Modafinil: expanded options for the treatment of excessive sleepiness

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Modafinil is an oral wake-promoting agent, initially approved in December 1998 for the treatment of excessive sleepiness associated with narcolepsy. Based on the results of additional randomized, placebo-controlled studies, the indication for modafinil was expanded in January 2004 to include excessive sleepiness associated with obstructive sleep apnea/hypopnea syndrome and shift work sleep disorder. Modafinil represents a safer alternative to CNS stimulants for the treatment of excessive sleepiness and it has become the most widely prescribed agent for excessive sleepiness associated with narcolepsy over the past 5 years. This article summarizes the key studies on modafinil, outlining the unique pharmacologic profile, efficacy and safety.

Keywords: attention, modafinil, narcolepsy, obstructive sleep apnea/hypopnea syndrome, shift work sleep disorder, sleepiness, wake-promoting

Modafinil is a unique wake-promoting medication that is chemically and pharmacologically distinct from CNS stimulants such as amphetamine and methylphenidate. Modafinil was first approved by the US Food and Drug Administration (FDA) in December 1998 for excessive sleepiness (ES) associated with narcolepsy. Following submission of a supplemental new drug application to the FDA, this wake-promoting agent was also approved in January 2004 for the treatment of ES associated with obstructive sleep apnea/hypopnea syndrome (OSAHS) and shift work sleep disorder (SWSD) (For OSAHS, modafinil is approved as an adjunct to standard treatments for the underlying obstruction) [Modafinil (PROVIGIL®) prescribing information. Cephalon Inc., PA, USA (2004)]. In randomized, placebo-controlled studies involving more than 1400 patients, modafinil has demonstrated consistent and significant efficacy for improving wakefulness in patients with ES associated with these three disorders of sleep or wakefulness, with a tolerability profile superior to that of CNS stimulants. This article reviews the preclinical and clinical experience with modafinil, including its pharmacologic profile, efficacy for the treatment of ES and related symptoms, tolerability and abuse liability.

Research on the mechanism of action of modafinil

Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) is an oral wake-promoting agent with a molecular formula of $C_{15}H_{15}NO_2S$. This compound was originally developed by French company Laboratorie Lafon in the 1980s. It received an official registration in France in 1992. In 1993, licensing rights to modafinil were bought by US pharmaceutical company Cephalon Inc., which subsequently purchased Lafon.

The precise mechanism of action of modafinil remains unknown. It was originally believed to exert wake-promoting effects through α_1-adrenergic activity. However, preclinical research has not supported a role of modafinil as an α-adrenergic agonist (although at least one preclinical study suggests that it may require an intact α_1-adrenergic system) [1]. Modafinil does not bind to receptors for norepinephrine, serotonin, γ-aminobutyric acid (GABA), adenosine, histamine-3, melatonin, glutamate, or benzodiazepines [2–5]. Preclinical studies demonstrate that it is not a noradrenergic, adenosine, or dopaminergic agonist, and does not inhibit monoamine oxidase B, or phosphodiesterase II through V [1].

Studies employing markers of neuronal activation have demonstrated only weak dopaminergic activity for modafinil compared with CNS stimulants. In a preclinical study that used *c-fos* to compare neuronal activation in cat brains following administration of amphetamine, methylphenidate, or modafinil (1.0, 2.5 and 5.0 mg/kg, respectively), both of the CNS stimulants caused widespread cortical activation in areas that included the nucleus accumbens – the area of the brain that is believed to mediate the rewarding effects of drugs of abuse. Patterns of activation with modafinil were more discrete, with strong *c-fos* labeling limited primarily to portions of the hypothalamus [6]. Other data have shown increased activity along dopamine and glutamate reward circuits with CNS stimulant use, but not with modafinil use [7]. Modafinil has a weak affinity for dopamine reuptake sites and preclinical data have shown that

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dopamine transporter knockout mice are nonresponsive to the wake-promoting effects of modafinil [8].

A study by Scammell and colleagues using *c-fos* demonstrated decreased neuronal activity in the ventrolateral preoptic area (VLPO) in rats given modafinil intraperitoneally, and increased neuronal activity in the tuberomammillary nucleus (TMN) [2]. These findings are consistent with the current understanding of mechanisms of wakefulness, with the VLPO serving as the hypothalamic sleep generator and the TMN, the hypothalamic wake generator. The activity of sleep-promoting neurons in the VLPO is suppressed by norepinephrine in order to promote and maintain wakefulness. A recent study by Gallopin in which rat brains were exposed to modafinil and norepinephrine demonstrated that modafinil may potentiate the sleep-inhibiting activity of norepinephrine in the VLPO [9]. As a result, modafinil appears to reinforce norepinephrine's sleep-inhibiting effects. This effect on the VLPO may allow ascending arousing neuronal pathways, including pathways in the TMN, to remain active. No significant effect was observed when modafinil was administered with other arousal neurotransmitters, including serotonin, carbachol, dopamine and histamine [8]. In the study by Scammell, strong *c-fos* labeling associated with modafinil was seen in the anterior cingulate cortex and other cortical regions that facilitate wakefulness [2]. Modafinil was also associated with increased activity of orexin/hypocretin-containing neurons, which exert excitatory effects on wake-promoting regions of the brain, including the TMN. Increasing evidence supports the important role that CNS orexin deficiencies play in the pathogenesis of narcolepsy [2].

Studies examining sleep patterns, behavior, and vital signs in animals given modafinil or CNS stimulants have shown that effects related to dopaminergic activity are prominent with the CNS stimulants but weak or absent with modafinil [10–18]. In a series of studies by Edgar and colleagues that compared modafinil with methamphetamine, both agents induced equivalent wakefulness in rats. However, methamphetamine was associated with 'rebound hypersomnia' in the immediate hours following resumption of sleep. In rats given modafinil, lost sleep was recovered slowly, through gradual increases in the percent of non-REM sleep over the next day [12]. Wakefulness with modafinil is not accompanied by increases in locomotor activity beyond that associated with normal wakefulness, and is not associated with significant increases in stereotypies, heart rate, blood pressure or anxiety [11,12,14–18].

Pharmacokinetic profile

Modafinil displays linear pharmacokinetics, with peak plasma concentrations achieved 2–4 h following dosing. Steady-state plasma levels are achieved following 2 to 4 days of dosing at 200 or 400 mg/day. The elimination half-life (approximately 15 h) supports a once-daily dosing schedule. Metabolism is predominantly (>90%) hepatic [19,20]. Several metabolites of modafinil have been recovered in urine. However, only two of these, modafinil sulfone and modafinil acid, reach appreciable concentrations in plasma and neither appears to exert wake-promoting effects [19,20].

