

A Systematic Review of Modafinil: Potential Clinical Uses and Mechanisms of Action

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Background: Modafinil is a novel wake-promoting agent that has U.S. Food and Drug Administration approval for narcolepsy and shift work sleep disorder and as adjunctive treatment of obstructive sleep apnea/hypopnea syndrome. Modafinil has a novel mechanism and is theorized to work in a localized manner, utilizing hypocretin, histamine, epinephrine, γ -aminobutyric acid, and glutamate. It is a well-tolerated medication with low propensity for abuse and is frequently used for off-label indications. The objective of this study was to systematically review the available evidence supporting the clinical use of modafinil.

Data Sources: The search term *modafinil OR Provigil* was searched on PubMed. Selected articles were mined for further potential sources of data. Abstracts from major scientific conferences were reviewed. Lastly, the manufacturer of modafinil in the United States was asked to provide all publications, abstracts, and unpublished data regarding studies of modafinil.

Data Synthesis: There have been 33 double-blind, placebo-controlled trials of modafinil. Additionally, numerous smaller studies have been performed, and case reports of modafinil's use abound in the literature.

Conclusions: Modafinil is a promising drug with a large potential for many uses in psychiatry and general medicine. Treating daytime sleepiness is complex, and determining the precise nature of the sleep disorder is vital. Modafinil may be an effective agent in many sleep conditions. To date, the strongest evidence among off-label uses exists for the use of modafinil in attention-deficit disorder, postanesthetic sedation, and cocaine dependence and withdrawal and as an adjunct to antidepressants for depression.

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Modafinil is a novel wake-promoting agent approved by the U.S. Food and Drug Administration (FDA) for use in treating narcolepsy¹⁻⁸ and shift work sleep disorder (SWSD)^{9,10} and as adjunctive treatment for obstructive sleep apnea/hypopnea syndrome (OSAHS).¹⁰⁻¹⁵ Modafinil's mechanism remains unknown, although evidence strongly supports a mechanism distinct from that of typical amphetamine-derived stimulants.¹⁶ Modafinil is associated with increased adrenergic, histaminergic, glutaminergic, and hypocretin activity and decreased γ -aminobutyric acid (GABA) activity in specific parts of the brain. A generally well-tolerated medication, modafinil is increasingly being used for many off-label indications.¹⁷ The objective of this study was to systematically review the available evidence supporting the clinical use of modafinil.

DATA SOURCES

To conduct this literature review, the search term *modafinil OR Provigil* was searched on PubMed. This resulted in 397 articles. Selected articles were mined for further potential sources of data. Abstracts from major scientific conferences were reviewed to identify articles relevant to the topic of this review. Lastly, the U.S. manufacturer of Provigil, Cephalon, Inc. (Frazer, Pa.), was asked to provide all publications, abstracts, and unpublished data regarding studies of modafinil.

DATA SYNTHESIS

Possible Mechanisms of Action

Modafinil's precise mechanism of action is not known. Conventional wake-promoting stimulants such as amphetamine and amphetamine analogs work as sympathomimetic drugs that increase levels of norepinephrine, serotonin, and dopamine by blocking reuptake and stimulating release at the presynaptic terminals.¹⁸ The increased levels of dopamine in the reticular activating system and the prefrontal cortex are thought to be responsible for the enhanced wakefulness and alertness produced by these drugs.¹⁹ Additionally, increased sympathetic tone produces predictable systemic side effects.²⁰

There is some evidence that modafinil's effects are mediated by activation of noradrenergic α_1 receptors, includ-

ing evidence that modafinil's wake-promoting behavioral effects in mice were blocked by an α_{1B} -antagonist.²¹ Additionally, modafinil was shown to increase phosphorylation of mitogen-activated protein kinase (MAPK) in cultured mouse cells, in an α_{1B} -dependent fashion.²¹ Additionally, when α receptors in mice were attenuated with stress, the motor effects of modafinil were correspondingly attenuated.²² Other evidence argues against a strong α_1 -agonist effect of modafinil. α -Agonists are effective in treating cataplexy in dogs, while modafinil is ineffective.²³

There is evidence that modafinil's mechanism of action differs substantially from that of conventional stimulants. In rats, modafinil and amphetamine both increase the brain's expression of the gene *c-fos*, a marker of neuronal activation.²⁴ After amphetamine administration, diffuse areas of the cortex and striatum are activated, with particularly strong effects in the caudate nucleus.²⁵ In contrast, modafinil produces a more localized pattern of *c-fos* activation focused primarily in the paraventricular and supra-chiasmatic nuclei, anterior hypothalamus, amygdala, and tuberomammillary nucleus (TMN).^{25,26} Thus, modafinil-induced neuronal activation is more localized to wakefulness areas compared to amphetamine-induced neuronal activation.^{26,27}

In other studies,²⁸ modafinil has been shown to decrease GABA release in the nucleus accumbens of rats. In contrast, amphetamine does not produce this effect.²⁸

Amphetamines strongly increase dopamine levels in the nucleus accumbens, striatum, and prefrontal cortex.²⁹ Amphetamine's reinforcing, motor-activating, and cognitive-enhancing effects are attributed to this activity.²⁹ Accordingly, haloperidol blocks the stimulant effects of amphetamine in rats at the dopamine-2 receptor.¹⁶ Modafinil produces only a weak dopaminergic increase in the nucleus accumbens, which is secondary to decreased GABA,³⁰ and haloperidol does not block the behavioral effects of modafinil in animals.¹⁶ This difference in dopaminergic activity is one explanation for the decreased addiction potential of modafinil.³¹

Modafinil appears to increase release of glutamate in the hippocampal formation and ventromedial and ventrolateral areas of the thalamus.^{32,33} This change may contribute to modafinil's vigilance-enhancing properties.^{32,33}

