Modafinil: new indications for wake promotion

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In January 2004, the wake-promoting agent, modafinil, was approved in the US for the treatment of excessive sleepiness (ES) associated with obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and shift-work sleep disorder (SWSD), representing an expansion of its labelling from the initial indication for ES associated with narcolepsy. A total of five randomised, placebo-controlled studies in these three disorders showed statistically significant benefits on various objective measures and subjective estimates of ES, including the Multiple Sleep Latency Test, Maintenance of Wakefulness Test, Epworth Sleepiness Scale and Karolinska Sleepiness Scale. Significant improvement was also seen in overall clinical condition (on the Clinical Global Impression of Change) and measures of sustained attention and reaction time (on the Psychomotor Vigilance Task). The clinical efficacy of modafinil, combined with improved safety over CNS stimulants, has made it the most prescribed medication for the treatment of ES associated with narcolepsy. Modafinil is the only medication approved for ES associated with OSAHS and SWSD (for OSAHS, it is indicated as an adjunct to standard treatments for the underlying obstruction). Unlike many other medications used for ES, modafinil is not known to be abused. The most common adverse event reported in clinical studies was headaches; most were transient and mild-to-moderate in severity. Modafinil also has the potential for interactions with other drugs metabolised via cytochrome P450 enzyme pathways. Potential obstacles to the use of modafinil include an under-recognition of ES and its consequences. Increased education, both of the public and the medical community, should improve the recognition and therapy of ES.

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


1. Introduction

Modafinil is the first in a class of nonsympathomimetic wake-promoting agents that are chemically and pharmacologically unrelated to CNS stimulants. Modafinil is the only agent in this class approved for use in the US.

Modafinil was first approved for use in the US in December 1998, for excessive sleepiness (ES) associated with narcolepsy. Following submission of a supplemental new drug application to the US FDA, this agent was approved in January 2004 for the treatment of ES associated with obstructive sleep apnoea/hypopnoea syndrome (OSAHS) and shift-work sleep disorder (SWSD) [1]. This article reviews the body of data on modafinil, including its preclinical pharmacology, pharmacokinetic profile, efficacy for the treatment of ES, safety profile, and studies on abuse potential.

2. Narcolepsy, obstructive sleep apnoea/hypopnoea syndrome and shift-work sleep disorder: the excessive sleepiness market

The three disorders in which modafinil is approved to treat ES represent distinct sleep disorders in the class of dyssomnias, defined by the International Classification
of Sleep Disorders, Revised (ICSD-R) as disorders of sleep or wakefulness [2]. Narcolepsy is primarily a disorder of sleep/wake dysregulation that results in an increased sleep drive during the day. It affects an estimated 0.03 – 0.16% of the general population. The sleep/wake dysregulation in narcolepsy appears to be related to a CNS deficiency in orexin/hypocretin-containing neurons [3,4]. ES is present in 100% of individuals with narcolepsy; these patients suffer from repeated, irresistible episodes of naps or lapses into sleep, generally ranging from 10 to 20 min in duration. These ‘sleep attacks’ represent the intrusion of rapid eye movement (REM) sleep into normal wakefulness, as evidenced by a shortened REM sleep latency. Other symptoms of narcolepsy, including cataplexy, hypnagogic hallucinations and sleep paralysis, also result from sleep/wake dysregulation with REM intrusions into wakefulness [2].

OSAHS is characterised by repetitive episodes of upper airway obstruction that occur during sleep, usually associated with a reduction in blood oxygen saturation [2]. It affects an estimated 2 – 4% of middle-aged adults in the US [5]. These airway obstructions cause apnoea/hypopnoea episodes, which trigger repeated arousals. The result is significantly disrupted and shortened sleep that is inadequate to restore normal homeostatic sleep pressure. Nasal continuous positive airway pressure (nCPAP) is the preferred therapy for treating the underlying airway obstruction in OSAHS, and this therapy has shown clear benefits in OSAHS patients for reducing ES [6]. However, residual ES is common among those who are treated with nCPAP.

SWSD is a circadian rhythm sleep disorder caused by a misalignment between the patient’s sleep/wake cycle and the internal processes that promote sleep and wakefulness (i.e., the patient’s circadian rhythms). As a result of this misalignment, which is related to the patient’s work schedule, sleep is promoted during waking hours and wakefulness during hours normally devoted to sleep. ES in SWSD is caused by the patient’s inability to adapt to the sleep/wake times required by the nonstandard work schedule, as well as disruptions in daytime sleep caused by external factors (e.g., daytime telephone calls, interruptions by family members). Daytime sleep in SWSD is shortened and highly fragmented, preventing full sleep recovery [2]. Excessive sleepiness during the nighttime wake period can be severe, with Multiple Sleep Latency Test (MSLT) scores at baseline in the randomised, placebo-controlled study of modafinil in SWSD lower than those seen in narcolepsy patients [7]. Estimates of SWSD vary; an estimated 24 million people in the US have irregular work schedules or work long hours on a regular basis; 6 million are night or evening shift workers, working all or part of their shifts during times normally devoted to sleep [101]. Of these workers, ~25% have been shown to fulfil criteria for a circadian rhythm sleep disorder [8].