Food delays the time to peak plasma concentration of modafinil by approximately 1 h, although it does not affect the overall bioavailability. The pharmacokinetics of modafinil are not affected by race or gender. Pharmacokinetic patterns were shown to be altered in studies of elderly patients, those with compromised renal function, and those with liver failure. The elderly patients exhibited a decreased clearance and a doubling of modafinil plasma levels at a dose of 300 mg/day, compared with historically matched, younger controls [19,20]. Lower dose therapy should be considered in this group. The pharmacokinetic activity of modafinil in children is generally similar to that in adults. However, while the peak plasma concentration is approximately the same between the two populations (after normalization for the dosage on a mg/kg basis), the total systemic exposure (AUC) to modafinil is lower in pediatric patients due to an apparent shorter half-life. Therefore, the duration of wake-promoting effect of modafinil may be reduced in this population. Modafinil is indicated for patients over 16 years of age.

In patients with a mean creatinine clearance of 16.6 ml/min given a single dose of modafinil, 200 mg, the concentration of the inactive metabolite modafinil acid was raised approximately ninefold (the clinical relevance of this increase remains unclear). Lower-dose therapy should also be considered for these patients [19,20]. Initiating modafinil therapy at half the usual starting dose (i.e., 100 mg/day) is specifically indicated for those with liver failure, based on a study of patients with cirrhosis of the liver. Compared with healthy controls, these patients showed a decrease in modafinil clearance of about 60% and a twofold increase in the steady-state concentration [20].

Table 1. Potential CYP450 drug interactions with modafinil based on *in vitro* studies[§].

P450 metabolic pathway	Metabolic effect in combination with modafinil	Commonly used drugs metabolized via this pathway
Potential induction: CYP3A4	Potential decrease in serum levels of drugs metabolized via these enzymes	CYP3A4: oral contraceptives, cyclosporin A, theophylline, triazolam
CYP1A2		
CYP2B6		
Potential inhibition: CYP2C19[§]	Potential increase in serum levels of drugs metabolized via these enzymes	CYP2C19: Diazepam, S-mephenytoin, propranolol, phenytoin
CYP2C9		CYP2C9: Warfarin, phenytoin
Potential induction:	Potential decrease in serum levels of	CYP3A4: Carbamazepine,
CYP3A4	Modafinil	Phenobarbital, rifampin
Potential inhibition:	Potential increase in serum levels of	CYP3A4: Ketoconazole, itraconazole
CYP3A4	Modafinil	

[§]CYP2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants that are primarily metabolized by CYP2D6 (e.g., clomipramine and imipramine), In patients who are deficient in CYP2D6, the amount of metabolism through CYP2C19 may be substantially increased [20,21].

Drug interaction studies

Modafinil is metabolized by cytochrome (CYP)450 enzymes, and may have an effect on other drugs metabolized by these enzymes. A list of altered metabolic pathways observed in studies using primary cultured human hepatocytes, along with commonly used drugs metabolized along these pathways, is provided in **Table 1** [20,21]. *In vivo* studies have examined potential interactions between modafinil and a number of these drugs, as well as between modafinil and the CNS stimulants amphetamine and methylphenidate. These studies are summarized in [22–25]**Table 2**.

Of particular note are the studies involving the co-administration of modafinil and oral contraceptives (ethinyl estradiol and norgestimate), and co-administration of modafinil and warfarin. Women taking oral contraceptives together with modafinil showed a mean decrease of 11% in the peak plasma concentration of ethinyl estradiol [25]. Based on these findings, it is recommended that women taking steroidal contraceptives use alternative or concomitant methods of contraception while taking modafinil, and for 1 month after discontinuing modafinil therapy [Modafinil (PROVIGIL®) prescribing information. Cephalon Inc., PA, USA (2004)].

No significant interactions were observed between modafinil and (*S*)- or (*R*)-warfarin in a single-blind, placebo-controlled study. Subjects in this study received a single dose of warfarin, 5 mg, followed by 7 days of plasma sampling and modafinil (200–400 mg) from days 8 through 41 [24]. Warfarin was administered again at day 35. The lack of significant interactions is important, given the high potential for interaction between warfarin and a large number of medications metabolized by CYP enzymes. Nevertheless, because of the potential for serious adverse consequences with altered warfarin activity, increased monitoring of prothrombin times or International Normalized Ratio (INR) is recommended when warfarin and modafinil are coadministered [Modafinil (PROVIGIL®) prescribing information. Cephalon Inc., PA, USA (2004)].

Clinical efficacy studies of modafinil in narcolepsy, OSAHS & SWSD

The wake-promoting activity of modafinil has been evaluated in five randomized, multicenter, placebo-controlled studies of patients with ES associated with narcolepsy, OSAHS, and SWSD [28–30]. Two 9-week narcolepsy studies, one conducted in 18 centers and one in 21 centers, provided the foundation for the original approval of modafinil for ES associated with narcolepsy [27,28]. In addition, two studies (one 12 weeks and one 4 weeks in duration) have been conducted in patients with ES associated with OSAHS, with one 12-week study conducted in patients with ES associated with SWSD [26,29,30]. A second study in SWSD patients was also performed that did not include direct assessments of ES; patients from this study are included in the discussions of the safety of modafinil [31]. These three disorders are classified as dyssomnias (disorders of sleep or wakefulness) in the *International Classification of Sleep Disorders (ICSD), Revised, Diagnostic and Coding Manual* [32]. Excessive sleepiness is a primary symptom in each of these disorders.

Table 2. Drug interaction studies of modafinil.

Modafinil plus	Study design	Pharmacokinetic interactions	Adverse events
Methylphenidate, 40 mg	Single-dose, crossover (n = 21)	No compared with separate administration Modafinil absorption delayed by ~ 1 h	Headache Euphoria
Dextroamphetamine, 10 mg	Single-dose, crossover (n = 24)	No compared with separate administration Modafinil absorption delayed by ~ 1 h	Dry mouth Palpitations
Clomipramine, 50 mg	Given on day 1 of first 3 days of modafinil treatment	No PK alterations[§]	89% clomipramine 33% modafinil 72% combination
Ethinyl estradiol, 0.035 mg/d; + norgestimate, 0.180–0.250 mg	28-day, single-blind (n = 41)	Ethinyl estradiol: 11% decrease C_{max} 18% decrease AUC	Change from baseline in alkaline phosphatase (not clinically significant)
Triazolam, 0.125 mg (part of ethinyl estradiol study)	Given before start of modafinil treatment and on last day	Triazolam: 42% decrease C_{max} 59% decrease AUC ~ 1 h decrease $T_{1/2}$	No significant AEs
Warfarin, 5 mg	Given on days 0 and 35 (modafinil given on days 28–31)	No PK alterations compared with warfarin + placebo	Headache
Cyclosporin	Single case	Cyclosporin: 50% decrease trough concentration	Not available

AEs: Adverse events; PK: Pharmacokinetic.

[§]One incident of increased levels of clomipramine and its active metabolite, desmethylclomipramine, was reported in a patient taking modafinil, 200–400 mg day. This patient was a poor metabolizer of CYP2D6 [22–25].