An additional mechanism for modafinil's action may be related to its modulation of the hypocretin system. Hypocretin, also referred to as orexin, is a hypothalamic peptide that has been strongly implicated in the regulation of appetite. It also may have a role in regulating wakefulness, as decreased levels of hypocretin have been found in narcoleptic canines.³⁴ Modafinil strongly activates hypocretin neurons in the lateral hypothalamus and induces hypocretin-secreting neurons in the perifornical area.^{19,26} Hypocretin peptides can stimulate glutaminergic nerve firing in the hypothalamic circuits associated with arousal regulation.³⁵

Hypocretin peptides stimulate the release of histamine in the TMN, influencing arousal and regulating the sleep-wake cycle.³⁶ Direct administration of hypocretin-A into the TMN produces prolonged wakefulness in rats.³⁷ Histamine levels were shown to increase by 150% when modafinil was injected peripherally in the rat.³⁸ In contrast, there was no change in histamine levels when modafinil was injected directly into the TMN, suggesting that modafinil's histaminergic effects are mediated by the hypocretin system.³⁸

In summary, the mechanisms underlying modafinil's clinical effects are complex and distinct from other known wakefulness agents. Modulation of glutamate, GABA, histamine, and hypocretin are involved, whereas effects on monoamine systems are less important. Anatomically, modafinil's effects focus on hypothalamus-based wakefulness circuits rather than diffuse neuronal activation.

General Safety and Tolerability

Modafinil is over 90% metabolized in the liver, with the remainder excreted renally. It modestly induces cytochrome P450 enzyme systems CYP1A2, CYP2B6, and CYP3A4/5 and suppresses the CYP2C19 system in vitro, although there are few clinically significant interactions.^{39,40} Modafinil has been reported to be safe even with the monoamine oxidase inhibitors tranylcypromine⁴¹ and phenelzine.⁴²

Modafinil is currently categorized as a Schedule IV drug by the FDA.¹⁵ Doses between 100 mg/day and 600 mg/day are effective in a dose-independent manner.⁴⁰ The most commonly reported side effects are headache, nausea, diarrhea, nervousness, anxiety, dyspepsia, and insomnia.¹⁵ In contrast to traditional stimulants, modafinil has shown no effect on sleep architecture, including rapid eye movement (REM) rebound, even in prolonged use in cats.⁴³⁻⁴⁵ Modafinil has not shown the propensity to produce withdrawal and tolerance that are associated with chronic amphetamine use.^{46,47}

Approved Clinical Uses

Narcolepsy. Narcolepsy is characterized by excessive daytime sleepiness, cataplexy, and other abnormal manifestations of REM sleep, such as sleep paralysis and hypnagogic hallucinations.⁴⁸ Modafinil was first approved by the FDA for treatment of narcolepsy.⁴⁹ In a double-blind, placebo-controlled, crossover trial (N = 50),⁴ 300 mg/day of modafinil was used in a fixed-dose manner (Table 1). No changes were noted in nighttime sleepiness, but it was noted that there was decreased daytime sleepiness and improvement on the Maintenance of Wakefulness Test (MWT). In a second double-blind, placebo-controlled, crossover study,³ similar findings were noted on the MWT. Two larger, randomized, double-blind controlled trials^{1,2} were conducted by the U.S. Modafinil in Narcolepsy Multicenter Study Group (N = 283 and N = 271). In

