Modafinil
A Review of its Use in Excessive Sleepiness Associated With Obstructive Sleep Apnoea/Hypopnoea Syndrome and Shift Work Sleep Disorder

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Data Selection
Sources: Medical literature published in any language since 1980 on modafinil, identified using MEDLINE and EMBASE, supplemented by AdisBase (a proprietary database of Adis International). Additional references were identified from the reference lists of published articles. Bibliographical information, including contributory unpublished data, was also requested from the company developing the drug.

Search strategy: MEDLINE search terms were ‘modafinil’ and (‘shift work’ or ‘obstructive sleep apnea/apnoea’ or ‘sleep apnea syndromes’ or ‘sleepiness’). EMBASE search terms were ‘modafinil’ and (‘sleep apnea disorder’ or ‘sleepiness’). AdisBase search terms were ‘modafinil’ and (‘shift work’ or ‘obstructive sleep apnoea’ or ‘sleepiness’). Searches were last updated 8 August 2005.

Selection: Studies in patients with excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome or shift work sleep disorder who received modafinil. Inclusion of studies was based mainly on the methods section of the trials. When available, large, well controlled trials with appropriate statistical methodology were preferred. Relevant pharmacodynamic and pharmacokinetic data are also included.

Index terms: Modafinil, shift work sleep disorder, obstructive sleep apnoea/hypopnoea syndrome, excessive sleepiness, pharmacodynamics, pharmacokinetics, therapeutic use.

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Summary

Abstract

Modafinil (Provigil®) is a wake-promoting agent that is pharmacologically distinct from CNS stimulants, such as amphetamine, dexamphetamine and methylphenidate. Modafinil is approved for use in the US and certain European countries for use in patients with excessive sleepiness associated with narcolepsy, obstructive sleep apnoea/hypopnoea syndrome (OSA/HS) or shift work sleep disorder (SWSD).

Oral modafinil promotes wakefulness in patients with OSA/HS and SWSD. It is an effective adjunctive therapy in patients with residual excessive sleepiness associated with OSA/HS who are receiving nasal continuous positive airway pressure (nCPAP) therapy. In SWSD, the drug improves night-time wakefulness without disrupting daytime sleep. Modafinil is generally well tolerated in patients with OSA/HS or SWSD and has a low abuse potential. Thus, modafinil is a valuable new treatment option for use in patients with excessive sleepiness associated with OSA/HS (as an adjunct to nCPAP) or SWSD.

The exact mechanism by which modafinil promotes wakefulness is unknown, although it appears that it primarily affects areas of the brain involved in controlling wakefulness.

Modafinil increased wakefulness in numerous animal models, including models of sleep deprivation and narcolepsy. Modafinil did not have detrimental effects on subjective and objective measures of nocturnal sleep in healthy volunteers. In sleep-deprived volunteers, modafinil significantly improved mood, fatigue, sleepiness and alertness/vigilance, compared with placebo. In addition, modafinil attenuated the cognitive impairment associated with sleep deprivation and, during laboratory night-shifts, significantly attenuated the decline in cognitive tests versus placebo. Modafinil appears to have a low potential for abuse.

Modafinil is rapidly absorbed; at steady state, a peak plasma concentration of 6.4 μg/mL was reached in 2.7 hours with modafinil 200mg once daily. Approxi-
mately 90% of a modafinil dose is metabolised, primarily to two inactive metabolites. The pharmacokinetics of modafinil were altered in older versus younger men and in patients with chronic hepatic impairment versus healthy volunteers.

Clinical Efficacy

Five randomised, double-blind, placebo-controlled trials examined the efficacy of oral modafinil 200–400mg once daily in patients with excessive sleepiness associated with OSA/HS or SWSD. Two of the OSA/HS trials were of parallel-group design (n = 157 and 309; treatment duration 4 and 12 weeks) and the third was a crossover trial (n = 30; treatment duration 2 weeks). Two studies in SWSD (n = 204 and 278) were of parallel-group design and of 12 weeks’ duration.