The demographic characteristics of the 1431 patients in these studies are summarized in [26–31]Table 3. All patients met accepted criteria for the symptom of ES, as well as standard *ICSD* diagnostic criteria for narcolepsy, OSAHS or SWSD [32]. Patients with other disorders of sleep or wakefulness were excluded. In the narcolepsy studies, patients met standard *ICSD* criteria for narcolepsy, including:

- Recurrent daytime naps or lapses into sleep that occurred almost daily for at least 3 months, plus sudden bilateral loss of postural muscle tone in association with intense emotion (cataplexy)
- Complaints of excessive sleepiness or sudden muscle weakness plus associated features – sleep paralysis, hypnagogic hallucinations, automatic behaviors, or disrupted major sleep episodes – with polysomnography demonstrating either sleep latency shorter than 10 min or rapid eye movement (REM) sleep latency shorter than 20 min

They also met more stringent criteria that included two or more sleep-onset REM periods and the absence of any other clinically significant active medical or psychiatric disorder. Patients with cataplexy were eligible for inclusion (7–90% of participants had signs or symptoms of cataplexy). Those who could not tolerate discontinuation of anticataplectic agents (primarily antidepressants) during the study periods were not eligible [27,28].

In the OSAHS studies, modafinil was used as an adjunct to nasal continuous positive airway pressure (nCPAP), which is the preferred therapy for treatment of the underlying airway obstruction. All patients included in the OSAHS studies were judged either fully or partially compliant with nCPAP – a total of 18 nCPAP noncompliers were enrolled in the 12-week study. However, a subsequent amendment to the study protocol excluded noncompliers, and these 18 patients were not included in the efficacy analysis [26,30]. All SWSD patients had excessive sleepiness associated with an ICSD diagnosis of SWSD. They were required to work

Table 3. Baseline patient characteristics in modafinil double-blind, placebo-controlled studies of excessive sleepiness.

	Narcolepsy	OSAHS	SWSD
N	530	446	455
Age, y			
Mean (±SD)	41.8 (13.3)	49.7 (9.4)	39.5 (9.2)
Range	17–68	24–76	20–62
Sex, n (%)			
Male	239 (45)	340 (76)	243 (53)
Female	291 (55)	106 (24)	212 (47)
Race, n (%)			
White	434 (82)	396 (89)	321 (71)
Black	77 (15)	29 (7)	99 (22)
Asian	0	6 (1)	2 (<1)
Other	19 (4)	15 (3)	32 (7)
Sleep efficiency, mean% (±SD)	87.0 (10.2)	85.8 (11.0)	73.6 (12.4)

OSAHS: Obstructive sleep hypopnea syndrome; SWSD: shift work sleep disorder [26–31].

at least five night shifts per month, with at least three of the shifts being consecutive. The shifts were between 6 and 12 h in length, with at least 6 of the shift hours occurring between 10 PM and 8 AM.

Demographic characteristics of the three patient populations were generally similar, with differences consistent with the known epidemiology of each disorder. The OSAHS studies had a higher percentage of men; these patients were also somewhat older and heavier than patients in the other two groups. In contrast, the SWSD patients were younger on average than those in the other two groups. This may reflect the fact that work shifts are often based on seniority, with younger individuals having less control over scheduling. The occupations of the SWSD patients (Table 4) are consistent with shift work occupations reported by the US Bureau of Labor Statistics, which tracks work patterns through periodic surveys [101].

Table 4. SWSD 3-week efficacy study: shift work occupation §.

Occupation	n (%)
Healthcare and social assistance	59 (29)
Manufacturing	24 (12)
Transportation and warehousing	23 (11)
Administration and support	20 (10)
Other services (except public administration)	20 (10)
Public administration	13 (6)
Professional/scientific/legal	9 (4)
Postal Service	7 (3)

SWSD: shift work sleep disorder [31,39].
§ ≥5% in either the placebo or modafinil groups.

Excessive sleepiness and related consequences were evaluated through a number of objective and subjective outcome measures. Objective measures of physiologic ES used were the Maintenance of Wakefulness Test (MWT) and Multiple Sleep Latency Test (MSLT) [32,33]. The MWT was a primary outcome measure in the two narcolepsy studies and the 12-week OSAHS study, while the MSLT was a primary outcome measure in the 4-week OSAHS study and the SWSD study. Both are accepted and sensitive tools for the objective evaluation of ES and wakefulness, and it has been shown that even small changes in sleep latency on these tests (e.g., 1–2 min) translate into significant clinical improvements in wakefulness [34].

In addition, all five studies used the Clinical Global Impression of Change (CGI-C) to determine the patients' change in overall clinical condition. The Epworth Sleepiness Scale (ESS), an eight-item questionnaire that provides a subjective estimate of the patient's level of sleepiness and the extent to which ES interferes with daily activities [35], was used in the narcolepsy and OSAHS studies. In the SWSD study, the Karolinska Sleepiness Scale (KSS) was used to subjectively estimate patients' levels of ES. This test asks patients to record their level of sleepiness on a scale of 1 (very alert) to 9 (very sleepy, great effort to keep awake or fight sleep). It is administered repeatedly over the course of the day; thus, it is useful for evaluating changes in the severity of ES over the course of the sleep–wake cycle [36].

Table 5. Baseline disease severity in modafinil double-blind, placebo-controlled studies of ES

	Narcolepsy			OSAHS§			SWSD	
Dose (mg)	***200***	***400***	***Placebo***	***200***	***400***	***Placebo***	***200***	***Placebo***
MWT, mean min (±SD)	5.9 (4.9)	6.2 (4.8)	5.9 (4.8)	13.1 (5.5)	13.6 (5.4)	13.8 (5.7)	NA	NA
MSLT, mean min (±SD)	2.9 (2.3)	3.0 (2.6)	2.5 (2.0)	NA	7.4 (4.8)	7.5 (4.6)	2.1 (1.5)	2.0 (1.8)
ESS/KSS score, mean (±SD)	17.7 (3.8)	17.6 (3.8)	18.0 (3.6)	15.7 (3.4)	14.6 (3.2)	14.6 (3.0)	7.3 (1.0)	7.1 (1.2)
PVT lapses of attention, mean (±SD)	NA	NA	NA	5.2 (11.5)	2.3 (3.9)	3.7 (6.6)	22.5 (23.0)	24.3 (26.4)
CGI-S rating, n (%)								
Not recorded		0		43 (10)			0	
Normal/mildly ill/slightly ill	91 (17)			121 (27)			0	
Moderately ill	237 (45)			199 (45)			280 (62)	
Markedly ill/severely or extremely ill	202 (38)			83 (19)			175 (38)	

ES: Excessive sleepiness; OSAHS: Obstructive sleep hypopnea syndrome; SWSD: Shift work sleep disorder [26–30].
§*All OSAHS patients were treated with nasal continuous positive airway pressure (nCPAP).*

The Psychomotor Vigilance Task (PVT) was used in the 12-week study of OSAHS and the SWSD study to assess patients' ability to sustain attention. The PVT is a computerized test that measures patients' reaction times to successive stimuli to evaluate deficits in attention and performance, two serious consequences of ES [37]. Several variables can be analyzed based on the results, including the number of lapses of attention (episodes of nonresponse >500 msec).