Table 1. Randomized, Double-Blind, Placebo-Controlled Trials Using Modafinil

| Study | Indication | Method | Sample Size | Results |
|--|---|---|---|--|
| US Modafinil in Narcolepsy Multicenter Study Group (1998) ¹ | Narcolepsy | 9 wk, placebo vs modafinil 200 mg/d vs modafinil 400 mg/d | N = 92 placebo N = 96 modafinil 200 mg N = 95 modafinil 400 mg | Modafinil subjects had improved MSLT (p < .0001), MWT (p < .0001), ESS (p < .0001), and CGI (p < .005) scores. |
| US Modafinil in Narcolepsy Multicenter Study Group (2000) ² | Narcolepsy | 9 wk, placebo vs modafinil 200 mg/d vs modafinil 400 mg/d | N = 93 placebo N = 89 modafinil 200 mg N = 89 modafinil 400 mg | Modafinil 400-mg subjects had improved MSLT scores compared to placebo subjects (p < .0001); modafinil 200 mg did not differ from placebo on this measure. MWT and ESS (p < .0001) and CGI (p < .03) scores were improved for modafinil at both doses. |
| Broughton et al (1997) ³ | Narcolepsy | 2 wk, crossover, 3 arms (placebo, 200 mg/d, 400 mg/d) | N = 75 | Modafinil improved MWT scores (p < .00001) with no difference between doses. |
| Billiard et al (1994) ⁴ | Narcolepsy | 4 wk, crossover, 300-mg/d fixed dose | N = 50 | No significant difference noted in night sleep, but benefit noted in MWT scores (p = .0004), daytime sleepiness, and daytime sleep (p = .0002). |
| Czeisler et al (2005) ⁹ | Shift work sleep disorder | 12 wk, 200-mg fixed dose | N = 110 placebo N = 99 modafinil | Modafinil subjects improved on the MSLT (p < .0001), the Psychomotor Vigilance Test (p = .012), the CGI (p < .0001), and subjective ratings of sleepiness (p < .0001). |
| Rosenberg et al (2003) ⁵⁵ | Shift work sleep disorder | 12 wk, 200- or 300-mg/d fixed dose | N = 278 | Modafinil group showed improvement on the FOSQ. |
| Black and Hirshkowitz (2005) ¹¹ | Obstructive sleep apnea/hypopnea syndrome | 12 wk, 200- or 400-mg/d fixed dose, adjunctive to CPAP | N = 104 placebo N = 104 modafinil 200 mg N = 101 modafinil 400 mg | Both modafinil groups showed improvement on the MWT (p < .001), the ESS (p < .0001), the CGI (p < .001), and the FOSQ (p < .001). |
| Pack et al (2001) ¹³ | Obstructive sleep apnea/hypopnea syndrome | 4 wk, 400-mg/d fixed dose, adjunctive to CPAP | N = 80 placebo N = 77 modafinil | Modafinil group showed improvement on the ESS (p < .0001) and the CGI (= 0.035) but not on the MSLT compared with the placebo group. |
| Kingshott et al (2001) ¹⁴ | Obstructive sleep apnea/hypopnea syndrome | 7 wk, 400-mg/d fixed dose, crossover, adjunctive to CPAP | N = 32 | No significant difference between groups on the ESS (p = .24), the MSLT (p = .16), Trailmaking B (p = .95), and the FOSQ (p = .41). |
| Randall et al (2005) ⁷⁶ | Chronic fatigue syndrome | 20 days, crossover, variable dose 200–400 mg/d | N = 14 | No significant difference between groups in mood, quality of life, and mental fatigue as measured by the Visual Analog Scale, the Medical Outcomes Study 36-Item Short Form Health Survey, and the 11-item Fatigue Questionnaire, respectively. |
| Stankoff et al (2005) ⁶⁷ | Multiple sclerosis fatigue | 35 days, variable dose 200–400 mg/d | N = 59 modafinil N = 56 placebo | No significant difference between groups on the Modified Fatigue Impact Scale (p = .27) or the ESS. Both groups improved from baseline on the Modified Fatigue Impact Scale (p < .0001). |
| Hogl et al (2002) ⁷¹ | Parkinson's disease fatigue | 2 wk, crossover, 3 arms (placebo, 100 mg/d, 200 mg/d) | N = 15 | Improvement on the ESS (p = .011) with modafinil. |
| Adler et al (2003) ⁷⁰ | Parkinson's disease fatigue | 3 wk, crossover, 200-mg/d fixed dose | N = 21 | Improvement on the ESS (p = .039) and the CGI (p = .07) with modafinil. No difference between groups on the UPDRS. |
| Ondo et al (2005) ⁷² | Parkinson's disease fatigue | 4 wk, variable dose 200–400 mg/d | N = 19 modafinil N = 18 placebo | No significant differences between groups on the ESS, the MSLT, the UPDRS, and the HAM-D. |
| Chan et al (2006) ⁷⁷ | Polio fatigue | 5 wk, crossover, 400-mg fixed dose | N = 14 | No significant difference between groups on the Piper Fatigue Scale, the ESS, the Digit Span, and reaction time tests. |
| Sevy et al (2005) ⁸⁸ | Antipsychotic fatigue | 8 wk, variable dose 100–200 mg/d | N = 13 modafinil N = 11 placebo | No significant difference between groups on the FSS or Visual Analog Fatigue Scale, although both groups improved from baseline. |
| Larijani et al (2004) ⁹¹ | Postanesthesia recovery time | 24-hr follow-up, single 200-mg dose | N = 17 modafinil N = 17 placebo | Modafinil improved subjective feelings of "being worn out" (p < .01), exhaustion (p < .01), and fatigue (p < .05), in a postoperation questionnaire. |

continued

Table 1. Randomized, Double-Blind, Placebo-Controlled Trials Using Modafinil (cont.)

| Study | Indication | Method | Sample Size | Results |
|---|---------------------------|--|--------------------------------------|---|
| Taylor and Russo (2000) ¹⁰¹ | ADHD (adult) | 2 wk, crossover between dextroamphetamine and modafinil, flexible modafinil dose average = 209 mg/d | N = 22 | Modafinil and dextroamphetamine groups both showed improvement on the DSM-IV ADHD Behavior Checklist for Adults ($p < .0001$) and the Controlled Oral Word Association Test ($p < .05$) compared with placebo. |
| Rugino and Samscock (2003) ¹⁰² | ADHD (child) | 6 wk, flexible dose average = 200 mg/d | N = 11 modafinil N = 11 placebo | Modafinil subjects improved on the Test of Variables of Attention ($p < .02$), the Conners' Parent and Teacher Rating Scales ($p = .04$), and parent subjective ratings ($p < .0001$). |
| Cephalon, Inc ¹⁰⁴ | ADHD (adult) | Placebo vs modafinil 100 mg/d vs modafinil 400 mg/d | N = 113 | No significant difference between groups on the DSM-IV ADHD Behavior Checklist for Adults. |
| Biederman et al (2005) ¹⁰⁵ | ADHD (child) | 9 wk, film-coated modafinil, flexible dose 170–425 mg/d | N = 164 modafinil N = 82 placebo | Modafinil (film-coated) improved ADHD Rating Scale-IV School Version and Home Version scores and CGI score ($p < .0001$). |
| Fava et al (2005) ¹⁰⁹ | Major depressive disorder | 8 wk, antidepressant augmentation, 200-mg/d fixed dose | N = 159 modafinil N = 155 placebo | Modafinil subjects showed significant benefit on the CGI ($p = .02$) and trend-level benefit on the HAM-D, the ESS, and the Montgomery-Asberg Depression Rating Scale. No change from placebo on the Brief Fatigue Inventory and the FSS. |
| Frye et al (2005) ¹¹⁵ | Bipolar depression | 6 wk, augmentation, variable dose 100–200 mg/d | N = 41 modafinil N = 44 placebo | Modafinil subjects improved in Inventory of Depressive Symptoms scores after 2 weeks ($p = .039$). More in the modafinil group than the placebo group were responders ($p = .038$). No difference between groups in manic emergence (Young Mania Rating Scale). |
| Dackis et al (2003) ¹⁴⁶ | Cocaine dependence | 4 days, 200 or 400 mg/d, crossover | N = 7 | Less self-rated euphoria with cocaine seen in modafinil subjects ($p = .02$). |
| Dackis et al (2005) ¹²⁰ | Cocaine dependence | 8 wk, 400-mg/d fixed dose | N = 30 modafinil N = 32 placebo | Modafinil subjects were more likely than placebo subjects to have negative urine benzoylecgonine ($p = .03$) and > 3 weeks of cocaine abstinence ($p = .02$). |
| Turner et al (2004) ¹²² | Schizophrenia cognition | Single 200-mg/d dose, crossover | N = 20 | Modafinil subjects showed increased accuracy in Digit Span ($p = .006$) and 3-dimensional Set Shifting Task (IDED; $p < .025$). |
| Pierre et al (2005) ¹²⁴ | Schizophrenia | 8 wk, augmentation, flexible dose average = 180 mg/d | N = 10 modafinil N = 10 placebo | Modafinil subjects had a significantly greater rate of improvement on the CGI ($p < .01$) and a more favorable CGI score at endpoint than placebo subjects. No significant change in positive or negative symptoms. |
| Sevy et al (2005) ⁸⁸ | Schizophrenia | 8 wk, 200-mg/d fixed dose | N = 13 modafinil N = 11 placebo | No significant difference between groups in fatigue (FSS), positive (Brief Psychiatric Rating Scale) and negative (Scale for the Assessment of Negative Symptoms) symptoms, or cognition. |
| Makris et al (2004) ¹²⁷ | Appetite suppression | One session on each of 3 doses of amphetamine and modafinil; 5 placebo sessions. Modafinil doses = 1.75, 3.5, or 7.0 mg/kg. Amphetamine doses = 0.035, 0.07, or 0.14 mg/kg | N = 11 | Modafinil and amphetamine both produced significant decrease in appetite ($p < .05$) as measured by number of mouthfuls of food and number of chews following modafinil administration. |

