Current PSYCHIATRY

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.

continued

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Off-label modafinil

Clinical Point

Unlike conventional stimulants, modafinil has minimal risk for abuse or dependence

Table 1

Modafinil's pharmacokinetics

Absorbed rapidly, with peak plasma concentrations at 2 to 4 hours
Apparent steady states reached after 2 to 4 days of dosing
Half-life: 15 hours
Major route of elimination (~90%) is metabolism, primarily by the liver

How it works

Although modafinil's precise mechanism of action is unknown, it is believed to promote wakefulness more selectively than conventional stimulants such as amphetamine and methylphenidate. Modafinil does not bind to norepinephrine, serotonin, dopamine, or benzodiazepine receptors.[1,2] It might target specific hypothalamic regions such as the tuberomammillary nucleus and orexin neurons, which are peptide neurotransmitters that promote wakefulness.[3,4]

Preclinical studies found that modafinil increases neuronal activation in the hypothalamus.[2,3] 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.[5]

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.[6,7]

Modafinil also significantly improved sleep latency and CGI-C scores in 2 clinical trials of patients with obstructive sleep apnea/hypopnea.[8,9] 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.[10]

Dosage and side effects. For patients with narcolepsy or obstructive sleep apnea, the recommended dose is 200 mg given in the morning.[11] 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.[11] Modafinil is rapidly absorbed and is metabolized primarily by

Table 2

Selected drug-drug interactions with modafinil

Action of modafinil	Potential drug interactions
Increases elimination of CYP 3A4 substrates	Carbamazepine, phenytoin may decrease modafinil levels Azole antifungals, protease inhibitors, and erythromycin may increase modafinil levels
Inhibits CYP 2C19 enzyme	Modafinil may increase levels of citalopram, diazepam, and sertraline
Decreases absorption of ethinyl estradiol	Modafinil can decrease effectiveness of oral contraceptives

CYP: cytochrome P-450
Source: Reference 11

Table 3

Can modafinil help patients with mood disorders?

Author	Study design	Modafinil dose	Conclusion
Major depressive disorder			
Fava et al, 2005[14]	8-week, double-blind, placebo-controlled; 331 subjects with partial or no response to SSRI monotherapy	200 mg/d	No significant difference between modafinil and placebo at final visit
DeBattista et al, 2003[15]	6-week, double-blind, placebo-controlled; 136 subjects with partial response to antidepressant therapy	100 to 400 mg/d	Significant improvement in sleepiness by week 1 and fatigue by week 2, but differences between modafinil and placebo were not statistically significant by end of study
Konuk et al, 2006[16]	6-week, open-label; 25 subjects with residual sleepiness or fatigue after SSRI therapy	100 to 200 mg/d	All patients showed significant improvement in sleepiness, fatigue, and HAM-D scores
Bipolar depression			
Frye et al, 2007[22]	6-week, double-blind, placebo-controlled trial; 85 subjects who did not respond to a mood stabilizer with or without concomitant antidepressant therapy	100 to 200 mg/d (mean 177 mg/d)	44% of modafinil patients achieved ≥50% reduction in IDS score compared with 23% in placebo group (P=0.03)

HAM-D: Hamilton Rating Scale for Depression; IDS: Inventory for Depressive Symptoms; SSRI: selective serotonin reuptake inhibitor

Clinical Point

Modafinil significantly improved depressive symptoms in several open-label studies but not in 2 controlled trials

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 euphorigenic 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

Off-label modafinil

Clinical Point

Modafinil may have a role in managing fatigue and sleepiness in patients with MDD or bipolar depression

Table 4

Modafinil and ADHD: What the evidence says

Author	Study design	Modafinil dose	Conclusion
Wigal et al, 2006[29]	Analysis of data from 3 double-blind, placebo-controlled trials; total 638 children/adolescents, some of whom had received prior stimulant therapy	170 to 425 mg/d	Whether or not patients received prior stimulant treatment, modafinil significantly improved ADHD symptoms and was well tolerated
Boellner et al, 2006[30]	8-week, open-label extension of a 4-week double-blind, placebo-controlled trial; 220 subjects ages 6-14	100 to 400 mg/d	Modafinil improved ADHD symptoms and overall clinical condition
Taylor et al, 2000[31]	2-week, double-blind, placebo-controlled crossover comparing modafinil with dextroamphetamine; 22 adults	Mean 206.8 mg/d	Both modafinil and dextroamphetamine significantly improved ADHD symptoms compared with placebo
Turner et al, 2004[32]	Double-blind, placebo-controlled crossover; 20 adults	Single 200-mg dose	Modafinil improved results on cognitive tests, including short-term memory span, visual memory, spatial planning, and sustained attention

ADHD: attention-deficit/hyperactivity disorder

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 apathy[17]
- depression with atypical features[18]
- seasonal affective disorder[19]
- partial response to antidepressants.[20,21]

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 noradrenaline 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]

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highest dose of oral olanzapine (15±2.5 mg/d). In controlled clinical trials of intramuscular olanzapine 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.