The baseline scores on these outcome measures are shown in Table 5 [26–30]. Mean scores on the MSLT ranged from 2.0 to 7.5 min (scores <5 min indicate severe ES) [32]. Mean MSLT scores in the SWSD patients ranged from 2.0 to 2.1, showing that ES in these patients was even more severe than that in the narcolepsy patients. Subjective estimates of sleepiness at baseline also showed moderate-to-severe ES in all of these patient groups, with mean ES scores ranging from 14.6 to 18.0 in the narcolepsy and OSAHS groups. In the patients with SWSD, the mean baseline KSS scores ranged from 7.1 to 7.3. The level of sleepiness in these patients approached the maximum level of sleepiness on the KSS (very sleepy, great effort to keep awake, fighting sleep). The majority of patients in these studies were at least moderately ill at baseline as determined by investigators on the Clinical Global Impression of Severity (CGI-S). The OSAHS and SWSD groups had substantially impaired performance at baseline, as illustrated by the number of PVT lapses of attention.

As shown in Table 6, statistically significant objective improvements in wakefulness on the MWT and MSLT were seen with modafinil at doses of 200 and 400 mg/day across all of these studies ($p < 0.05$) [26–30]. Improvement in overall clinical condition was observed in 36–74% of patients on the CGI-C (i.e., they were considered very much, much, or minimally improved; $p < 0.05$ for all patient groups, change from baseline vs. placebo). Compared with the narcolepsy patients (78%) and SWSD patients (8%), more patients in the OSAHS studies (14%) were considered very much improved; approximately 25–30% in each study were considered much improved, with similar numbers minimally improved.

Similar improvements were seen in subjective estimates of wakefulness on the ESS/KSS ($p < .001$), and in the ability to sustain attention on the PVT (mean change from baseline in lapses of attention, -0.2 to -3.8; $p < .05$). In the SWSD patients, lapses decreased from 22.6/20 min test period to 20.3 in the modafinil group, compared with an increase from 24.3 to 31.2 in the placebo group. In the OSAHS patients, in the 12-week OSAHS study, respective PVT lapses at baseline and final visit were 5.2 and 2.3 for the 200 mg group, 2.3 and 1.8 for the 400 mg group, and 3.7

Table 6. Mean change from baseline (±SD) in primary and secondary outcome measures in the double-blind, placebo-controlled studies of modafinil in excessive sleepiness.

	Narcolepsy (9 week, combined results)			OSAHS (12 week)			OSAHS (4 week)		SWSD (12 week)	
Dose (mg)	***200***	***400***	***Pbo***	***200***	***400***	***Pbo***	***400***	***Pbo***	***200***	***Pbo***
MWT sleep latency, min	2.3 (4.6)§	2.1 (4.8)§	-0 7 (4.39)	1.6 (4.8)§	1.5 (5.0)§	-1.1 (4.6)	NA	NA	NA	NA
MSLT sleep latency, min	1.9 (3.4)§§	2.1 (3.7)§	0.9 (2.8)	NA	NA	NA	1.0 (3.7)§§§	-0.2 (4.1)	1.7 (3.8)§§	0.3 (2.8)
CGI-C, percent improved§	61§	66§	37	60§	68§	37	66§§§	34	74§	36
ESS score	-3.9 (4.8)§	-5 0 (5.0)§	-1.5 (3.6)	-4.5 (4.7)§	-4.7 (4.3)§	-1.8 (3.5)	-4.6 (4.3) §	-2.0 (3.6)	NA	NA
KSS score	NA	NA	NA	NA	NA	NA	NA	NA	-1.5 (1.5)§	-0 4 (1.5)
PVT lapses of attention	NA	NA	NA	-2.8 (6.5)§	-0 8 (3.5)§§§	-0.2 (5.0)	NA	NA	-3.8 (21.0)§§	7.2 (20.8)

Results represent the percent of patients improved from baseline.

CGI-C: Clinical Global Impression of Change; ESS: Epworth Sleepiness Scale; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; NA: Data not applicable (measurement scale not used in particular study); Pbo: Placebo; PVT: Psychomotor Vigilance Task [26–30]

§p< 0001 vs. placebo; §§p<.01 vs. placebo; §§§p<.05 vs. placebo.

and 3.6 for placebo (these numbers of lapses both at baseline and end point were lower in the OSAHS than the SWSD patients, as each test session was only half as long [10 vs. 20 min] and the OSAHS patients were being treated with nCPAP at the time baseline measurements were taken). Similar improvements in sustained attention were reported in the studies of ES associated with narcolepsy on the Steer Clear, a 30min, computer-simulated driving program that requires sustained attention to avoid hitting obstacles [38].

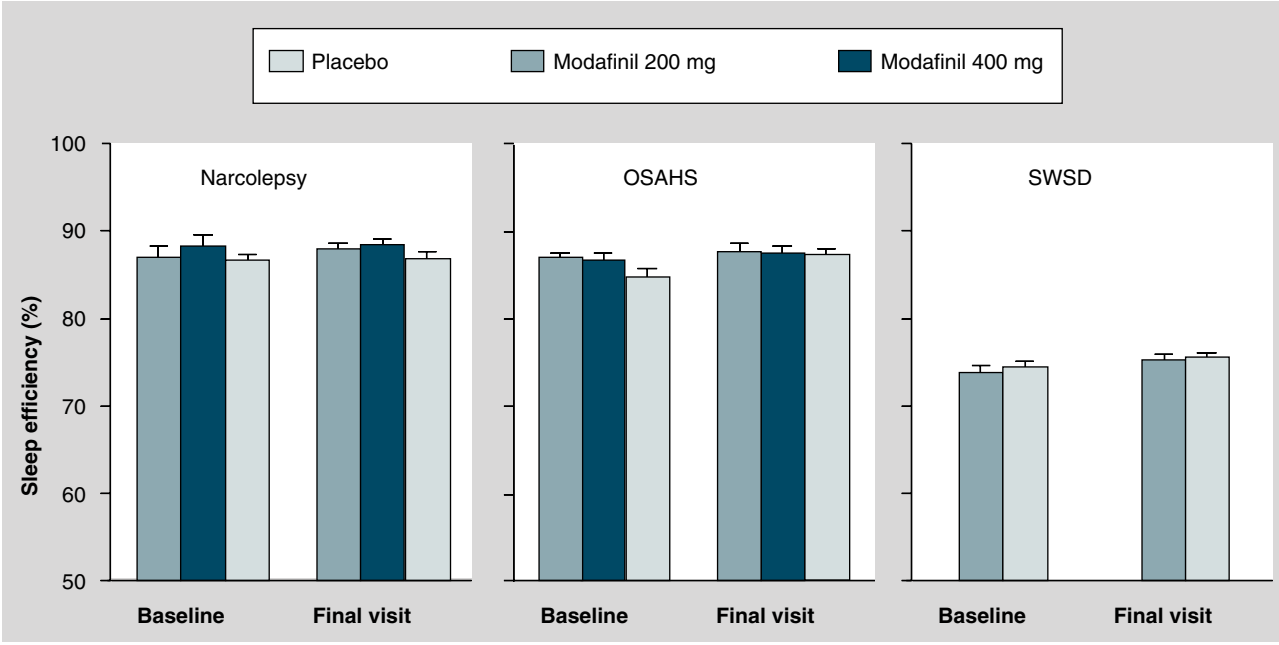
These studies also included a number of polysomnographic measures, including sleep efficiency – the time asleep as a percent of the total time in bed. Polysomnographic monitoring was performed at night in the narcolepsy and OSAHS groups, while daytime polysomnography was performed in the SWSD patients. As shown in **Figure 1**, sleep efficiency did not change significantly at study end compared with baseline in any of the placebo-controlled studies, showing that modafinil did not affect the ability to sleep when sleep was desired [39].