Abbreviations: ADHD = attention-deficit/hyperactivity disorder, CGI = Clinical Global Impressions scale, CPAP = continuous positive airway pressure, ESS = Epworth Sleepiness Scale, FOSQ = Functional Outcomes of Sleep Questionnaire, FSS = Fatigue Severity Scale, HAM-D = Hamilton Rating Scale for Depression, MSLT = Multiple Sleep Latency Test, MWT = Maintenance of Wakefulness Test, UPDRS = Unified Parkinson's Disease Rating Scale.

these trials, the main outcome measures were the MWT, the Multiple Sleep Latency Test (MSLT), the Epworth Sleepiness Scale (ESS), and the Clinical Global Impressions scale (CGI). Both trials showed similar efficacy as early as week 3 in the above measures. Open-label extensions were conducted for the 2 multicenter trials for up to 136 weeks.⁵⁰⁻⁵² In the open-label phase, modafinil was shown to continue to be effective on the ESS, with a low percentage of patients discontinuing the medication. In another long-term open-label study (N = 140),⁵³ subjective ratings continued to show modafinil to be beneficial for 64% of patients for up to 114 months, with a mean duration of treatment of 22 months in the study.

Shift work sleep disorder. Shift work sleep disorder (SWSD) is a circadian rhythm disorder that typically presents as insomnia or excessive sleepiness that occurs transiently with the work schedule.⁵⁴ In a multicenter, double-blind, placebo-controlled trial (N = 209),⁹ 200 mg of modafinil was evaluated during 12 weeks. The modafinil group performed better on the Psychomotor Vigilance Test, had improved sleep latency while working at night, and had fewer accidents while driving home from work. However, despite these benefits, there were no statistically significant differences in sleep episodes at work, accidents while working, and caffeine consumption during work and in the day after a night shift. In a second double-blind, placebo-controlled study (N = 278),⁵⁵ quality-of-life measures were evaluated in people taking modafinil. The modafinil group showed improved scores on the Functional Outcomes of Sleep Questionnaire (FOSQ) and the mental health portion of the Medical Outcomes Study 36-Item Short Form Health Survey. In a long-term, open-label study (N = 118),⁵⁶ modafinil did not show any difference from placebo on the FOSQ over 12 months, although it was well tolerated.

Obstructive sleep apnea/hypopnea syndrome. Obstructive sleep apnea/hypopnea syndrome is marked by frequent blockages in the upper airway during sleep that disrupt sleep and is associated with excessive daytime sleepiness, hypertension, cardiac disease, and stroke.⁵⁷ The treatment of choice for OSA is continuous positive airway pressure (CPAP), generally applied nasally.⁵⁸ In a double-blind, placebo-controlled trial (N = 309),¹¹ modafinil was shown to have benefit on the ESS by week 4, and, by week 12, benefit was seen on the ESS, CGI, and FOSQ with doses of 200 or 400 mg daily. In another double-blind, placebo-controlled trial (N = 157),¹³ subjects who received 400 mg/day of modafinil demonstrated a benefit over placebo on the ESS by as early as 1 week, and CGI results were improved at 4 weeks. However, no difference was noted in MSLT results. In a third double-blind, placebo-controlled, crossover trial (N = 32),¹⁴ modafinil was not shown to separate from placebo on the FOSQ; on neurocognitive tests including Trailmaking B, reaction time, and memory; and on the MSLT.

Potential Nonapproved Clinical Uses

Fatigue and sedation associated with specific medical conditions. Multiple sclerosis is a disease of diffuse central nervous system lesions that manifest throughout the body and with periods of waxing and waning intensity. Low energy is one of the more chronic and disabling features of the disease.^{59,60} Upwards of 66% of patients suffer from daily fatigue.⁶¹ The mechanism for fatigue is poorly understood in multiple sclerosis but may be of central origin⁶² and may also contain a neuromuscular component.⁶³ An open-label study (N = 50)⁶⁴ of multiple sclerosis fatigue showed that most patients reported decreased fatigue and improved functioning on the Kurtzke Expanded Disability Status Scale (EDSS) in response to 100 or 200 mg daily of modafinil added to their existing medication regimen. Modafinil was well tolerated in this sample, with side effects increasing in a dose-dependent fashion.⁶⁴ Other authors have also reported open-label success with modafinil for multiple sclerosis-related fatigue.^{60,65} In a randomized, single-blind, placebo-controlled trial (N = 72),⁶⁶ 200 mg/day of modafinil taken for 2 weeks was shown to be superior to placebo on the multifaceted Modified Fatigue Impact Scale (MFIS), the Visual Analog Scale for Fatigue (VAS-F), and the ESS. However, 400 mg/day of modafinil did not show increased efficacy compared to placebo over the same time period.⁶⁶ A double-blind, placebo-controlled trial (N = 115)⁶⁷ showed no benefit of modafinil over placebo on the MFIS, the VAS-F, and the ESS. In both groups, there was a statistically significant improvement in each outcome measure compared to baseline. However, there was no separation between placebo and active treatment. Therefore, a strong placebo effect may have precluded demonstrating efficacy for modafinil.