In patients with excessive sleepiness associated with OSA/HS who were receiving nCPAP, modafinil 200 or 400 mg/day improved wakefulness, as assessed by Epworth Sleepiness Scale (ESS) scores, to a significantly greater extent than placebo in the parallel-group studies, but not in the smaller crossover study. At study end, sleep-onset latency, assessed by the Maintenance of Wakefulness Test (MWT) or Multiple Sleep Latency Test (MSLT), improved to a significantly greater extent with modafinil 200 or 400 mg/day versus placebo in the parallel-group studies. In the crossover study, sleep-onset latency improved to a significantly greater extent with modafinil 400 mg/day than with placebo according to the MWT, but not the MSLT. Additional analysis of the 4-week parallel-group study found that performance on Psychomotor Vigilance Task (PVT) testing was improved to a significantly greater extent with modafinil 400 mg/day than with placebo.

In the parallel-group studies in patients with OSA/HS, significantly more modafinil 200 or 400 mg/day recipients than placebo recipients experienced clinical improvement. However, in the crossover study, there was no significant between-treatment difference in the proportion of patients whose condition was rated as ‘better’. No reduction in nCPAP use occurred in the parallel-group studies, although a significant reduction in nCPAP use was seen with modafinil 400 mg/day versus placebo in the crossover study. Modafinil did not have an adverse impact on night-time sleep in any of the studies. Moreover, aspects of functional status and health-related quality of life (HR-QOL) were improved to a significantly greater extent with modafinil 200 or 400 mg/day than with placebo in the parallel-group studies, although no such between-treatment difference was seen in the crossover study.

In night-shift workers with SWSD, a significantly greater proportion of modafinil 200 mg/day than placebo recipients experienced clinical improvement according to Clinical Global Impression of Change ratings at the final visit. Improvements in night-time wakefulness (assessed using MSLT sleep-onset latency and Karolinska Sleepiness Scale scores) and performance (PVT testing) were significantly greater in modafinil 200 mg/day than placebo recipients at study end. Modafinil did not have an adverse impact on daytime sleep. Significantly greater improvements in functional status and HR-QOL occurred with modafinil 200 or 300 mg/day than with placebo.

Tolerability

Modafinil was generally well tolerated in patients with excessive sleepiness associated with OSA/HS or SWSD in randomised, double-blind, placebo-controlled studies. Adverse events were generally of mild-to-moderate severity.
In three studies in patients with OSA/HS, the most commonly reported adverse events (i.e. occurring in ≥5% of patients) included headache, infection, nausea, anxiety, accidental injury, diarrhoea, hypertension, nervousness, dizziness, insomnia, rhinitis and dry mouth. Headache, nausea and nervousness occurred significantly more frequently in modafinil than in placebo recipients.

In a study in SWSD, the most commonly reported adverse events (i.e. occurring in ≥5% of patients) in modafinil recipients included headache, nausea, infection, accidental injury, abdominal pain, nervousness, insomnia, dry mouth and tooth disorder; only insomnia occurred in a significantly greater proportion of modafinil than placebo recipients.

1. Introduction

The dyssomnias are a group of sleep disorders characterised by difficulty in initiating or maintaining sleep, or excessive sleepiness.[1] Both obstructive sleep apnoea/hypopnoea syndrome (OSA/HS) and shift work sleep disorder (SWSD) are examples of dyssomnias.[1] OSA/HS is an intrinsic sleep disorder; excessive sleepiness arises out of the sleep disruption that occurs in patients with this syndrome. SWSD is a circadian rhythm sleep disorder; it comprises symptoms of excessive sleepiness or insomnia that occur transiently in relation to work schedules.[1]

Modafinil (Provigil®)\(^1\) is an orally administered benzhydrylsulfinylacetamide derivative with documented efficacy in narcolepsy (reviewed by McClellan and Spencer\(^2\)). It is indicated in the US and certain European countries to improve wakefulness in patients with excessive sleepiness associated with narcolepsy, OSA/HS (as an adjunct to standard treatment with nasal continuous positive airway pressure [nCPAP] therapy) or SWSD. This article reviews the use of modafinil in patients with excessive sleepiness associated with OSA/HS or SWSD.