Other Adverse Events: Dose-relatedness of adverse events was assessed using data from this same clinical trial involving 3 fixed oral dosage ranges (5±2.5, 10±2.5, or 15±2.5 mg/d) compared with placebo. The following treatment-emergent events showed a statistically significant trend: asthenia, dry mouth, nausea, somnolence, tremor.

In an 8-week, randomized, double-blind study in patients with schizophrenia, schizophreniform disorder, or schizoaffective disorder comparing fixed doses of 10, 20, and 40 mg/d, statistically significant differences were seen between doses for the following: baseline to endpoint weight gain, 10 vs 40 mg/d; incidence of treatment-emergent prolactin elevations >24.2 ng/mL (female) or >18.77 ng/mL (male), 10 vs 40 mg/d and 20 vs 40 mg/d; fatigue, 10 vs 40 mg/d and 20 vs 40 mg/d; and dizziness, 20 vs 40 mg/d.

Vital Sign Changes—Oral olanzapine was associated with orthostatic hypotension and tachycardia in clinical trials. Intramuscular olanzapine for injection was associated with bradycardia, hypotension, and tachycardia in clinical trials (*see* PRECAUTIONS).

Weight Gain—In placebo-controlled 6-week schizophrenia studies, weight gain was reported in 5.6% of oral olanzapine patients (average 2.8-kg gain) compared to 0.8% of placebo patients (average 0.4-kg loss); 29% of olanzapine patients gained >7% of their baseline weight, compared to 3% of placebo patients. During continuation therapy (238 median days of exposure), 56% of patients met the criterion for having gained >7% of their baseline weight. Average gain during long-term therapy was 5.4 kg.

Laboratory Changes—Olanzapine is associated with asymptomatic increases in SGPT, SGOT, and GGT and with increases in serum prolactin and CPK (*see* PRECAUTIONS). Asymptomatic elevation of eosinophils was reported in 0.3% of olanzapine patients in premarketing trials. There was no indication of a risk of clinically significant neutropenia associated with olanzapine in the premarketing database.

In clinical trials among olanzapine-treated patients with baseline random triglyceride levels of <150 mg/dL (N=659), 0.5% experienced triglyceride levels of ≥500 mg/dL anytime during the trials. In these same trials, olanzapine-treated patients (N=1185) had a mean triglyceride increase of 20 mg/dL from a mean baseline of 175 mg/dL. In placebo-controlled trials, olanzapine-treated patients with baseline random cholesterol levels of <200 mg/dL (N=1034) experienced cholesterol levels of ≥240 mg/dL anytime during the trials more often than placebo-treated patients (N=602; 3.6% vs 2.2% respectively). In these same trials, olanzapine-treated patients (N=2528) had a mean increase of 0.4 mg/dL in cholesterol from a mean baseline of 203 mg/dL, which was significantly different compared to placebo-treated patients (N=1415) with a mean decrease of 4.6 mg/dL from a mean baseline of 203 mg/dL.

ECG Changes—Analyses of pooled placebo-controlled trials revealed no statistically significant olanzapine/placebo differences in incidence of potentially important changes in ECG parameters, including QT, QTc, and PR intervals. Olanzapine was associated with a mean increase in heart rate of 2.4 BPM compared to no change among placebo patients.

