil, 100 to 200 mg/d, or placebo for 6 weeks (Table 3, page 69).22 The number of patients receiving an antidepressant or mood stabilizer was not significantly different between the modafinil and placebo groups.

The primary outcome measure was change in the Inventory for Depressive Symptoms (IDS) score from baseline to endpoint. Forty-four percent of patients receiving modafinil achieved a ≥50% reduction in IDS score, compared with 23% of the placebo group; this difference was statistically significant (P=0.03).

In this study, modafinil was well tolerated and did not induce mania or hypomania. Cases of modafinil-induced mania have been reported elsewhere.23,24

The mechanisms of modafinil’s antidepressant effects are unclear. The drug does not cause release of norepinephrine or dopamine. One study proposed that modafinil acts by releasing histamine and activating norepinephrine receptors.25 Activation of these receptors increases dopamine and norepinephrine in these areas, and excites histaminergic tuberomammillary neurons, increasing histamine levels. Another trial suggested that modafinil may improve mood by mechanisms similar to the antidepressant effects induced by sleep deprivation.26

Table 4

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Modafinil dose</th>
<th>Conclusion</th>
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</thead>
<tbody>
<tr>
<td>Wigal et al, 200619</td>
<td>Analysis of data from 3 double-blind, placebo-controlled trials; total 638 children/adolescents, some of whom had received prior stimulant therapy</td>
<td>170 to 425 mg/d</td>
<td>Whether or not patients received prior stimulant treatment, modafinil significantly improved ADHD symptoms and was well tolerated</td>
</tr>
<tr>
<td>Boellner et al, 200620</td>
<td>8-week, open-label extension of a 4-week double-blind, placebo-controlled trial; 220 subjects ages 6-14</td>
<td>100 to 400 mg/d</td>
<td>Modafinil improved ADHD symptoms and overall clinical condition</td>
</tr>
<tr>
<td>Taylor et al, 200021</td>
<td>2-week, double-blind, placebo-controlled crossover comparing modafinil with dextroamphetamine; 22 adults</td>
<td>Mean 206.8 mg/d</td>
<td>Both modafinil and dextroamphetamine significantly improved ADHD symptoms compared with placebo</td>
</tr>
<tr>
<td>Turner et al, 200422</td>
<td>Double-blind, placebo-controlled crossover; 20 adults</td>
<td>Single 200-mg dose</td>
<td>Modafinil improved results on cognitive tests, including short-term memory span, visual memory, spatial planning, and sustained attention</td>
</tr>
</tbody>
</table>

ADHD: attention-deficit/hyperactivity disorder

**Clinical Point**

Modafinil may have a role in managing fatigue and sleepiness in patients with MDD or bipolar depression.
highest dose of oral clonidine (15 vs. 2.5 mg). In controlled clinical trials of intranasal clonidine for injection, there were no statistically significant differences from placebo in occurrence of any treatment-emergent extrapyramidal symptoms, assessed by either rating scales, incidence or spontaneously reported adverse events. There was a statistically significant increase in blood pressure with clonidine compared to placebo (4.7% vs. 1.7%).

Adrenarche Events — In placebo-controlled clinical trials of clonidine, weight gain was reported in 3.9% of clonidine-treated children (average weight gain of 20.5 kg) compared to 0.6% of placebo-treated children (average weight gain of 2.8 kg). In clonidine-treated children, the mean baseline weight was 17.5 kg, whereas placebo-treated children had a mean baseline weight of 17.4 kg. In placebo-controlled trials, clonidine-treated patients with baseline random cholesterol levels of 103-194 mg/dL were 8.8% less likely to achieve a healthy cholesterol level of <240 mg/dL anytime during the trials more often than placebo-treated children (3.6% vs 2.2% respectively). In three single trials, clonidine-treated children (23-28) had a mean increase in weight of 200 mg/DL, from a mean baseline of 175 mg/DL, whereas in placebo-controlled trials, clonidine-treated patients with baseline random cholesterol levels of 130-200 mg/DL were 7.5% less likely to achieve a healthy cholesterol level of <240 mg/DL anytime during the trials more often than placebo-treated children (2.5% vs. 1.5% respectively). In all single trials, clonidine-treated children (P<0.05) had a mean increase in weight of 200 mg/DL compared to no change among placebo children.

Case 2: Alternate Tx for ADHD

Matt, age 8, is referred to our outpatient child psychiatric clinic after his parents noted declining school performance associated with increased aggression and irritability. Our assessment strongly supports a diagnosis of ADHD without comorbid conditions. We start Matt on methylphenidate, 5 mg twice daily, which quickly improves his ADHD symptoms. However, the medication causes GI side effects and profound sleep and weight changes.

Matt’s parents request that their son be treated with a different type of agent. A trial of atomoxetine is not as effective as the initial methylphenidate dosing and produces similar side effects. We then consider modafinil because of its side effect profile. We start Matt on 100 mg once daily and titrate up to 200 mg/d 4 weeks later. Matt and his parents notice an immediate improvement in his ADHD symptoms with no side effects.