The pharmaceutical market for narcolepsy is well defined, with three drugs in the US (modafinil, amphetamine and methylphenidate) all approved to treat the symptoms of ES. Since its approval in 1998, modafinil has been the dominant agent in this market, with ~ 1.4 million prescriptions in 2003 (~ 70% of total prescriptions written for narcolepsy-related ES) [9,10]. Amphetamine and methylphenidate each represent slightly > 10% of total prescriptions. Whereas the use of amphetamine has decreased over the past 5 years, methylphenidate use has risen [9,10], largely due to the introduction of sustained- and extended-release forms that allow for once-daily dosing.

Unlike with narcolepsy, the tracking of pharmaceutical use for ES associated with OSAHS and SWSD is still in its infancy. Modafinil is currently the only medication specifically approved for ES associated with these disorders, and reliable data on prescription trends have not yet emerged. Based on the prevalence estimates of these disorders, however, each represents a significant potential market.

As in narcolepsy, the CNS stimulants are capable of producing wakefulness in OSAHS and SWSD patients with ES; however, their use may be problematic in many patients. Amphetamine and methylphenidate are classified as Schedule II drugs under the Controlled Substances Act, due to a high potential for abuse leading to severe physical or psychological dependence [11]. The potential for abuse with these agents is due to increased dopamine levels in and activation of the nucleus accumbens, the area of the brain that is believed to mediate the rewarding effects of drugs of abuse. Data have shown increased activity along dopaminergic and glutamate reward circuits with CNS stimulant use, but not with modafinil use [12]. The adverse effects of CNS stimulants are also related to substantial dopaminergic activity in the nucleus accumbens. These effects include increases in locomotor activity, agitation, anxiety, and insomnia. The effects of CNS stimulants on blood pressure and heart rate may potentially preclude their use in some OSAHS and SWSD patients, as increased cardiovascular morbidity has been reported in both of these disorders [2].

3. Pharmacological profile

3.1 Chemistry and preclinical pharmacology
Modafinil (2-[(diphenylmethyl)sulfinyl]acetamide) is an oral wake-promoting agent with a molecular formula of C_{15}H_{15}NO_{2}S (Figure 1) [1]. It is structurally and chemically unrelated to CNS stimulants. Clinical research on modafinil in the US began in 1993, when Cephalon, Inc., a Pennsylvania-based biotechnology firm, licensed the rights to this agent from its developer, the French pharmaceutical company Laboratoire L Lafon (Cephalon subsequently purchased Lafon). As part of the development programme for modafinil, Cephalon conducted preclinical and Phase I/II studies that supplemented previous French research on the mechanism of action of modafinil and potential drug interactions.

Despite comprehensive research, the precise mechanism of action of modafinil remains to be defined, although recent research has offered new insights. A number of studies have
examined the binding affinity of modafinil to various receptors, including neurotransmitters commonly involved in the activity of psychoactive drugs. Modafinil has not been shown to bind to receptors for noradrenaline, serotonin, GABA, adenosine, histamine-3, melatonin, or benzodiazepines [3,13-15]. Modafinil has a weak but selective binding affinity for dopamine re-uptake sites [13]. It is not an inhibitor of monoamine oxidase B or phosphodiesterases 2 – 5 [16]. Modafinil was originally categorised as an α1-adrenergic agonist. However, preclinical studies have shown that it is not a direct or indirect α1-adrenergic agonist (although at least one preclinical investigation in animal models suggests that an intact α1-adrenergic system may be required) [16].

Other preclinical studies have offered more insight into the mechanism of action of modafinil by observing its activity at various sites in the brain [17]. In a study that measured c-fos expression in cats, Lin et al. [17] found diffuse brain activation with amphetamine and methylphenidate. Strong c-fos labelling was seen in the nucleus accumbens. In contrast, modafinil was selective for areas of the hypothalamus believed to be involved in mediating normal wakefulness. Amphetamine and methylphenidate showed weak activity in these areas [17].

In a subsequent study that more specifically examined these hypothalamic sleep/wake pathways, modafinil 75 mg/kg given intraperitoneally to rats significantly increased neuronal activity in the tuberomammillary nucleus (TMN) and decreased activity in the ventrolateral preoptic area (VLPO) compared with vehicle infusions (p < 0.05) [3]. Neuronal activation was again measured via c-fos expression. The increased activity in the TMN was associated with significantly increased neuronal activity in the anterior cingulate cortex and other cortical areas (p < 0.05).

The activity of modafinil at these sites is consistent with the facilitation of wake promotion. The activity of sleep-promoting neurons in the VLPO, the hypothalamic ‘sleep generator’, is increased during sleep and inhibited by the neurotransmitter, noradrenaline, during wakefulness. A recent study in which rat brains were exposed to modafinil and noradrenaline demonstrated that modafinil may potentiate the sleep-inhibiting activity of noradrenaline in the VLPO. As a result, modafinil appears to reinforce noradrenaline’s sleep-inhibiting effects. This effect on the VLPO may allow ascending arousing neuronal pathways, including pathways in the TMN (the hypothalamic ‘wake generator’), to remain active [18]. The TMN contains histaminergic projections to the cortex; activation of the anterior cingulate and other areas of the cortex through these pathways is believed to be essential for maintaining normal wakefulness [3,19].