Long-term extension studies

The studies of ES in narcolepsy and OSAHS included long-term extension phases in which continued improvements in ES were evaluated (the SWSD studies also included open-label extension phases, but did not include assessments of ES). Following a 2-week washout period, eligible patients in the narcolepsy studies were enrolled in a 40-week, open-label extension, followed by two 48-week subsequent extensions, for a total of 136 weeks. During the 40-week open-label period, improvements in subjective estimates of wakefulness were assessed with the ESS at weeks 2, 8, 24 and 40. The patients were assessed at weeks 24 and 48 of each subsequent 48 week extension period [39,40].

Flexible dosages of 200, 300 or 400 mg/day were allowed during the open-label periods. Most dosage adjustments during open-label treatment occurred within the first 8 weeks. The majority of patients (>80%) were titrated up to 300 or 400 mg/day after week 2 [39]. The ESS improvements seen in the double-blind periods were maintained over 136 weeks of open-label treatment. From an open-label baseline score of 17.4 (reflecting the return of sleepiness during the washout period), the mean ESS score was reduced to 12.4 at week 136 ($p < .001$). Similar improvements in subjective estimates of wakefulness were seen over 12 months of long-term treatment in patients enrolled in the 12-week OSAHS study [39], and over 12 weeks in patients enrolled in the 4-week study [41]. In the 12-month extension study, ESS scores were reduced from a mean of

Figure 1. Mean sleep efficiency (time asleep as a percent of the total time in bed) in clinical studies of modafinil.



Results are presented as the mean (±SEM). Source: [9].
OSAHS: Obstructive sleep apnea/hypopnea syndrome; SWSD: Shift work sleep disorder.

approximately 14.5 to 10.0 at month 12, while in the 12-week study, they were reduced from a baseline mean of 14.4 to 7.6. Tolerance was not observed in these studies.

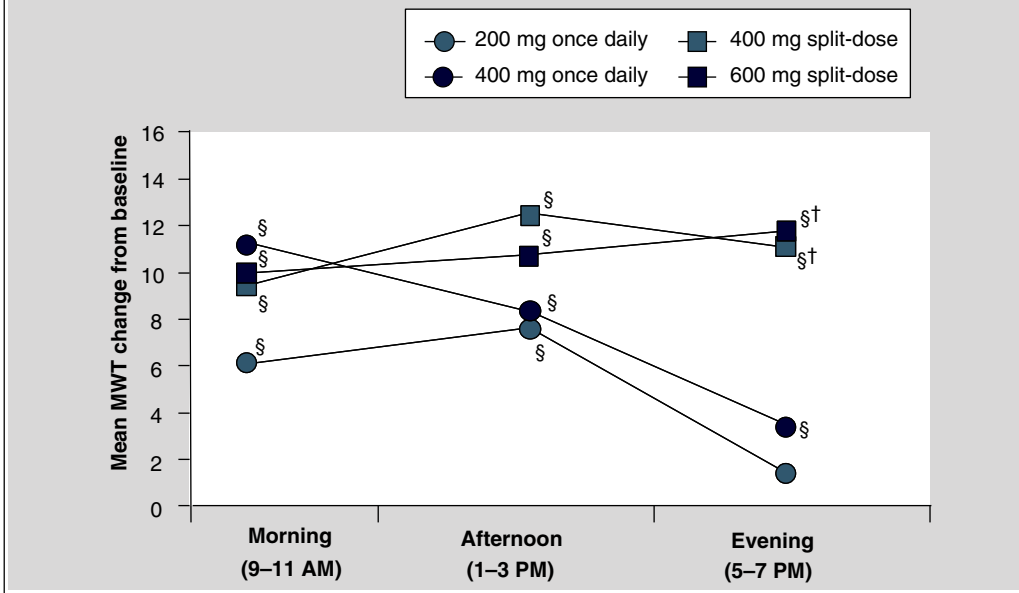
Additional efficacy studies

Several additional studies in patients with narcolepsy have examined both objective and subjective improvements in wakefulness with modafinil. These included a third randomized, placebo-controlled study (n = 75), consisting of three double-blind, 2-week crossover periods, a 16-week open-label period, and a 2-week randomized, placebo-controlled abrupt discontinuation period [42,43]. In the double-blind, crossover phases, modafinil significantly improved wakefulness on the MWT, as shown by increases in mean sleep latency of 40% and 54% at dosages of 200 and 400 mg/day, respectively ($p < 0.001$) [42]. Of the 69 patients who continued into the open-label phase and 2-week discontinuation period, MWT sleep latency was 70% longer with modafinil compared with placebo by the end of the discontinuation period [43].

A 6-week, flexible-dose study evaluated improvements in subjective estimates of wakefulness on the ESS with modafinil when given at flexible doses of 200 to 400 mg/day. The 151 patients in this study had shown prior unsatisfactory responses to treatment with CNS stimulants (dextroamphetamine, methylphenidate, or pemoline) [44]. Treatment with CNS stimulants was considered unsatisfactory for one or more of the following reasons: low tolerability due to side effects (agitation, jitteriness, mood swings); cardiovascular concerns (palpitations, tachychardia, or increased blood pressure); concerns regarding tolerance, dependence, or abuse potential; the need for drug holidays; or other reasons. Approximately half of the patients had taken at least one drug holiday, primarily due to adverse effects or to prevent the development of tolerance. Modafinil significantly improved subjective estimates of wakefulness on the ESS at week 1, and improvement was maintained throughout the course of the study ($p < 0.001$) [44].

Split-dose regimens have been examined to determine whether these dosing schedules can sustain improvements in wakefulness in narcolepsy patients who have satisfactory responses to modafinil in the early part of the day, but who experience ES in the late afternoon or evening. Three earlier studies showed that split-dose regimens improve wakefulness, but did not compare these regimens with once-daily

Figure 2. Mean (SEM) change from baseline in MWT sleep latency times.