In children and adolescents. Wiggal et al20 reviewed pooled data from 3 randomized, double-blind, placebo-controlled studies of modafinil in pediatric ADHD (Table 4, page 70). Modafinil was well tolerated and improved ADHD symptoms and behaviors regardless of patients’ stimulant use history.
In a recent open-label study, 220 children and young adolescents with ADHD who had completed 4 weeks of a double-blind, placebo-controlled trial were evaluated for an additional 8 weeks. Modafinil improved ADHD symptoms and overall clinical condition as determined by the parent- or clinician-completed ADHD Rating Scale-IV Home Version, the parent-completed Conners’ ADHD/DSM-IV Scale Parent Version, and the clinician-rated CGI scale. Insomnia, headache, and decreased appetite were the most commonly reported adverse events.

In adults. The results of 2 double-blind, placebo-controlled trials of modafinil in adults with ADHD have been positive:

- In 1 study, modafinil (mean 206.8 mg/d) was more effective than placebo and comparable to dextroamphetamine in improving ADHD symptoms.\(^{31}\)
- In another, modafinil (a single 200-mg dose) increased cognitive performance during treatment.\(^ {32}\)

**Summary.** Once-daily dosing and minimal abuse potential make modafinil an attractive option for ADHD. Comparative studies with stimulants and nonstimulants such as atomoxetine as well as longer-term independent studies are needed. Modafinil might increase the risk of Stevens-Johnson syndrome when used in children and adolescents.\(^ {11}\)

**Schizophrenia.** Double-blind, randomized placebo-controlled studies have evaluated modafinil for improving cognitive function and reducing negative symptoms in patients with schizophrenia. Results have been inconsistent.

One double-blind, randomized, placebo-controlled crossover study of 20 patients with chronic schizophrenia found that modafinil, 200 mg/d, significantly improved short-term verbal memory span and attentional set shifting—the ability to discriminate and selectively attend to various stimulus dimensions (Table 5).\(^ {33}\) Two other controlled studies showed no differences between the effects of modafinil and placebo on schizophrenia’s fatigue, cognition, or positive or negative symptoms.\(^ {34,35}\)

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### Table 5

**Modafinil for schizophrenia or cocaine dependence: More research is needed**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study design</th>
<th>Modafinil dose</th>
<th>Conclusion</th>
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<tbody>
<tr>
<td><strong>Schizophrenia</strong></td>
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<tr>
<td>Turner et al,</td>
<td>Double-blind, placebo-controlled crossover; 20 adults</td>
<td>200 mg/d</td>
<td>Modafinil significantly improved attentional set shifting and short-term verbal memory span</td>
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<tr>
<td>2004(^ {30})</td>
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<td></td>
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<tr>
<td>Sevy et al,</td>
<td>8-week, double-blind, placebo-controlled; 24 subjects</td>
<td>Up to 200 mg/d</td>
<td>No significant difference between modafinil and placebo in reducing fatigue or positive or negative symptoms or in improving cognition</td>
</tr>
<tr>
<td>2005(^ {44})</td>
<td></td>
<td></td>
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<tr>
<td>Pierre et al,</td>
<td>8-week, double-blind, placebo-controlled; 20 subjects</td>
<td>100 to 200 mg/d</td>
<td>Modafinil did not significantly improve neurocognitive or negative symptoms</td>
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<td>2007(^ {20})</td>
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<td><strong>Cocaine dependence</strong></td>
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<tr>
<td>Dackis et al,</td>
<td>8-week, double-blind, placebo-controlled; 62 cocaine-dependent subjects</td>
<td>400 mg/d</td>
<td>Patients receiving modafinil provided significantly more cocaine-negative urine samples and were significantly more likely to achieve ≥3 weeks cocaine abstinence than those receiving placebo</td>
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<td>2005(^ {30})</td>
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**Clinical Point**

In several studies, modafinil improved ADHD symptoms in children/adolescents, but evidence for its use in adult ADHD is mixed.
Summary. Although open-label studies have shown modafinil has beneficial effects on cognitive symptoms, controlled data are scarce. Reports of modafinil-induced psychosis or mania\textsuperscript{11} may limit the drug’s usefulness in schizophrenia patients.

Cocaine dependence. No medications are FDA-approved for treating cocaine dependence. A placebo-controlled, double-blind trial found that modafinil blunts cocaine euphoria under controlled conditions.\textsuperscript{36} This effect is hypothesized to be secondary to modafinil’s glutamate-enhancing and gamma-aminobutyric acid inhibitory effects.\textsuperscript{37}

To test this hypothesis, a double-blind, placebo-controlled trial randomly assigned 62 cocaine-dependent subjects to a single morning dose of modafinil, 400 mg, or placebo for 8 weeks during manual-guided, twice-weekly cognitive-behavioral therapy. Modafinil-treated patients provided significantly more cocaine-negative urine samples (P=0.03) and were significantly more likely to achieve ≥3 weeks of cocaine abstinence (P=0.05) compared with those who received placebo (Table 5, page 77).\textsuperscript{38}

Summary. A single study supports using modafinil to improve outcomes in cocaine-dependent patients receiving standardized psychosocial treatment. More research is needed.

References

Modafinil’s pharmacologic profile—including a lack of reinforcing and addictive properties—makes it a promising alternative to conventional stimulants for treating nonsleep-related psychiatric conditions, especially comorbid substance dependence. Although not robust, the evidence is promising, particularly for treating attention-deficit/hyperactivity disorder and as adjunctive therapy for fatigue and excessive sleepiness associated with major depressive disorder and bipolar disorder.
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