2. Pharmacodynamic Properties

The pharmacodynamic profile of modafinil has been reviewed previously.\(^2\) This section provides a brief overview, updating the pharmacodynamic properties of modafinil most relevant to OSA/HS and SWSD.

2.1 Mechanism of Action

Modafinil is a centrally acting agent that is structurally and pharmacologically distinct from CNS stimulants such as amphetamine, dexamphetamine and methylphenidate.\(^3\)

The exact mechanism by which modafinil promotes wakefulness is not known.\(^4\) It appears that the drug primarily affects areas of the brain thought to be involved in controlling wakefulness. A study in rats found that compared with vehicle, modafinil increased Fos expression (an indicator of neuronal activation) in the tuberomammillary nucleus and in orexin neurons in the perifornical area, cell groups in the hypothalamus implicated in the control of wakefulness.\(^5\) Modafinil also decreased Fos activity in the ventrolateral preoptic area, an area that contains sleep-promoting neurons.\(^5\) In this study, modafinil did not substantially increase Fos expression in the anterior hypothalamic area (AHA) or suprachiasmatic nuclei (SCN),\(^5\) although in other animal studies,\(^6,7\) the drug induced Fos expression in both these areas (the SCN are implicated in the regulation of circadian rhythms). This relatively selective effect for the hypothalamus is in contrast to the action of stimulants such as methylphenidate and amphetamine, which promote neuronal activation throughout the brain.\(^6,7\)

\(^1\) Also registered as Alertec®, Modasomin®, Modiodal®, Modavigil® and Vigil®. The use of trade names is for product identification purposes only and does not imply endorsement.

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Modafinil did not bind to adenosine, dopamine, GABA, serotonin, benzodiazepine, noradrenaline (norepinephrine), histamine H₃ or melatonin receptors in vitro.¹⁴,⁸ The results of animal studies demonstrate that modafinil interacts with several neurotransmitters and neuropptide pathways (e.g. glutamatergic,⁹ GABA-ergic,⁹-¹³ serotonergic,¹⁴-¹⁶ histaminergic¹⁷ and orexinergic⁵). In particular, it is thought that the activity of modafinil may be related to a reduction in GABA-ergic transmission in areas of the brain involved in the regulation of wakefulness.⁹,¹²

The role of dopamine in modafinil-induced wakefulness remains uncertain. Modafinil increased striatal extracellular dopamine in narcoleptic dogs, and the wake-promoting effects of the drug were abolished in dopamine transporter knockout mice, suggesting that modafinil needs dopamine transporters to achieve its wake-promoting action.¹⁸ Also, modafinil demonstrated weak affinity for the dopamine uptake carrier site in vitro,⁸ and increased dopamine release was seen in the rat prefrontal cortex with modafinil administration.¹⁶ However, other studies suggest that modafinil does not have direct effects on dopamine transmission.¹³,¹⁹ and demonstrated that the wakefulness induced by modafinil was not antagonised by haloperidol (a dopamine receptor antagonist).²⁰-²²

Recent data indicate that modafinil potentiates the inhibitory effect of noradrenaline on sleep-promoting neurons in the ventrolateral preoptic nucleus.²³ Earlier data suggested that modafinil is neither a direct nor indirect α₁-adrenoceptor agonist, although its mechanism of promoting wakefulness appears to require an intact α₁-adrenergic system.⁸,¹¹,²⁰,²¹,²⁴ Modafinil does not inhibit the activity of monoamine oxidase B²⁵ or phosphodiesterases II–V.⁴

2.2 Effects on Wakefulness and Locomotor Activity in Animals

Modafinil increased wakefulness in numerous animal models,²⁶-³³ including models of sleep deprivation²⁷,³¹ and narcolepsy.³² Modafinil also reduced hypersomnolence in an animal model of sleep-disordered breathing.³⁴