Other Adverse Events Observed During Clinical Trials—The following treatment-emergent events were reported with oral olanzapine at multiple doses ≥1 mg/d in clinical trials (8661 patients, 4165 patient-years of exposure). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. *Frequent* events occurred in ≥1/100 patients; *infrequent* events occurred in 1/100 to 1/1000 patients; *rare* events occurred in <1/1000 patients. ***Body as a Whole***—*Frequent:* dental pain, flu syndrome; *Infrequent:* abdomen enlarged, chills, face edema, intentional injury, malaise, moniliasis, neck pain, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; *Rare:* chills and fever, hangover effect, sudden death. ***Cardiovascular***—*Frequent:* hypotension; *Infrequent:* atrial fibrillation, bradycardia, cerebrovascular accident, congestive heart failure, heart arrest, hemorrhage, migraine, pallor, palpitation, vasodilatation, ventricular extrasystoles; *Rare:* arteritis, heart failure, pulmonary embolus. ***Digestive***—*Frequent:* flatulence, increased salivation, thirst; *Infrequent:* dysphagia, esophagitis, fecal impaction, fecal incontinence, gastritis, gastroenteritis, gingivitis, hepatitis, melena, mouth ulceration, nausea and vomiting, oral moniliasis, periodontal abscess, rectal hemorrhage, stomatitis, tongue edema, tooth caries; *Rare:* aphthous stomatitis, enteritis, eructation, esophageal ulcer, glossitis, ileus, intestinal obstruction, liver fatty deposit, tongue discoloration. ***Endocrine***—*Infrequent:* diabetes mellitus; *Rare:* diabetic acidosis, goiter. ***Hemic and Lymphatic***—*Infrequent:* anemia, cyanosis, leukocytosis, leukopenia, lymphadenopathy, thrombocytopenia; *Rare:* normocytic anemia, thrombocythemia. ***Metabolic and Nutritional***—*Infrequent:* acidosis, alkaline phosphatase increased, bilirubinemia, dehydration, hypercholesteremia, hyperglycemia, hyperlipemia, hyperuricemia, hypoglycemia, hypokalemia, hyponatremia, lower extremity edema, upper extremity edema; *Rare:* gout, hyperkalemia, hypernatremia, hypoproteinemia, ketosis, water intoxication. ***Musculoskeletal***—*Frequent:* joint stiffness, twitching; *Infrequent:* arthritis, arthrosis, leg cramps, myasthenia; *Rare:* bone pain, bursitis, myopathy, osteoporosis, rheumatoid arthritis. ***Nervous System***—*Frequent:* abnormal dreams, amnesia, delusions, emotional lability, euphoria, manic reaction, paresthesia, schizophrenic reaction; *Infrequent:* akinesia, alcohol misuse, antisocial reaction, ataxia, CNS stimulation, cogwheel rigidity, delirium, dementia, depersonalization, dysarthria, facial paralysis, hypesthesia, hypokinesia, hypotonia, incoordination, libido decreased, libido increased, obsessive compulsive symptoms, phobias, somatization, stimulant misuse, stupor, stuttering, tardive dyskinesia, vertigo, withdrawal syndrome; *Rare:* circumoral paresthesia, coma, encephalopathy, neuralgia, neuropathy, nystagmus, paralysis, subarachnoid hemorrhage, tobacco misuse. ***Respiratory***—*Frequent:* dyspnea; *Infrequent:* apnea, asthma, epistaxis, hemoptysis, hyperventilation, hypoxia, laryngitis, voice alteration; *Rare:* atelectasis, hiccup, hypoventilation, lung edema, stridor. ***Skin and Appendages***—*Frequent:* sweating; *Infrequent:* alopecia, contact dermatitis, dry skin, eczema, maculopapular rash, pruritus, seborrhea, skin discoloration, skin ulcer, urticaria, vesiculobullous rash; *Rare:* hirsutism, pustular rash. ***Special Senses***—*Frequent:* conjunctivitis; *Infrequent:* abnormality of accommodation, blepharitis, cataract, deafness, diplopia, dry eyes, ear pain, eye hemorrhage, eye inflammation, eye pain, ocular muscle abnormality, taste perversion, tinnitus; *Rare:* corneal lesion, glaucoma, keratoconjunctivitis, macular hypopigmentation, miosis, mydriasis, pigment deposits lens. ***Urogenital***—*Frequent:* vaginitis*; *Infrequent:* abnormal ejaculation,* amenorrhea,* breast pain, cystitis, decreased menstruation,* dysuria, female lactation,* glycosuria, gynecomastia, hematuria, impotence,* increased menstruation,* menorrhagia,* metrorrhagia,* polyuria, premenstrual syndrome,* pyuria, urinary frequency, urinary retention, urinary urgency, urination impaired, uterine fibroids enlarged,* vaginal hemorrhage*; *Rare:* albuminuria, breast enlargement, mastitis, oliguria. (*Adjusted for gender.)