Preclinical comparisons of modafinil and amphetamine have shown distinct pharmacological profiles, indicating that the mechanism of action of modafinil is different than that of dopaminergic stimulants [13,14,17,20-24]. Notable are the lack of significant increases in neuronal activity and dopamine levels in the nucleus accumbens, and the lack of effect of the dopamine antagonist, haloperidol, on the activity of modafinil [20]. Haloperidol neither inhibits wakefulness nor reduces locomotor activity induced by modafinil, whereas both occur readily with amphetamine. However, although modafinil shows only weak affinity for dopamine re-uptake sites [13], several studies have observed that the effects of modafinil appear to be, at least in part, mediated by dopamine. Wisor et al. [25] found that the effects of modafinil are abolished in dopamine transporter (DAT) knockout mice, suggesting that the low affinity of modafinil for the DAT may nevertheless play a role in wake promotion. Nishino et al. [26] suggested that the low affinity of modafinil for the DAT site may be associated with its efficacy in wake promotion.

Direct comparisons of modafinil and amphetamine-related compounds, however, have shown that modafinil produces equivalent wakefulness without increasing locomotor activity beyond that associated with normal wakefulness, and without producing the ‘rebound hypersomnia’ that is associated with amphetamine withdrawal [24]. Additional preclinical pharmacological studies have shown that modafinil is not associated with the increases in anxiety, stereotypes, blood pressure, and heart rate that are characteristic of amphetamine and methylphenidate [14,16,20,21,27-31]. It should be noted that preclinical findings may be of limited applicability to the clinical use of these agents, especially as preclinical studies often employ very high doses. When used as directed in persons who are at low risk for drug abuse, amphetamine and methylphenidate have a good track record of efficacy and acceptable adverse event profiles.

### 3.2 Clinical pharmacokinetics

The primary pharmacokinetic activities of modafinil are shown in Table 1. The 15-h elimination half-life allows for once-daily dosing. Peak plasma concentrations are achieved 2 – 4 h following dosing, and steady-state plasma levels are achieved after 2 – 4 days of dosing at 200 – 400 mg/day [32,33]. Metabolism is almost exclusively (~ 90%) through the liver, with < 10% excreted as unchanged drug in the urine. At least seven metabolites of modafinil have been identified, but only two (modafinil acid and modafinil sulfone) reach appreciable concentrations in plasma, and neither appears to contribute to the wake-promoting activity of the drug [32,33].

The pharmacokinetics of modafinil do not appear to change significantly in many patient populations. Pharmacokinetics...
are not affected by gender or race. Food does not affect the bioavailability of modafinil, but delays the time to peak plasma concentration by ~ 1 h [1]. Elderly patients may metabolise modafinil more slowly than younger patients and therefore may be appropriate candidates for lower-dose therapy. 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 normalisation for the dosage on a mg/kg basis), the total systemic exposure (AUC) to modafinil is lower in paediatric 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 those >16 years of age [1].

Modafinil concentrations were not affected when given to patients with chronic renal failure (mean creatinine clearance of 16.6 ml/min); however, the concentration of the inactive metabolite, modafinil acid, was increased approximately nine-fold. Those with compromised renal function should also be considered for dosage adjustments (the effects of these levels of modafinil acid are unknown) [33].

Pharmacokinetic studies in patients with cirrhosis of the liver showed a decrease in modafinil clearance of ~ 60% compared with healthy patients, along with a doubling of the steady-state concentration [33]. Based on these data, the prescribing information directs that modafinil be initiated at half the usual starting dose (100 mg) in patients with severe hepatic impairment, with or without cirrhosis [1].

### 3.3 Drug interaction studies

Modafinil is metabolised by the cytochrome P450 (CYP) enzyme system, and may have an effect on other drugs metabolised by this system. In in vitro studies using primary human hepatocyte cultures, modafinil induced CYP 1A2, -2B6 and -3A4 in a concentration-dependent manner, suggesting that it may reduce plasma levels of drugs metabolised by these enzymes (e.g., ethinyl oestradiol and cyclosporin) [33,34]. Modafinil also suppressed CYP 2C9 and inhibited CYP 2C19 activity, suggesting that it may prolong the elimination of drugs metabolised by these enzymes (e.g., warfarin, diazepam, and phenytoin) [34]. Because CYP 2C19 also provides an ancillary pathway for the metabolism of certain tricyclic antidepressants that are primarily metabolised by CYP 2D6 (e.g., clomipramine and imipramine), the amount of metabolism through CYP 2C19 may be increased substantially in patients who are deficient in CYP 2D6 [34].

In vivo studies have compared modafinil with a number of drugs metabolised through these CYP enzyme pathways, in addition to the CNS stimulants, methylphenidate and dextroamphetamine. Single-dose, crossover comparisons of modafinil 200 mg with methylphenidate 40 mg and dextroamphetamine 10 mg did not show significant alterations in pharmacokinetics with any of these agents, although absorption of modafinil was slightly delayed [35,36]. Among the studies involving drugs metabolised via CYP pathways, the most notable finding was an 11% decrease in the peak plasma concentration of ethinyl oestradiol after chronic administration of modafinil 400 mg [37]. Because the efficacy of steroidal contraceptives may be reduced with coadministration of modafinil, additional or alternative methods of contraception should be used in patients being treated with modafinil, and for 1 month after modafinil therapy is discontinued.