Modafinil increased locomotor activity in several animal models,²¹,²⁶,³⁵ although in one study this increase was shown to reflect the increased amount of time spent awake, as there was no increase in the intensity of locomotor activity (i.e. locomotor activity count per minute of wakefulness).²⁶ Moreover, no increase in locomotor activity was seen with increasing doses of modafinil (from 125 to 8000 μg/kg) in narcoleptic dogs.²²

2.3 Effects on Wakefulness, Sleep and Cognition in Human Volunteers

Numerous trials have examined the effects of modafinil in human volunteers. Some studies enrolled healthy volunteers (n = 10–60) who were not sleep deprived,³⁶-⁴¹ some used sleep-deprivation protocols (n = 6–50)³²-⁴⁸ and two, one of which is available as an abstract,¹⁹ used laboratory night-shift protocols (n = 16⁴⁰ and 32⁵⁰). All trials were double-blind³⁶-⁵⁰ and used active³⁷,³⁸,⁴³,⁴⁴,⁴⁶,⁴⁸ and/or placebo³⁶-⁵⁰ controls; some studies were randomised.³⁶,³⁹,⁴²,⁴⁷,⁴⁹,⁵⁰ Modafinil was administered as a single dose in the morning,³⁶,³⁹-⁴¹ as a single dose in the evening,³⁷,³⁸,⁴²,⁴⁸ as nightly doses for 4 nights,⁴⁹,⁵⁰ at different timepoints (night, morning and afternoon) over 3 days⁴³,⁴⁴,⁴⁶ or at 8-hour intervals for up to 3 days.⁴⁵,⁴⁷

Unlike dexamfetamine, single doses of modafinil 100 or 200mg did not have detrimental effects on subjective and objective measures of nocturnal sleep in young (mean age 30 years)³⁷ or elderly (mean age 68 years)³⁸ healthy volunteers. Among healthy volunteers, single doses of modafinil 100–200mg³⁶,³⁹,⁴¹ or 4 mg/kg⁴⁰ had no significant effects on cognition in one study,³⁶ but improved cognitive function to a significantly greater extent than placebo (p < 0.05) in three others.³⁹-⁴¹ Detrimental mood changes (e.g. increased somatic anxiety) occurred with modafinil in one study,³⁶ but not in another study.⁴⁰

Compared with placebo, modafinil 200–400 mg/day significantly (p < 0.05) improved mood⁴⁶, fatigue⁴⁶ and sleepiness⁴⁶,⁴⁸ in sleep-deprived volun-
teers. With modafinil 200–600 mg/day, sleep-deprived volunteers experienced significant improvements in alertness/vigilance versus placebo (p < 0.05). Following sleep deprivation, modafinil 300 mg/day recipients experienced significantly (p < 0.05) less sleep disturbance during the first recovery night than dexamfetamine recipients.[43]

Modafinil 200–400 mg/day attenuated the cognitive impairment associated with sleep deprivation.[42,46] Compared with placebo, modafinil ameliorated deterioration in several parameters, including attentional processes,[47] logical reasoning,[46] reaction time[42,46,48] and short-term memory.[42,46]

Compared with placebo, modafinil 200mg significantly improved alertness and performance during a laboratory night-shift.[49,50] The increase in Karolinska Sleepiness Scale (KSS) scores (a subjective measure of sleepiness) was significantly smaller with modafinil than with placebo (p < 0.05), as was the increase in the number of attention lapses (p < 0.05).[49] Moreover, modafinil 200 mg/day significantly (p < 0.05) attenuated the decline in certain cognitive tests (Wisconsin Card Sorting Test, Haylings Sentence Completion Test and Torrance Test of Creative Thinking-Verbal) compared with placebo.[50]

2.4 Other Effects

No deterioration in blood pressure (BP) control occurred with modafinil 200 or 400mg once daily in a pooled analysis, available as an abstract, of patients (n = 274) with OSA and a current or past history of hypertension.[51] There was also no significant change from baseline in heart rate. The pooled analysis included data from three randomised, double-blind, placebo-controlled studies in patients with OSA.