Maintenance of Wakefulness Testing (MWT) for the morning (9:00–10:00 h) afternoon (13:00–15:00 h) and evening (17:00–19:00 h) sessions for each modafinil treatment regimen [47].
§$p < 0.01$, change from baseline versus placebo
†$p < 0.05$ modafinil 400 mg split-dose and 600 mg split-dose versus 200 mg daily.

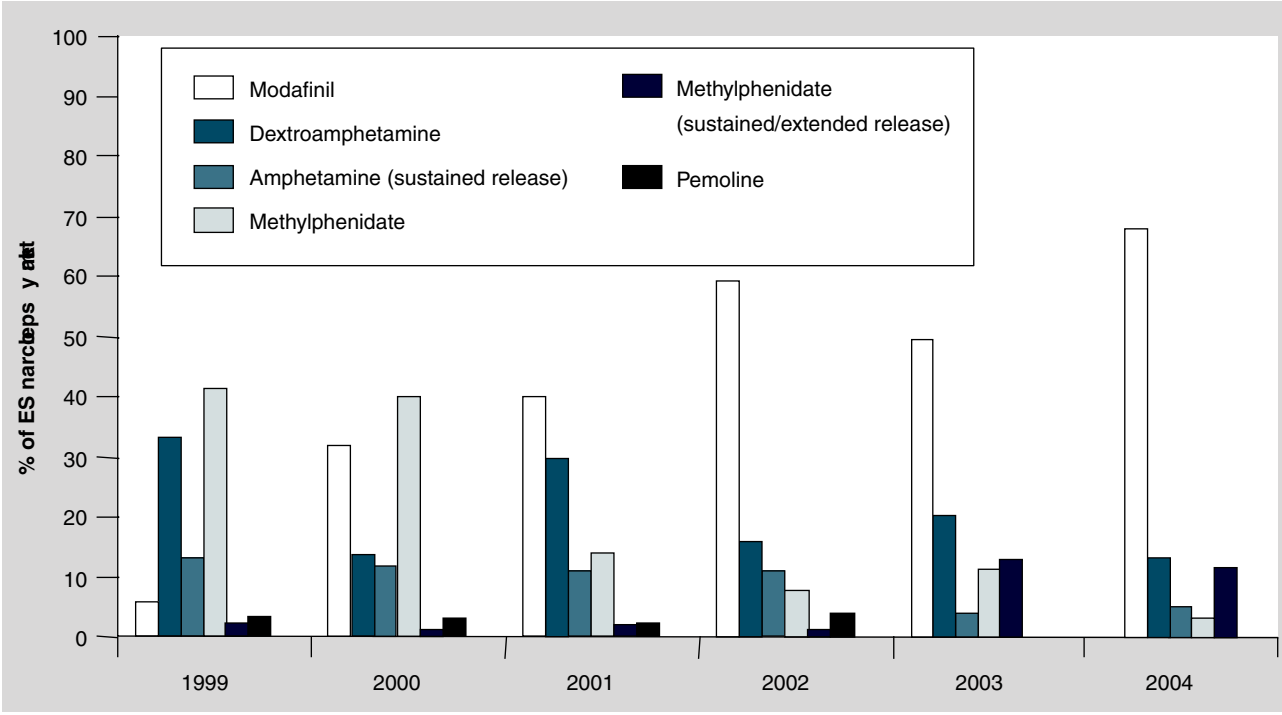
dosing [42,45]. Two more recent studies specifically compared split-dose regimens of 400 or 600 mg with once-daily regimens of 200 or 400 mg. In a three-period, crossover study in which modafinil was administered at 200 mg every morning, 400 mg every evening, or 400 mg in a split-dose regimen (200 mg in the morning and at noon), sleep latencies on the MWT were significantly increased with both 400 mg doses compared with the 200 mg dose ($p < 0.05$) [46]. Each period consisted of a 1-week placebo washout, followed by 3 weeks of double-blind treatment. The study used a modified, extended version of the MWT, consisting of 30 min test sessions conducted seven times at each follow-up visit (9 and 11 AM; and 1, 3, 5, 7 and 9 PM) [46]. In addition, a 600 mg split-dose regimen (400 mg in the morning and 200 mg in the early afternoon) was found to achieve more consistent wakefulness throughout the day (morning, afternoon, and evening) compared with 200 or 400 mg every morning or a 400 mg split-dose regimen (**Figure 2**)[47]. Doses higher than the maximum approved dose of 400 mg have not been extensively studied. There are anecdotal reports, however, of narcolepsy patients achieving greater efficacy with doses greater than or equal to 800 mg. Tachyphylaxis has not been reported.

Clinical experience with modafinil

Of the three disorders for which modafinil is approved to treat ES, experience has been most extensive in narcolepsy, and modafinil is the most-prescribed agent for ES in this patient group. The steady increase in usage [48,49](**Figure 3**) reflects the combination of clinical efficacy and favorable safety with modafinil. Prior to the approval of modafinil, CNS stimulants were most commonly used to treat ES in narcolepsy patients. While these agents can alleviate ES, their potential for abuse with chronic use in some patients and their adverse effects (including anxiety, agitation, insomnia, increased locomotor activity, sterotypies, and increased heart rate and blood pressure) limit their use in some patients. Modafinil has been recognized as a standard of care for the treatment of ES associated with narcolepsy by the American Academy of Sleep Medicine (AASM), based on the results of well-designed, randomized, placebo-controlled studies and additional confirmatory data [50]. Modafinil is the only agent to be given this classification under the AASM guidelines (Modafinil has not been studied with the concomitant use of CNS stimulants).

Concerns over CNS stimulant use are magnified in the treatment of ES associated with OSAHS and SWSD, as both groups are at

Figure 3. Percent share of the US narcolepsy market for modafinil, amphetamine compounds, methylphenidate compounds, and pemoline, 1999–present.



Data represent the first quarter for each year [48,49].

increased risk for adverse cardiovascular morbidity [32]. The growth of modafinil for ES associated with OSAHS will most likely depend on whether it adversely affects the use of nCPAP, which is the preferred therapy for the underlying airway obstruction [26]. Evidence in patients receiving nCPAP suggests that cognitive deficits associated with OSAHS may not resolve with nCPAP, raising the possibility that the intermittent hypoxia seen in OSAHS may have a long-term detrimental effect on cognitive function.

Shift-work sleep disorder represents an additional challenge in that the disorder is underdiagnosed and ES is under-recognized in this population. Problems with under-recognition may be increased in specialties outside of sleep medicine, especially among primary care providers, who see significant numbers of ES patients in practice. Patients must be continually monitored for signs and symptoms of ES, and advised that their level of sleepiness may not return to normal; for example, in the study of SWSD, although a significant improvement was seen on the MSLT, the mean MSLT score was still in the range considered to be ES at the end of the study. The number of PVT lapses in attention, while also significantly reduced, remained high (approximately 20 lapses/session).