Importantly, the potential interactions between modafinil and warfarin, suggested by in vitro studies, did not materialise in a study on the single-dose pharmacokinetics of warfarin in patients taking modafinil for > 1 month [38]. Nevertheless, because of the well-documented potential for interactions between warfarin and other agents, increased monitoring of prothrombin times or International Normalised Ratio is recommended when warfarin and modafinil are coadministered [1]. One case study showed decreased plasma concentrations of cyclosporin (and a reduction in immunosuppressive effect) when given concomitantly with modafinil to a renal transplant patient [32]. Another showed an increase in plasma levels of clomipramine and its active metabolite, desmethylclomipramine, when given to a narcolepsy patient along with modafinil 200 – 400 mg/day. A study in which modafinil and clomipramine were coadministered failed to find any significant alterations in pharmacokinetics [32].

### 4. Clinical efficacy

#### 4.1 Baseline characteristics and disease severity in placebo-controlled studies of modafinil

A total of six randomised, placebo-controlled, multi-centre studies (two 9-week narcolepsy studies, one at 18 centres and one at 21 centres; one 12-week and one 4-week OSAS study; and two 12-week SWSD studies) formed the basis for approval of modafinil for ES associated with these disorders. The demographics of the patients in these trials are summarised in Table 2 [7,39-43]. Overall, 1431 patients were included in the intent-to-treat populations (defined as those who received at least one dose of study medication and one

### Table 1. Pharmacokinetic activity of modafinil.

<table>
<thead>
<tr>
<th>Property</th>
<th>Activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacokinetics</td>
<td>Linear, independent of dose</td>
</tr>
<tr>
<td>Time to peak plasma</td>
<td>2 – 4 h</td>
</tr>
<tr>
<td>concentration (Cmax)</td>
<td></td>
</tr>
<tr>
<td>Time to steady-state</td>
<td>2 – 4 days</td>
</tr>
<tr>
<td>Plasma protein binding</td>
<td>Moderate (~ 60%)</td>
</tr>
<tr>
<td>Half-life (t1/2)</td>
<td>15 h (multiple dose)</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Hepatic (~ 90%)</td>
</tr>
<tr>
<td>Urinary excretion</td>
<td>Primarily metabolites; &lt; 10% unchanged drug</td>
</tr>
</tbody>
</table>

Adapted from [32,33].
Latency Test (MSLT) [42], as a primary end point. The Clinical Task (PVT) was used to measure the patients’ ability to sustain attention [47]. The use of this computerised, performance-based measure was considered important, given the well-documented increased risk in accidents, ‘near miss’ accidents, and mistakes experienced by persons with ES during the work period and the commute to and from work [9,48]. Ability to sustain attention was assessed using PVT lapses of attention – brief episodes of nonresponse (> 500 ms).

The baseline scores on these measures are shown in Table 3 [7,40-43]. Mean scores on the MSLT ranged from 2.0 to 7.5 minutes, indicating that most patients suffered from moderate to severe ES (scores < 5 min indicate severe ES) [2]. 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. Most patients in these studies were at least moderately ill at baseline as determined by investigators on the Clinical Global Impression of Severity (CGI-S). Despite previous treatment with nCPAP prior to randomisation, the patients in the OSAHS studies had residual ES, and all were at least mildly ill at baseline. Similarly severe ES was seen on the ESS and KSS at baseline, and the OSAHS and SWSD groups had substantially impaired performance at baseline, as illustrated by the number of PVT lapses of attention.

### 4.2 Efficacy outcomes

Patients in the narcolepsy studies were randomised to either placebo or modafinil 200 or 400 mg for 9 weeks. The 18-centre study used a rapid dose titration schedule, with both modafinil groups receiving 200 mg on day 1 and the 400 mg group moving up to this dose on day 2 [41]. In the 21-centre study, a more refined step-up protocol was used, with each active treatment group receiving modafinil 100 mg on days 1 – 7, and 200 mg on day 8. Starting on day 9, patients in the 400-mg group were moved to the higher dose [40].

In the 12-week OSAHS trial, patients were randomised to either placebo or modafinil 200 or 400 mg. Dosing began at 100 mg/day, and was increased by 100 mg every 2 days until the study dose was reached. In the 4-week OSAHS trial, patients were randomised to placebo or modafinil 100 mg for 1 week, increased to 400 mg for weeks 2 – 4 [42,43]. Those in the SWSD trial were randomised to placebo or modafinil 200 mg, taken 1 h prior to the work shift, for 12 weeks [7].

Consistent improvement in wakefulness was seen both in similar end points across studies, and in different end points within studies. As shown in Figure 2, statistically significant objective improvements in wakefulness on the MWT and MSLT were seen with both modafinil doses and at every time point (p < 0.05) except week 8 in the SWSD study [7,41,42]. A total of 36 – 74% of patients showed improvement in overall clinical condition on the CGI-C, defined as very much, much, or minimally improved (p < 0.05 for all patient groups, change from baseline versus placebo). Similar improvements were seen in the ability to sustain attention on the PVT (mean change from baseline in lapses of attention, -0.8 to -3.8; p < 0.05) and in subjective estimates of sleepiness on the ESS/KSS (p < 0.001) (Figure 3) [7,40-43].