Parkinson's disease is characterized by tremors, rigidity, and generalized slowing of movements. Fatigue may be mediated by various aspects of therapy or by the primary defect in dopamine.⁶⁸ In an initial open-label trial (N = 10),⁶⁹ modafinil was shown to improve ESS scores while not increasing Unified Parkinson's Disease Rating Scale (UPDRS) scores. A double-blind, crossover study (N = 21)⁷⁰ showed similar benefit of modafinil on the ESS without worsening baseline Parkinson's disease symptoms on the UPDRS over a 3-week study period with a 1-week washout. In another double-blind, randomized, placebo-controlled, crossover trial (N = 15),⁷¹ modafinil was used in doses of 100 or 200 mg in the morning for 2 weeks and compared with 2 weeks of placebo treatment. Statistically significant benefit on the ESS was seen when the subjects received modafinil. A larger double-blind, placebo-controlled trial (N = 40, intention to treat [ITT])⁷² of modafinil using the same outcome measures failed to demonstrate a separation from placebo with doses of 200 to 400 mg daily for 4 weeks. The authors⁷² noted that, while the overall effect of modafinil was minimal over

placebo, for some patients a rapid and significant improvement was noted, suggesting that some Parkinson's disease patients may benefit from modafinil.

Chronic fatigue syndrome is characterized by severe, disabling fatigue in addition to musculoskeletal pain, sleep disturbance, impaired concentration, and/or headaches.⁷³ The mechanism for chronic fatigue syndrome is not currently fully understood. Pharmacologic treatments have been generally unsatisfying, although cognitive-behavioral therapy and graded exercise therapy have shown some positive results.⁷⁴ An initial case report⁷⁵ suggested that modafinil was effective in treating the fatigue of 1 patient who had suffered with chronic fatigue syndrome for over 13 years such that he was able to return to work. However, in a small, randomized, double-blind, placebo-controlled, crossover study (N = 14),⁷⁶ modafinil was shown to have no statistical separation from placebo over 20 days of treatment. Outcome variables included tests of attention and subjective ratings of fatigue, quality of life, and mood. This was a small study, however, and may have suffered from a low statistical power to show differences between groups.⁷⁶

Modafinil was evaluated in a double-blind, placebo-controlled, crossover trial (N = 14)⁷⁷ for treatment of sedation in patients with a prior diagnosis of polio. In this study, no difference was observed between conditions on the ESS, the Piper Fatigue Scale (PFS), the Digit Span, and reaction time tests over the course of the 5-week treatment arms.

Fatigue is also common in patients with the human immunodeficiency virus (HIV). In an open-label study (N = 30),⁷⁸ 80% of subjects self-reported that they had less fatigue on modafinil treatment. Among these responders, those with a preexisting mood disorder were noted to have improvement in depression scores on the Hamilton Rating Scale for Depression (HAM-D) and a general increase in cognitive functioning on neuropsychological tests. No change was noted in CD4 lymphocyte count or HIV viral load during the 4-week study. This study was limited by the lack of a control group with which to compare the results.

The cognitive-enhancing properties of modafinil have been evaluated in 2 small studies of patients with dementia. In an open-label study (N = 8),⁷⁹ patients with vascular dementia, subcortical dementia, or Alzheimer dementia were treated with modafinil 100 to 200 mg daily for 6 weeks. They were assessed with the ESS, caregiver reports, and wrist actigraphy. Five of the patients showed improvements on the outcome measures, although no cognitive benefits were noted in the study. In a retrospective review (N = 5),⁸⁰ modafinil was considered "moderately" effective either as monotherapy or in combination with other Alzheimer disease medication. One patient with a history of hallucinations noted an increase in hallucinations during the time on modafinil treatment.

Fibromyalgia is a chronic musculoskeletal pain disorder characterized by pain at established soft tissue trigger points, nonrestorative sleep, and mood disorders. Currently, there is no consensus treatment for fibromyalgia. Modafinil in doses ranging from 150 to 300 mg/day was reported to decrease fatigue and improve alertness in 2 of 4 patients with chronic fibromyalgia without depression.⁸¹ The Global Assessment of Functioning (GAF) score in this small sample increased from 55 to 70 (from moderate impairment to minimal impairment). One patient in this sample reported increased anxiety that was mitigated by decreasing the modafinil dose by 50 mg.⁸¹

Other case reports have shown that modafinil can be helpful in patients with primary biliary cirrhosis,⁸² amyotrophic lateral sclerosis,⁸³ and myasthenia gravis.⁸⁴

Sedation as a side effect of medication. Sedation is a common side effect of psychotropic medication and one that frequently interferes with treatment adherence. Modafinil has been used for treatment of sedation associated with antipsychotic, antidepressant, and mood-stabilizing agents.⁸⁵⁻⁸⁷

In a recent double-blind, placebo-controlled trial (N = 24),⁸⁸ modafinil was shown to be no better than placebo in improving wakefulness and cognition in people with schizophrenia. However, both the control and active groups showed a statistically significant improvement in wakefulness and cognition from baseline.⁸⁸ There are several case reports, however, that demonstrate benefit with modafinil. Makela et al.⁸⁹ described 3 patients taking various antipsychotics who were experiencing debilitating levels of sedation secondary to their treatment. These patients each noted a decrease in their number of hours needed for sleep each night, and an increase in energy during the day when taking 200 mg/day of modafinil. The authors did not report any significant side effects in these patients, including changes in their presenting psychiatric symptoms.