The following treatment-emergent events were reported with intramuscular olanzapine for injection at one or more doses ≥2.5 mg/injection in clinical trials (722 patients). This list may not include events previously listed elsewhere in labeling, those events for which a drug cause was remote, those terms which were so general as to be uninformative, and those events reported only once or twice which did not have a substantial probability of being acutely life-threatening. ***Body as a Whole***—*Frequent:* injection site pain; *Infrequent:* abdominal pain, fever. ***Cardiovascular***—*Infrequent:* AV block, heart block, syncope. ***Digestive***—*Infrequent:* diarrhea, nausea. ***Hemic and Lymphatic***—*Infrequent:* anemia. ***Metabolic and Nutritional***—*Infrequent:* creatine phosphokinase increased, dehydration, hyperkalemia. ***Musculoskeletal***—*Infrequent:* twitching. ***Nervous System***—*Infrequent:* abnormal gait, akathisia, articulation impairment, confusion, emotional lability. ***Skin and Appendages***—*Infrequent:* sweating.

Postintroduction Reports—Reported since market introduction and temporally (not necessarily causally) related to olanzapine therapy: allergic reaction (eg, anaphylactoid reaction, angioedema, pruritus or urticaria), diabetic coma, jaundice, neutropenia, pancreatitis, priapism, rhabdomyolysis, and venous thromboembolic events (including pulmonary embolism and deep venous thrombosis). Random cholesterol levels of ≥240 mg/dL and random triglyceride levels of ≥1000 mg/dL have been reported.

DRUG ABUSE AND DEPENDENCE: Olanzapine is not a controlled substance.

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Summary. Modafinil may have a role in managing residual fatigue and excessive sleepiness associated with MDD and bipolar depression. Evidence for a mood-elevating effect is minimal; additional studies are needed. Adjunctive modafinil and conventional stimulants have not been compared head-to-head in patients with mood disorders. Modafinil's tolerability profile and lack of euphorigenic and reinforcing properties make it a potentially attractive alternative, however.

ADHD. Approximately 30% of ADHD patients do not respond to or are unable to tolerate conventional stimulant medications such as methylphenidate and dextroamphetamine.[27] Several studies have evaluated modafinil as a potential treatment for ADHD based on the drug's action on arousal and attention systems. Although modafinil's precise mechanism of action in ADHD is unknown, proposed mechanisms include:

- hypothalamic and cerebral cortex neuronal activation
- action on histamine that results in internal vigilance.[28]

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 dosage 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. Wigal et al[29] 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.

Table 5

Modafinil for schizophrenia or cocaine dependence: More research is needed

Author	Study design	Modafinil dose	Conclusion
Schizophrenia			
Turner et al, 2004[33]	Double-blind, placebo-controlled crossover; 20 adults	200 mg/d	Modafinil significantly improved attentional set shifting and short-term verbal memory span
Sevy et al, 2005[34]	8-week, double-blind, placebo-controlled; 24 subjects	Up to 200 mg/d	No significant difference between modafinil and placebo in reducing fatigue or positive or negative symptoms or in improving cognition
Pierre et al, 2007[35]	8-week, double-blind, placebo-controlled; 20 subjects	100 to 200 mg/d	Modafinil did not significantly improve neurocognitive or negative symptoms
Cocaine dependence			
Dackis et al, 2005[38]	8-week, double-blind, placebo-controlled; 62 cocaine-dependent subjects	400 mg/d	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

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.[30] 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]

continued

Clinical Point

In several studies, modafinil improved ADHD symptoms in children/adolescents, but evidence for its use in adult ADHD is mixed

Off-label modafinil

Clinical Point

In open-label studies modafinil improved cognitive symptoms in schizophrenia but results from controlled trials are inconclusive

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[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.[36] This effect is hypothesized to be secondary to modafinil's glutamate-enhancing and gamma-aminobutyric acid inhibitory effects.[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***).[38]

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

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Bottom Line

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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Related Resource

• Ballon JS, Feifel D. A systematic review of modafinil: potential clinical uses and mechanisms of action. *J Clin Psychiatry* 2006;67(4):554-66.

Drug Brand Names

Atomoxetine • Strattera
Bupropion • Wellbutrin
Carbamazepine • Carbatrol, Tegretol, others
Citalopram • Celexa
Dextroamphetamine • Dexedrine, DextroStat
Diazepam • Valium
Erythromycin • Ery-Tab, Eryc, others
Fluoxetine • Prozac
Lithium • Eskalith, Lithobid
Methylphenidate • Ritalin, others
Modafinil • Provigil
Phenytoin • Dilantin
Sertraline • Zoloft
Venlafaxine • Effexor
Zolpidem • Ambien

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Clinical Point

Modafinil plus cognitive-behavioral therapy improved outcomes for cocaine-dependent patients