### Table 2. Baseline characteristics in modafinil studies of excessive sleepiness.

<table>
<thead>
<tr>
<th></th>
<th>Narcolepsy</th>
<th>OSAHS</th>
<th>SWSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>530</td>
<td>446</td>
<td>455</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (± s.d.)</td>
<td>41.8 (13.3)</td>
<td>49.7 (9.4)</td>
<td>39.5 (9.2)</td>
</tr>
<tr>
<td>Range</td>
<td>17 – 68</td>
<td>24 – 76</td>
<td>20 – 62</td>
</tr>
<tr>
<td>Sex, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>239 (45)</td>
<td>340 (76)</td>
<td>243 (53)</td>
</tr>
<tr>
<td>Female</td>
<td>291 (55)</td>
<td>106 (24)</td>
<td>212 (47)</td>
</tr>
<tr>
<td>Race, N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>434 (82)</td>
<td>396 (89)</td>
<td>321 (71)</td>
</tr>
<tr>
<td>Black</td>
<td>77 (15)</td>
<td>29 (7)</td>
<td>99 (22)</td>
</tr>
<tr>
<td>Asian</td>
<td>0</td>
<td>6 (1)</td>
<td>2 (&lt; 1)</td>
</tr>
<tr>
<td>Other</td>
<td>19 (4)</td>
<td>15 (3)</td>
<td>32 (7)</td>
</tr>
</tbody>
</table>

N: Number of patients; OSAHS: Obstructive sleep apnoea/hypopnoea syndrome; SWSD: Shift-work sleep disorder.

Adapted from [7,39-43].

Post-baseline follow-up. All patients met accepted criteria for the symptom of ES, as well as standard diagnostic criteria for narcolepsy, OSAHS or SWSD.

The three study populations were similar with respect to demographic characteristics. Patients evaluated in the OSAHS studies were somewhat older (mean age: 49.7 years versus 41.8 and 39.5 years for narcolepsy and SWSD, respectively), and the per cent of men was higher in the OSAHS population (76%), consistent with the known epidemiology of OSAHS.

A number of objective and subjective outcome measures were used in five of the six studies to measure ES, overall clinical condition, and sustained attention and reaction time (one of the SWSD trials was designed primarily to assess safety; therefore, it was not included as part of the efficacy analysis, although it was included in the safety analysis). Each study used an objective measure of physiological ES, the Maintenance of Wakefulness Test (MWT) [44] or the Multiple Sleep Latency Test (MSLT) [42], as a primary end point. The Clinical Global Impression of Change (CGI-C) was also used as a primary outcome measure in all five studies to assess improvements in overall clinical condition. In the narcolepsy and OSAHS studies, the patients’ subjective estimates of sleepiness and the extent to which ES interfered with daily activities were assessed using the Epworth Sleepiness Scale (ESS) [45]. This eight-item, patient-completed Likert scale has become widely adopted as a subjective assessment tool in sleep medicine. In the SWSD study, the nine-point Karolinska Sleepiness Scale (KSS) was used as the subjective measure of sleepiness, due to its widespread use in the assessment of ES in circadian rhythm sleep disorders [46].

In the OSAHS and SWSD studies, the Psychomotor Vigilance Task (PVT) was used to measure the patients’ ability to sustain attention [47]. The use of this computerised, performance-based measure was considered important, given the well-documented increased risk in accidents, ‘near miss’ accidents, and mistakes experienced by persons with ES during the work period and the commute to and from work [9,48]. Ability to sustain attention was assessed using PVT lapses of attention – brief episodes of nonresponse (> 500 ms).
improvements in sustained attention were reported in the studies of ES associated with narcolepsy on the Steer Clear, a 30-min, computer-simulated driving program that requires sustained attention to avoid hitting obstacles [49].

Patients from the narcolepsy and OSAHS studies were eligible to enroll in open-label extension phases in which they received modafinil in flexible-dose regimens of 200 – 400 mg [50-52]. Follow-up through 136 weeks of treatment in the narcolepsy open-label study demonstrated that significant improvements in wakefulness were maintained over the long-term (Figure 4) [50,51]. Similar findings were seen over 12 months of long-term treatment in patients enrolled in the 12-week OSAHS study [50], and over 12 weeks in patients enrolled in the 4-week study [52]. In the 12-month extension, ESS scores were reduced from a mean of ∼14.5 – 10.0 at month 12, whereas in the 12-week study, they were reduced from a baseline mean of 14.4 to 7.6 (patients from the SWSD studies were also enrolled in open-label extension phases; however, these did not include assessments of ES).

### 4.3 Additional efficacy studies

A number of other studies have assessed the efficacy of modafinil for the treatment of ES or related symptoms, such as fatigue. In narcolepsy, a 24-week study (consisting of three 2-week double-blind crossover periods, a 16-week open-label period, and a 2-week randomised, placebo-controlled abrupt discontinuation period) demonstrated improvements in the ability to maintain wakefulness on the MWT and in subjective estimates of sleepiness on the ESS that were similar to those observed in the two 9-week studies [53,54]. A 6-week, open-label, flexible dose study showed statistically significant improvements on the CGI-C and ESS in patients who had shown a prior unsatisfactory response to CNS stimulants (dextroamphetamine, methylphenidate or pemoline) [55].