It is noteworthy that in these studies^{88,89} modafinil was generally well tolerated; however, another report⁹⁰ described a case of clozapine toxicity associated with modafinil use that may have resulted from an interaction between modafinil and clozapine at the cytochrome P450 2C19 liver enzyme system.

Modafinil has been reported to reduce the post-anesthesia recovery time. In a double-blind, placebo-controlled study (N = 34),⁹¹ patients were given 1 dose of 200 mg of modafinil upon awakening from anesthesia and rated over the course of 24 hours for symptoms of fatigue. Patients who received the modafinil reported significantly less fatigue than those who received placebo. As more surgeries are done on an outpatient basis, leaving patients to recover at home, decreasing recovery time boosts the safety of such treatment.

A mainstay of pain treatment is opiate-based medications, and many patients suffer side effects of sedation.

While some patients ultimately develop a tolerance, for many patients the sedation persists. This side effect presents a dilemma for physicians and patients, as the sedation can be disabling and can limit the amount of pain medication that can be prescribed. Traditional stimulants are a common treatment for this sedation, but have their own inherent risks.⁹² Based on the ESS, a significant improvement in sedation was demonstrated in a retrospective chart review⁹³ in patients with sedation secondary to pain medication (N = 11) that received 200 to 600 mg/day of modafinil. Furthermore, treatment with modafinil did not disrupt sleep architecture, as often happens with amphetamines.

It is notable that, in a small, randomized, placebo-controlled, crossover trial (N = 12)⁹⁴ in which volunteer subjects received a painful stimulus, those who received modafinil rated their pain slightly higher, though not statistically significantly, compared to those who received placebo.

Non-fatigue effects in specific conditions.

Attention-deficit/hyperactivity disorder. Attention-deficit/hyperactivity disorder (ADHD) is a common psychiatric diagnosis and is estimated to affect 2% to 18% of children⁹⁵ and approximately 4% of adults.⁹⁶ Amphetamine and methylphenidate-based stimulants have been the traditional mainstays of therapy to improve attention and to decrease restlessness.⁹⁷ Recently, nonamphetamine drugs such as tricyclic antidepressants,⁹⁸ atomoxetine,⁹⁹ and bupropion¹⁰⁰ have been shown to have efficacy for ADHD symptoms. In one double-blind, crossover, placebo-controlled study (N = 22)¹⁰¹ comparing dextroamphetamine, modafinil, and placebo, both active medications were of equal efficacy in treating ADHD in adults as measured by the DSM-IV ADHD Behavior Checklist for Adults. Rugino and Samscock¹⁰² report a randomized, placebo-controlled trial (N = 24, ITT) of modafinil in children. They found, with an average daily dose of 200 mg, that children on modafinil treatment had a statistically significant improvement on the Test of Variables of Attention, a computerized continuous-performance test measuring sustained attention, and the Conners' Parent and Teacher Rating Scales, but only a nonsignificant positive trend on the ADHD Rating Scale-IV. The study was terminated before it could reach sufficient power for the last outcome variable when the principal investigator left the study.¹⁰² Another recent study¹⁰³ proposes that modafinil may improve cognitive performances in adults with ADHD. The benefits were similar to what was seen in healthy controls, although the clinical significance may be higher for those with ADHD.

In contrast to these positive studies,¹⁰¹⁻¹⁰³ the manufacturer of modafinil reports unpublished data from a double-blind, placebo-controlled trial (N = 113)¹⁰⁴ that it conducted examining 100 or 400 mg/day of modafinil in children with ADHD that did not show statistical benefit

of modafinil on the DSM-IV ADHD Behavior Checklist for Adults.

In a large, multicenter, double-blind, placebo-controlled trial (N = 248, ITT),¹⁰⁵ modafinil was shown to have a statistically significant benefit as measured by the ADHD Rating Scale-IV Home and School Versions and the Conners' Parent and Teacher Rating Scales during a 9-week study period. A new film-coated preparation of modafinil was utilized in this study and provided new dosing possibilities. This study used a flexible dosing protocol in which subjects could receive from 170 to 425 mg/day of modafinil, titrated based on tolerability and efficacy.

Depression. Insomnia and the resulting fatigue is a frequent symptom in depression, although it is often difficult to treat.¹⁰⁶ In an open-label study (N = 27),¹⁰⁷ 200 mg/day of modafinil, when added to antidepressant treatment in patients who were partially responsive to the antidepressant, was found to improve depression-associated lethargy and somnolence as measured by the GAF. In another case report,¹⁰⁸ 7 patients were shown to also benefit from co-administration of modafinil with selective serotonin reuptake inhibitor (SSRI) antidepressants within 2 weeks of starting modafinil. All patients in that report had significant fatigue that resolved with the modafinil augmentation. However, the benefit appears to be broader than improvement of fatigue alone, as HAM-D scores improved in both cognitive and physical features. A randomized, placebo-controlled, double-blind study (N = 314)¹⁰⁹ produced similar findings. Patients diagnosed with major depressive disorder who continued to have significant symptoms of depression (mean HAM-D score > 14) despite an adequate trial of monotherapy with an SSRI antidepressant were randomly assigned to receive either placebo or 200 mg/day of modafinil in addition to their existing SSRI treatment. The dual treatment group revealed significantly greater improvements at the end of the 8-week trial based on CGI scores and a nonsignificant trend toward greater improvement in HAM-D scores. The benefit of modafinil was more robust among the more severely depressed subgroup, suggesting that modafinil may be particularly useful as an augmenting agent in this population. Overall, modafinil augmentation was well tolerated in this study.¹⁰⁹

There have been few reports of using modafinil as monotherapy in depression. In one case report,¹¹⁰ the patient failed treatment with paroxetine, bupropion, and citalopram. Each drug was discontinued due to partial response and/or intolerable side effects such as gastrointestinal discomfort. The patient's primary depressive symptoms included hyperphagia with 70-lb weight gain over 3 years; decreased energy, interest, concentration, and memory; self-deprecatory thoughts; and decreased libido. Symptoms were measured with the HAM-D-24 and showed effect within 1 week of starting 200 mg of modafinil/day.¹¹⁰ In a retrospective chart review (N = 45),¹¹¹ modafinil was linked to an improvement in Beck

Depression Inventory, HAM-D, and Zung Self-Rating Depression Scale scores without a concurrent increase in anxiety as measured by the Hamilton Rating Scale for Anxiety. Fifteen patients were on modafinil monotherapy, and the other 30 patients used modafinil adjunctively to conventional antidepressant treatment.¹¹¹ However, without a comparator group, the results of this study are difficult to interpret.