Use of modafinil has been steadily expanding since its initial approval, with a number of studies assessing its potential benefits in disorders in which ES and related symptoms such as fatigue are common. Of particular note is the number of studies that have been conducted in neurology and psychiatry [51–59], reflecting the variety of disorders in these specialties that exhibit core symptoms of sleepiness or fatigue (e.g., multiple sclerosis, Parkinson's disease, traumatic brain injury, myotonic dystrophy, stroke, depression, and schizophrenia). Overall, statistically significant improvements in wakefulness and/or fatigue have been observed in these studies, although in some studies in depression, placebo treatment has exhibited comparable but delayed improvement, and in patients with fatigue related to multiple sclerosis, significant improvement has only been observed at lower doses (i.e., 200 mg/day) [59].

The improvements seen in the ability to sustain attention in patients with ES have also engendered interest in the use of modafinil for disorders involving deficits in attention, memory, and executive functioning. The most

notable example is attention deficit hyperactivity disorder (ADHD), and studies in adults [60] and children [61] have shown significant improvements with modafinil on such measures as the Adult ADHD Behavior Checklist and Test of Variable Attention.

Safety & tolerability

Safety data on modafinil include more than 3700 patients with primary disorders of sleep or wakefulness. Of these, more than 1500 were enrolled in the double-blind, placebo-controlled studies of ES in narcolepsy, OSAHS, and SWSD. The most common adverse events in these patients are shown in **Figure 4** [39]. Headache was the most common adverse event, occurring in 34% of modafinil patients. Most adverse events were mild-to-moderate, transient and occurred within the first month of treatment. Serious adverse events occurred in 17 of the 937 modafinil patients and eight of the 567 placebo patients. Of these, six (chest pain, leukopenia and neutropenia, extrasystoles and palpitations, dyspnea, and hypoventilation) were deemed related to modafinil therapy; no fatalities were reported [39]. Headache and anxiety were the only dose-related adverse events. In the placebo-controlled studies, 8% of modafinil and 3% of placebo patients discontinued therapy due to an adverse event, most commonly headache [39].

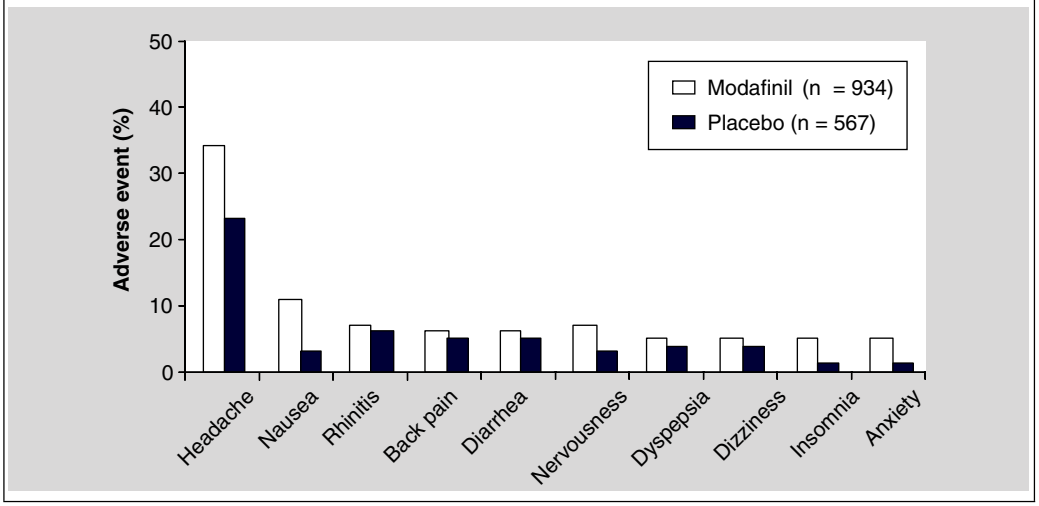
Adverse events in all patients with primary disorders of sleep or wakefulness were consistent with those observed in the randomized, placebo-controlled studies of ES associated with narcolepsy, OSAHS, and SWSD. Long-term safety data (encompassing 675 patients treated for >12 months and 309 for ≥ 24 months) have not revealed patterns of adverse events that differ from those seen in the randomized, placebo-controlled studies.

The two studies on ES associated with OSAHS both included monitoring of nightly hours of nCPAP use. No significant change in mean hours of nCPAP use was observed in either of the placebo-controlled phases of these studies [26,30], although a significant decrease was seen in a double-blind, two-period crossover study of 32 patients who received placebo or modafinil, 200 mg/day followed by 400 mg/day for 9 days or placebo for 5 days, received placebo or 200 mg of PROVIGIL for 5 days, followed by 400 mg for 9 days . [Kingshott] However, there was a small but statistically significant decrease in nCPAP use in both of the open-label extension phases, ranging from approximately 20 min to a half hour [39,41]. The impact of this decrease on clinical outcomes remains unknown. However, given that nCPAP is the most effective therapy for relieving underlying airway obstruction in OSAHS patients, nCPAP usage must be closely monitored and patients continually reassessed for any potential adverse consequences. Longer studies of nCPAP use (i.e., >1 year) in this population will be important. Modafinil is indicated in OSAHS as adjunctive therapy to the underlying obstruction(s) in persons who continue to experience residual ES despite treatment for the underlying obstruction [39].

Blood pressure monitoring in the placebo-controlled studies of ES associated with narcolepsy, OSAHS, and SWSD showed no statistically significant or clinically meaningful changes in mean systolic and diastolic blood pressure or heart rate in patients receiving modafinil compared with placebo. The overall mean change in systolic blood pressure in the entire population was -0.3 mmHg for modafinil, versus -1.3 for placebo. No significant differences emerged when patients were assessed according to history of hypertension or baseline level of blood pressure [63]. However, a retrospective analysis showed that more patients receiving modafinil required a new or increased use of antihypertensive agents compared with placebo (2.4 vs. 0.7%). The differential use was slightly more pronounced in the OSAHS patients (3.4 vs. 1.1%). Blood pressure monitoring is indicated in patients taking modafinil [Modafinil (PROVIGIL®) prescribing information. Cephalon Inc., PA, USA (2004)].

The risk of adverse events appears to be reduced when modafinil is titrated gradually. The two studies on ES associated with narcolepsy employed different dose-titration protocols. In the 18-center study, both modafinil groups received 200 mg on day 1, with the 400 mg group moving up to the higher dose on day 2 [28]. In the second, conducted at 21 centers, a more refined step-up protocol was used, with each active treatment group receiving 100 mg of modafinil on days 1 through 7, and 200 mg on day 8. Commencing on day 9, patients in the 400 mg group were moved to the higher dose [27]. A higher percentage of patients receiving the 400 mg dose in the 18-center study withdrew due to adverse events compared with the 200 mg and placebo groups (12 vs. 1 and 0%, respectively. In the 21-center study, only 1% of patients in the 400mg group withdrew due to adverse events). The difference was deemed probably, but not definitively, related to the titration regimens.