A number of studies or case reports have assessed the use of modafinil for treating ES and/or fatigue in several different disorders. These have included ES associated with Parkinson’s disease [56,57], myotonic dystrophy [58-60], depression [61-63], schizophrenia [64-66], traumatic brain injury [67], stroke [68], and opioid use [69], as well as fatigue in multiple sclerosis [70-72] and depression [61,62]. The majority of these studies have reported improvements in sleepiness and/or fatigue, although most have been designed as smaller pilot studies or single-blind trials; few have been randomised trials with a double-blind, placebo-controlled design. In addition, some studies on the treatment of ES and fatigue in patients with depression have shown significant improvement with the use of selective serotonin re-uptake inhibitors (SSRIs) plus modafinil in the earlier measurement periods (e.g., weeks 1 – 2), but no significant difference at later measurement periods. This has generally not been

| Table 3. Baseline disease severity in modafinil studies of excessive sleepiness. |
|---------------------------------|------------------|------------------|------------------|------------------|
| Dose (mg) | Narcolepsy | OSAHS* | SWSD |
| MWT, mean min (± s.d.) | 200 | 400 | Placebo | 200 | 400 | Placebo | 200 | Placebo |
| MSLT, mean min (± s.d.) | 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 (± s.d.) | 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 (± s.d.) | NA | NA | NA | 5.2 (11.5) | 2.3 (3.9) | 3.7 (6.6) | 22.5 (23.0) | 24.3 (26.4) |
| Sleep efficiency, mean % (± s.d.) | 87.0 (10.2) | 85.8 (11.0) | 73.6 (12.4) |
| CGI-S rating, N (%) | Not recorded | 0 | 43 (10) | 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) |

*All OSAHS patients were treated with nasal continuous positive airway pressure (nCPAP). CGI-S: Clinical Global Impression of Severity; ESS: Epworth Sleepiness Scale; KSS: Karolinska Sleepiness Scale; MSLT: Multiple Sleep Latency Test; MWT: Maintenance of Wakefulness Test; N: Number of patients; NA: Not available; OSAHS: Obstructive sleep apnoea/hypopnoea syndrome; PVT: Psychomotor Vigilance Task; SWSD: Shift-work sleep disorder.

Adapted from [7,40-43].
due to a deterioration of efficacy with modafinil but rather, to subsequent improvements in efficacy in groups receiving SSRIs plus placebo. Finally, some research in MS patients with moderate-to-severe fatigue has shown efficacy at the lower modafinil dose (200 mg) but not the 400 mg dose [70], raising the question of whether the mechanisms responsible for fatigue are different from those responsible for sleepiness in patients with pathological levels of fatigue.

The issue of dosing has been the subject of several studies of ES associated with narcolepsy. Modafinil is currently approved at a dosage of 200 mg, given once-daily in the morning (or 1 h prior to the start of the work shift for ES associated with SWSD). Single doses of up to 400 mg may be given; however, the randomised, placebo-controlled studies did not demonstrate a consistent dose relationship at this higher dose. It has been observed that limitations imposed by MWT testing protocols may have prevented a dose–response effect from emerging. The first MWT session was conducted ∼ 1 h after the patients took their dose of modafinil in the morning, before the drug had a chance to reach peak plasma levels (a total of four MWT sessions were conducted at each study visit, separated by 2-h intervals).

There are reports of greater efficacy in narcolepsy patients using higher-dose (≥ 800 mg) regimens, and studies have demonstrated significant improvements in wakefulness using split-dose (morning and early afternoon) regimens [53,54]. A split-dose regimen may be particularly important for some patients who have a satisfactory response to modafinil in the early part of the day but experience ES in the late afternoon or evening.

Studies using split-dose regimens and/or modified versions of the MWT have shown significantly improved wakefulness with these regimens compared with the 200 mg dose, in patients experiencing late-day ES. In a three-period, crossover study in which modafinil was given at 200 or 400 mg/day in the morning, or 400 mg in a split dose (200 mg morning and noon), sleep latencies on the MWT were significantly increased, with both 400 mg doses compared with the 200 mg dose (p < 0.05). 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 (09.00 and 11.00 h; and 13.00, 15.00, 17.00, 19.00 and 21.00 h) [73]. More recently, 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/day in the morning or a 400 mg split-dose regimen (Figure 5) [74].