Camacho and Stein¹¹² report a single case in which modafinil at 200 mg twice per day, added to fluoxetine at 40 mg/day, produced significant improvement in social phobia and amphetamine dependence in a woman who also suffered from major depression and had failed trials of different classes of psychotropic medications, including antidepressants, second-generation antipsychotics, conventional stimulants, lithium, and anticonvulsants. Upon starting modafinil, the patient had decreased amphetamine craving and reduced time thinking about amphetamines. She denied any feeling of a "high" that she had with amphetamines. Additionally, many of her social phobia symptoms remitted and she was able to find work.¹¹²

There is one report¹¹³ of 2 cases in which modafinil had beneficial effects on hypersomnia associated with bipolar affective disorder. Stimulants are often avoided in bipolar disorder, as sleep loss has been shown to affect the beginning and continuation of manic symptoms.¹¹⁴ While modafinil was effective in these patients with hypersomnia, the lasting effects on their mood are unclear.¹¹³ A recent, 6-week, double-blind, placebo-controlled study¹¹⁵ of 85 patients with bipolar (I or II) depression examined the effect of adding modafinil to preexisting regimens of mood stabilizer and antidepressants. Modafinil augmentation produced significantly greater improvements in depression than placebo.¹¹⁵ In this study, episodes of mania or hypomania did not occur more frequently with modafinil than with placebo. However, a recent report¹¹⁶ implicates modafinil as the trigger for a first manic episode in a patient being treated for narcolepsy.

The mechanism by which modafinil improves mood is not known. One possibility is that the potential antidepressant qualities of modafinil are mediated by the same mechanisms that underlie the antidepressant effects produced by sleep deprivation, a nonpharmacologic technique with a proven, though transient, ability to enhance mood in many depressed patients. One report¹¹⁷ suggests that modafinil may work synergistically with sleep deprivation therapy. However, the mechanism underlying the antidepressant qualities of sleep deprivation also remains unknown.¹¹⁸

Cocaine dependence. Modafinil has been shown to decrease the euphoria associated with cocaine. Additionally, when modafinil and cocaine were coadministered, there were no increased side effects in terms of heart rate, blood pressure, electrocardiogram changes, or temperature in a

double-blind, placebo-controlled trial (N = 7).¹¹⁹ Another double-blind, placebo-controlled trial (N = 62)¹²⁰ evaluated modafinil in the treatment of cocaine dependence and withdrawal. Patients received either 400 mg/day of modafinil or placebo and were followed for 8 weeks. The modafinil group demonstrated a statistically significant decrease in positive urine samples for the cocaine metabolite benzoylecgonine and a significantly longer period of abstinence from cocaine. However, there were no differences noted between the groups in withdrawal symptoms or long-term cravings.¹²⁰

Schizophrenia. Conventional stimulants are associated with the potential risk of worsening psychosis in patients with psychotic disorders. However, in a recent open-label study (N = 11),¹²¹ modafinil produced a positive effect on cognition and significantly increased the mean GAF score over the 4-week study. In a double-blind, placebo-controlled, crossover study (N = 20),¹²² modafinil in doses up to 200 mg daily added to the antipsychotic regimen of schizophrenia patients significantly improved cognitive set shifting, a known area of deficit functioning in schizophrenia, compared to placebo. Additionally, in a recent case report¹²³ of a patient with significant weight gain due to clozapine who had previously been refractory to weight-loss techniques, modafinil was cited as an important factor in the onset of weight loss despite continuation of clozapine.

In 2 recent double-blind, placebo-controlled trials (N = 24 and N = 20),^{88,124} modafinil did not differ from placebo with regard to changes in fatigue, cognition, or positive and negative symptoms over 8 weeks. In one of these studies,¹²⁴ however, overall clinical-rated improvement measured by the CGI scale was significantly higher for the modafinil-treated patients. Of note, 1 subject receiving modafinil terminated the study early because of increased psychosis that required hospitalization.⁸⁸ Aside from this case, there has been one other report of increased psychosis associated with modafinil.¹²⁵ However, in this report, the patient was taking a higher than usual dose of modafinil, 800 mg daily, and had severe, refractory undifferentiated schizophrenia treated with clozapine.¹²⁵

Obesity. Obesity is an epidemic problem, as over 60% of the U.S. population is overweight or obese.¹²⁶ Amphetamines have traditionally been used for their appetite-suppressant qualities, although their chronic use for this purpose is limited by the many systemic effects of amphetamines. In a recent double-blind study (N = 11),¹²⁷ it was shown that modafinil may also suppress appetite and could be used for weight loss. At 200 mg daily, the dose needed for weight loss, there were no significant vital signs changes or other major side effects. Subjects were able to maintain adequate nutrition, but ate less food overall. However, this was a small study, and the data were collected over a short period of time.¹²⁷ Long-term studies

conducted outside of a laboratory setting would be helpful to ascertain the full extent of modafinil's potential as a weight-loss agent.