Figure 4. Adverse events ≥5% (doses combined) and > placebo in the randomized, placebo-controlled studies of modafinil in narcolepsy, obstructive sleep apnea/hypopnea syndrome; and shift work sleep disorder [39].



Tolerance/abuse liability

Withdrawal effects upon discontinuation of therapy and the potential for abuse have been the subject of significant interest with modafinil, as both are significant concerns with CNS stimulants. Two narcolepsy studies – the 21-center, 9-week study and the 24-week, three-period crossover study – included 2-week abrupt discontinuation periods in which patients were monitored for the emergence of adverse events associated with the development of tolerance (including increased appetite, fatigue, agitation, vivid dreams and hypersomnia). No symptoms specifically associated with the development of tolerance emerged [36,43].

The potential for abuse of CNS stimulants has led to the classification of amphetamine and methylphenidate as Schedule II medications under the Controlled Substances Act. Drugs in this schedule have demonstrated a high potential for abuse leading to severe physical or psychologic dependence [64]. The high potential for abuse with these agents is due to increased dopamine levels in and activation of the nucleus accumbens. In contrast, modafinil is a Schedule IV medication, indicating a limited risk of physical and/or psychologic abuse or dependence.

Studies using animal models have examined the stimulant-discriminative and reinforcing properties of modafinil [65,66]. These studies have shown that modafinil possesses weak reinforcing and stimulant-discriminative effects. However, these effects are approximately 250 times less potent than those of amphetamine. Place preference (a preference for modafinil over placebo) could not be induced in animals not previously exposed to a drug of abuse [66].

Clinical studies have compared the stimulant and euphoria effects of modafinil with those of CNS stimulants (including amphetamine, methylphenidate and cocaine) in healthy persons and those experienced with drugs of abuse. In a study of 16 healthy men and women, D-amphetamine, 15 mg, significantly increased scores on the Amphetamine (stimulant) and Morphine-Benzedrine Group (MBG; euphoria) scales of the Short-Form Addiction Research Center Inventory (ARCI) compared with placebo (the ARCI is a 49-item, true–false questionnaire validated for assessing the abuse potential of drugs). While modafinil also demonstrated increases on the Amphetamine and MBG scales, it was clearly differentiated from D-amphetamine on the Amphetamine scale, and did not produce pronounced elation or euphoria on the MBG scale [67].

Another study compared modafinil (200, 400 and 800 mg) with methylphenidate (40 and 90 mg) in 24 men with a history of cocaine abuse and 12 women with a history of polysubstance abuse [68,69]. The study used a crossover design, with a 2-day washout between drug administrations. Men and women were tested in separate phases. In the men, methylphenidate produced significant stimulant effects on the Amphetamine scale of the ARCI compared with placebo ($p \leq 0.05$). In contrast, no

amphetamine-like subjective effects were seen even with the highest dose, 800 mg, of modafinil compared with placebo. Neither drug resulted in significant changes on the MBG scale, suggesting that neither modafinil nor methylphenidate produces euphoria to the extent associated with amphetamine [68].

In the women, a significant difference in maximum response was observed on the ARCI Amphetamine scale for both doses of modafinil compared with placebo ($p < 0.05$). In addition, a significant difference ($p < 0.05$) was seen for modafinil, 800 mg, compared with placebo and methylphenidate on the MBG scale [69].

A third study compared the effects of modafinil (0, 200, 400 or 600 mg), cocaine (0, 100, 200 or 300 mg), and placebo in nine men and women who were experienced cocaine abusers. The patients had spent a mean of US$1378 each on cocaine during the week prior to the study [70].

The subjective measures in this study included the Drug-Effect Questionnaire, a 45-item inventory that assesses feelings of 'any drug effect,' 'stimulated,' 'high' or 'rush.' Also used was the End-of-Day Questionnaire, which ask patients about the 'good effects' of the drug and how much they would be willing to pay for the drug on the street [70].

On the Drug-Effect Questionnaire, only the highest dose of modafinil showed a significant difference compared with placebo in terms of 'any effect' ($p \leq 0.05$). In contrast, scores with all three doses of cocaine were significantly different than placebo and corresponding modafinil doses. The participants also reported feeling significantly more 'stimulated' with the two higher doses of cocaine compared with placebo and the corresponding modafinil doses ($p \leq 0.05$), while no significant effect was seen with modafinil. Patients reported significantly greater feelings of 'high' or 'rush' with cocaine compared with both modafinil and placebo ($p \leq 0.05$) [70].

In the End-of-Day Questionnaire, patients reported significantly higher levels of 'good effects' scores with all three doses of cocaine, but only with the highest dose of modafinil ($p \leq 0.05$). Participants were willing to pay significantly more for the two higher doses of cocaine compared with placebo ($p \leq 0.05$), while they would not pay more than placebo for any dose of modafinil [70].

Postmarketing surveillance on modafinil has been conducted since 1999 by the Haight Ashbury Free Clinics, a network of clinics with more than 30 years of experience in compiling epidemiologic data on national and local drug abuse patterns [71]. This surveillance program is extensive and comprised of information from multiple national and state databases such as DAWN, MEDWATCH, and national drug use surveys [72]. Medical and popular literature are also evaluated, as is information from providers in addiction, pain management, pediatrics, geriatrics and primary care. Neither these postmarketing surveillance efforts nor other methods designed to detect drug abuse have detected generalized interest in modafinil as a drug of abuse, although isolated cases have been identified.

Importantly, there have not been patterns of abuse observed in abusers of CNS stimulants or polysubstance abusers. In a case study of previous abusers of methylphenidate, amphetamine or cocaine who were later prescribed modafinil, some individuals reported improvement in mood, energy and cognitive functioning with modafinil, but none took modafinil in a fashion that appeared to mimic their previous abuse patterns. Overall, messages related to modafinil represent fewer than 1% of total messages in Internet chat rooms relating to 'smart drugs' [71].

Expert opinion

Modafinil is the first, and to date the only, non-sympathomimetic agent in the USA approved to treat the symptom of ES. The initial indication for the treatment of ES associated with narcolepsy was expanded in 2004 to include ES associated with OSAHS and SWSD. (Modafinil is indicated in OSAHS as adjunctive therapy to the underlying obstruction[s] in persons who continue to experience residual ES despite treatment for the underlying obstruction.)

Outlook

Double-blind, placebo-controlled studies in these disorders have consistently demonstrated improvements in wakefulness with modafinil at doses of 200 or 400 mg/day. The efficacy of modafinil has made it the most prescribed agent for the treatment of ES associated with narcolepsy, and modafinil is the only wake-promoting agent approved for use in OSAHS and SWSD. Clinical experience has been favorable with modafinil use in these indications. Modafinil use is likely to diversify further into other disorders characterized by ES and/or fatigue, as well as disorders characterized by cognitive impairments due to varying underlying pathologies.

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