5. Safety and tolerability

5.1 Adverse events

More than 1500 patients were included in the safety analyses in the double-blind, placebo-controlled studies of modafinil...
for ES associated with narcolepsy, OSAHS and SWSD. The most common adverse events (occurring in ≥ 5% of modafinil patients and > placebo) were headache (34%), nausea (11%), nervousness (7%), rhinitis (7%), back pain (6%), diarrhoea (6%), anxiety, dizziness, dyspepsia and insomnia (5% each). Most adverse events were mild-to-moderate in severity, transient, and occurred within the first month of therapy. A total of 17 of 934 modafinil and 8 of 567 placebo patients experienced a serious adverse event; six events were considered probably related to modafinil treatment (chest pain, leucopenia and neutropenia, extrasystoles and palpitations, dyspnoea and hypoventilation). There were no deaths related to modafinil therapy. Two adverse events, headache and anxiety, were considered to be dose related, with consistent increases in symptoms across the range of dosages used. Headache occurred in 32, 26 and 40%, and anxiety in 3, 4 and 7% of patients receiving modafinil 200, 300 and 400 mg/day, respectively [1].

In the narcolepsy studies, the different titration protocols appeared to have an impact on the incidence of adverse events. In the 18-centre study, in which the 400 mg dose was started on day 2, a higher percentage of patients in the 400 mg group withdrew due to adverse events compared with the 200 mg and placebo groups (12 versus 1 and 0%, respectively) [41]. In the 21-centre study, which used a more extended titration regimen, only 1% of patients in the 400 mg group withdrew due to adverse events [40].

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 versus -1.3 mmHg for modafinil and placebo, respectively. No significant differences emerged when patients were assessed according to history of hypertension or baseline level of blood pressure [75]. However, a retrospective analysis showed that more patients receiving modafinil required a new or increased use of antihypertensive agents compared with placebo (2.4 versus 0.7%). The differential use was slightly more pronounced in the OSAHS patients (3.4 versus 1.1%). Blood pressure monitoring is indicated in patients taking modafinil.

Polysomnography was conducted at night in the double-blind, placebo controlled studies of narcolepsy and OSAHS patients and during the day in the SWSD patients. Among the polysomnographic measures was an assessment of sleep efficiency (i.e., the time asleep as a percentage of the total time in bed). There were no significant differences between modafinil and placebo in sleep efficiency, demonstrating that modafinil did not affect the patients’ ability to sleep when sleep was desired.

Overall, > 3700 modafinil patients have been evaluated for safety in ES associated with narcolepsy, OSAHS, SWSD,
and other disorders of sleep or wakefulness. The incidence and nature of adverse events has been consistent with those reported in the randomised, placebo-controlled studies. 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 randomised, placebo-controlled studies.

5.2 Abrupt discontinuation

One of the 9-week narcolepsy studies included a 2-week discontinuation phase, in which patients receiving modafinil were randomised to continue receiving the drug or to abrupt discontinuation. Over the 14 days, no specific symptoms associated with withdrawal (e.g., fatigue, agitation, vivid dreams, hypersonnia, increased appetite) emerged, although sleepiness returned in these patients [40]. A similar lack of withdrawal effects was seen in the 2-week, double-blind, discontinuation period at the end of the 24-week narcolepsy study [53,54]. These findings are consistent with the absence of tolerance.

5.3 Nasal continuous positive airway pressure use in obstructive sleep apnoea/hypopnoea syndrome

The two OSAHS studies both included monitoring of nightly hours of nCPAP use. No significant change in mean hours of nCPAP usage was seen in either of the placebo-controlled phases of these studies. However, there was a small but statistically significant decrease in nCPAP use in both of the open-label extension phases, ranging from ~ 20 – 30 min [50,52]. The impact of this decrease on clinical outcomes remains unknown. However, given that nCPAP is the most effective therapy for relieving the underlying airway obstruction in OSAHS patients, nCPAP usage must be closely monitored over the long-term and patients continually reassessed for any potential adverse consequences.

5.4 Abuse liability

Modafinil is classified as a Schedule IV medication under the Controlled Substances Act, due to a limited risk of physical and/or psychological abuse or dependence. In comparison, the other agents commonly used for ES, amphetamine and methylphenidate, are both classified as Schedule II medications, due to a high potential for abuse leading to severe physical or psychological dependence [11].

Findings in studies using animal models are consistent with a low potential for abuse for modafinil [76,77]. These data have shown that modafinil does have weak reinforcing and stimulant-discriminative effects; however, these effects are ~ 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 [77].

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, compared with placebo, D-amphetamine 15 mg significantly increased scores on the Amphetamine (stimulant) and Morphone-Benzedrine Group (MBG; euphoria) scales of the Short-Form Addiction Research Center Inventory (ARCI – a 49-item, true–false questionnaire validated for assessing the abuse potential of drugs). Whereas modafinil also showed 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 [78].

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 [79,80]. 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 ≤ 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 [79].

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 [80].

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 persons who were experienced cocaine abusers. All patients had a score of at least 5 on the Drug Abuse Screening Test, a 28-item inventory that assesses potential consequences of drug use and the ability to stop or limit use of drugs. The patients had spent a mean of US$1378 each on cocaine during the week prior to the study [81].

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 asks patients about the 'good effects' of the drug and how much they would be willing to pay for the drug on the street [81].

On the Drug-Effect Questionnaire, only the highest dose of modafinil showed a significant difference compared with placebo in terms of ‘any effect’ (p ≤ 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 ≤ 0.005), whereas 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 ≤ 0.05) [81].

On 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 ≤ 0.05). Participants were willing to pay significantly more for the two higher doses of cocaine compared with placebo (p ≤ 0.05), whereas they would not pay more than placebo for any dose of modafinil.