Cerebral palsy. Cerebral palsy refers to a group of chronic disorders that affect body movements, muscle tone, balance, and posture. In one published report,¹²⁸ 10 pediatric patients with spastic cerebral palsy were treated for 1 month with open-label modafinil (50–100 mg/day). All patients were videotaped ambulating for rating purposes by blinded physical therapists. In the video review, 7 of the 9 patients who completed follow-up after 1 month had decreased spasticity as measured by the Modified Ainsworth Scale for spasticity. The mechanism for this therapeutic effect on cerebral palsy is unknown but is theorized to involve the central mechanisms of spasticity that quite likely originate in the brainstem.¹²⁸ A retrospective review (N = 30)¹²⁹ showed that 76% of subjects with cerebral palsy reported a decrease in spasticity that was confirmed on physical examination. Twenty-three percent of subjects withdrew before the study concluded because of minor and reversible side effects. The authors report planning to conduct a more thorough, double-blind trial in the future.¹²⁹

Potential abuse of modafinil. Recently, modafinil has received media attention, as some track and field athletes have tested positive for its use.¹³⁰ It appears to be appealing to some athletes as a tool to train longer and more intensively by reducing fatigue.¹³¹ For athletes, modafinil has important advantages over conventional stimulants, as it does not cause hypertension and tachycardia and was not under suspicion for detection until recently. As a result of this increasing trend, modafinil has recently been banned by the World Anti-Doping Agency as a stimulant substance related in effect to amphetamines.¹³²

Modafinil is also increasingly being sought by students and others who work long hours as a way to help extend their alertness and reduce their need for sleep. Modafinil is gaining increasing popularity in high-stress, long-work-hour environments, such as Wall Street.¹³³ However, despite the growing popularity of modafinil and its increased abuse, modafinil has been shown to have little efficacy in non-sleep-deprived individuals.¹³⁴ Chronic cocaine users were able to fully discriminate between modafinil and cocaine on a drug discrimination test and reported no euphorogenic activity.¹³⁵ There is no evidence that modafinil can produce a high that would lead people toward addictive behavior.^{46,136,137}

DISCUSSION

Modafinil is a wakefulness- and alertness-enhancing agent currently approved for treatment of excessive daytime sleepiness associated with narcolepsy, obstructive sleep apnea/hypopnea syndrome, and shift work sleep disorder. It appears to produce its effects via different

neural mechanisms than conventional stimulants or other psychotropic drugs with similar effects on wakefulness and alertness. Importantly, it does not seem to stimulate dopamine transmission in the brain or have sympathomimetic effects, which cause both the benefit and side effects of conventional stimulants. Off-label use of modafinil appears to be widespread for conditions in which wakefulness, energy, or attention are reduced. Unfortunately, much of the data that exist to date on these off-label uses are anecdotal or small-scale, uncontrolled studies. Increasingly, double-blind studies are being published, many of which have shown equivocal results where smaller, uncontrolled studies had shown initial promise. Unfortunately, many of these double-blind studies suffer from underpowered recruitment of subjects, and, therefore, true therapeutic benefits seen in some open-label studies may be hidden in the controlled studies that failed to demonstrate statistical significance. To date, the strongest evidence among off-label uses exists for the use of modafinil in attention-deficit disorder, postanesthetic sedation, and cocaine dependence and withdrawal and as an adjunct to antidepressants for depression.

A significant proportion of the prescriptions for modafinil are for off-label uses, although, with recently added indications for SWSD and OSA, there may be a smaller percentage of off-label prescriptions than previously. Use of modafinil has increased tremendously since it was launched in the United States in 1998.¹³⁸ Given the relative dearth of systematic study of modafinil outside of the currently approved uses, it is reasonable to conclude that its popularity among clinicians is not entirely based on rigorously proven efficacy. To what then can modafinil's surprising popularity among physicians, who are generally conservative when it comes to new treatments, be attributed? There is no scientific evidence and also no apparent strong perception among those who have used modafinil that it produces greater efficacy compared to conventional stimulants such as methylphenidate or amphetamine formulations, or that it extends the therapeutic spectrum to conditions that are not benefited by conventional stimulants (the one possible exception being cerebral palsy). In fact, there is some doubt to whether modafinil's therapeutic effects are as robust and consistent as the effects of conventional stimulants, a case in point being ADHD, for which modafinil has not become a significant monotherapy alternative to stimulants. Conversely, evidence to date suggests that modafinil is well tolerated, safe, and lacking any of the euphorogenic or reinforcing properties that can lead to addiction and clinician reluctance about prescribing conventional stimulants. This lack of reinforcing/addictive qualities of modafinil, together with prescription regulations less stringent than those associated with conventional stimulants (e.g., no triplicate prescription forms required), is likely a strong contributing factor in the popularity of

modafinil among physicians seeking a drug that can have arousal-enhancing effects without the stigma, inconvenience, or medical-legal risks associated with prescribing conventional stimulants.

Yet it is of interest that one study¹³⁹ found modafinil to be no more effective than caffeine, a less expensive and equally safe natural stimulant available over the counter. Therefore, part of modafinil's popularity may also be due to the appeal of its novel synthetic development and convincing marketing.

Recently, the maker of modafinil in the United States, Cephalon, Inc., submitted new drug applications for new preparations of modafinil. The first is a film-coated preparation of modafinil, which comes in different dosages than Provigil and has primarily been studied for once-daily use in ADHD.^{105,140-143} Additionally, Cephalon has submitted a new drug application for armodafinil, which is the R-isomer of modafinil. It is a once-daily preparation and has been studied in narcolepsy, SWSD, and OSA.¹⁴⁴

Modafinil is a promising drug with a large potential for many uses in psychiatry and general medicine. Treating daytime sleepiness is complex, and determining the precise nature of the sleep disorder is vital. Modafinil may be an effective agent in many sleep conditions.¹⁴⁵ However, caution should still be exercised in its use, particularly in off-label uses, until more rigorous studies are available and more is known about its mechanisms of action and possible long-term effects.

Drug names: amphetamine (Adderall and others), atomoxetine (Strattera), bupropion (Wellbutrin and others), citalopram (Celexa and others), clozapine (FazaClo and others), dextroamphetamine (Dextrostat, Dexedrine, and others), fluoxetine (Prozac and others), lithium (Lithobid, Eskalith, and others), methylphenidate (Ritalin, Metadate, and others), modafinil (Provigil), paroxetine (Paxil, Pexeva, and others), phenelzine (Nardil), tranlycypromine (Parnate).

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