Figure 5. Improvements in wakefulness on the Maintenance Of Wakefulness Test with modafinil 200 or 400 mg as a single dose in the morning, compared with 400 and 600 mg split-dose regimens.
Adapted from [74].
Postmarketing surveillance on modafinil has been conducted since 1999 by the Haight Ashbury Free Clinics, a network of clinics with > 30 years of experience in compiling epidemiological data on national and local drug abuse patterns [82]. This surveillance programme is extensive and comprised of information from multiple national and state databases such as DAWN, MEDWATCH, and national drug use surveys [83]. Medical and popular literature are also evaluated, as is information from providers in addiction, pain management, paediatrics, geriatrics, and primary care. Neither these postmarketing surveillance efforts nor other methods designed to detect drug abuse have detected generalised 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 < 1% of total messages in internet chat rooms relating to 'smart drugs' [83].

6. Conclusion

Modafinil is a unique wake-promoting agent that has been approved for the treatment of ES associated with narcolepsy, OSAHS, and SWSD in the US. Preclinical and clinical studies have demonstrated modafinil's significant wake-promoting efficacy for ES associated with these disorders, as well as significant improvements in overall clinical condition and the ability to sustain attention. The safety data on modafinil, encompassing > 3500 patients, have demonstrated its favourable tolerability profile in the treatment of ES associated with disorders of sleep or wakefulness. Studies on the abuse liability of modafinil support a low potential for abuse with this agent.

7. Expert opinion

Since its introduction in 1998 for narcolepsy-associated ES, modafinil has rapidly penetrated the narcolepsy market, becoming the predominant agent prescribed for this symptom. Its steady adoption by sleep specialists for narcolepsy is the result of a number of factors, including its efficacy in treating the symptom of ES, its lower incidence of adverse events related to generalised stimulation of the CNS (including unwanted motor activity, anxiety, and nervousness), its lower potential for abuse compared with CNS stimulants, and the lack of significant prescribing restrictions compared with schedule II controlled substances. Modafinil represents a significant improvement over CNS stimulants for the treatment of ES.

Obstructive sleep apnoea is a very common cause of ES, and a significant number of patients remain somnolent despite nCPAP therapy. These patients, as well as patients with SWSD, have been shown to have significant improvement in daytime alertness with modafinil. SWSD, in particular, represents a challenge in that the disorder is underdiagnosed and ES is under-recognised in this population. Problems with under-recognition may be increased in specialties other than sleep medicine – especially among primary care providers, who see significant numbers of ES patients in practice.

In addition, there may be a greater perception that SWSD patients are ‘not really ill’ and therefore, that pharmacotherapy is inappropriate. In reality, sleepiness in this population can reach severe levels, surpassing that seen in narcolepsy patients, and data on shift workers have shown that these individuals have a dangerously high risk of accidents related to ES, difficulty concentrating, and increased reaction times. It is essential to keep in mind that neither modafinil nor the CNS stimulants ‘normalise’ the patient’s level of wakefulness in all cases; patients must be advised that their level of sleepiness may not return to normal, and they should be encouraged to return for frequent reassessment of their level of sleepiness.

There is no question that CNS stimulants are effective for producing wakefulness. Few data are available to directly compare the efficacy of CNS stimulants for wake promotion with that of modafinil. Researchers have attempted to compare relative efficacy in measures of sleep latency with different agents in separate studies. A common technique is to ‘normalise’ the greatest effect of each drug in terms of the degree to which narcolepsy patients treated with the drug approached normal sleep latency values. In a comparison of studies involving modafinil and four CNS stimulants, relative sleep latencies were longer with methamphetamine, methylphenidate, and dextroamphetamine than with modafinil [84]. This analysis had several limitations, however, in that it evaluated only a single end point (per cent change in mean sleep latency) and the number of study subjects was small. In addition, each medication produced both statistically and clinically significant improvements in sleep latency. Although some patients tolerate CNS stimulants well, even at higher-than-recommended doses, the individual patient’s adverse effects and potential for abuse must be considered in prescribing a medication for ES.

Whereas previous research with modafinil has focused mainly on ES and fatigue, future studies are more likely to focus on measures of cognitive performance, including attention, short-term memory, and executive functioning. Improvement in these areas of functioning can have significant implications for a number of disorders, including attention deficit hyperactivity disorder, depression, and diseases involving injury or insult to the brain (e.g., Alzheimer’s disease and cerebral infarction). In addition, studies have begun to examine the ability of modafinil to sustain attention and performance in ‘normal’ patients working under conditions of sleep deprivation. For example, a study in sleep-deprived...
pilots undergoing flight simulations showed attenuation of decrements in performance of 15 – 30% over 37 h, compared with 60 – 100% for placebo [85].

Several studies have begun to address the issues of whether increasing the dose or adjusting the dose timing can sustain wakefulness over a greater period of time, and future trials are likely to employ more significant modifications to dosing protocols, compared with the current indication. Given the number of disorders that display core symptoms and/or signs of sleepiness, fatigue, depression, and impaired cognitive function, the avenues for research with modafinil are expanding rapidly, and are likely to continue to do so.

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Modafinil: new indications for wake promotion


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