In patients with OSA/HS, no significant difference between modafinil and placebo administration was observed with regards to BP in one study.[52] In another study,[53] there was a statistically significant increase in sitting systolic BP with modafinil (+1.0mm Hg vs –2.6mm Hg in placebo recipients; p = 0.035); however, it was not deemed clinically meaningful (see section 4.1 for study details).

Modafinil 300mg increased body temperature in sleep-deprived volunteers, whereas a physiological decline in body temperature was observed in placebo recipients between approximately 2200 and 0800h.[46,54] Modafinil 200mg was also shown to have a thermogenic effect during a sweating test in healthy volunteers who were not sleep deprived.[55]

The potential for modafinil to be associated with abuse and dependency appears to be much lower than that of amphetamine-like stimulants.[56] Modafinil 200–800mg produced no or minimal stimulant-like subjective effects (e.g. euphoria) in small studies (n = 6–24) in healthy volunteers[57] and volunteers with recent histories of cocaine use.[58-60] Postmarketing surveillance data also indicate a low abuse potential for modafinil.[61]

3. Pharmacokinetic Properties

This section provides a brief overview of the pharmacokinetics of modafinil, focusing on the dosage recommended in OSA/HS and SWSD (200 mg/day) [section 6]. Most of the data concerning the pharmacokinetics of the drug were obtained from a study in healthy men (section 3.1 and section 3.2),[3] supplemented by data from the prescribing information[4,62] and a review article.[63] The use of modafinil in special patient populations (section 3.3) and its drug interaction potential (section 3.4) are also discussed.

3.1 Absorption and Distribution

Repeat administration of oral modafinil 200–800mg once daily to healthy volunteers was associated with dose-proportional increases in the modafinil peak plasma concentration (C_max) and area under the plasma concentration-time curve (AUC).[3] Steady-state is reached after 2–4 days of drug administration.[4] Once-daily administration of modafinil was associated with an accumulation ratio of ≈1.5 at day 7.[3]

Modafinil is rapidly absorbed. At day 7, mean C_max was 6.4 μg/mL with modafinil 200mg once daily, with a corresponding mean time to C_max

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With repeat administration, the mean plasma elimination half-life ($t_{1/2}$) was 17 hours (table I). The $t_{1/2}$ of the $d$-isomer was approximately 4-fold shorter than that of the $l$-isomer (4.3 vs 16.0 hours at steady state with 200mg once daily).

### 3.3 Special Patient Populations

Elderly healthy men (mean age 63 years; $n = 12$) had mean modafinil AUC values (AUC from time zero to infinity; $AUC_\infty$) that were significantly higher (68 vs 57 μg • h/mL; $p < 0.05$) than those in younger healthy men (mean age 29 years; $n = 12$) after a single dose of modafinil 200mg. In addition, mean apparent clearance was significantly lower in older versus younger men (0.63 vs 0.72 L/kg; $p < 0.05$).

The modafinil $C_{max}$ at steady-state was 112% higher and the $t_{1/2}$ was 104% longer in nine patients with chronic hepatic impairment (Child class B–C) than in 12 healthy volunteers. Modafinil 100mg twice daily was administered to patients with hepatic impairment for 8 days and to healthy volunteers for 15 days.

The pharmacokinetics of single-dose modafinil 200mg were not altered to a significant extent in patients with severe renal impairment (creatinine clearance $\leq 1.2$ L/h [≤20 mL/min]). However, exposure to the metabolite modafinil acid increased 9-fold.

### 3.4 Potential Drug Interactions

In vitro, modafinil has been shown to inhibit the cytochrome P450 (CYP) isoenzyme CYP2C19 (moderately potent, reversible inhibition), modestly induce CYP1A2, CYP3A4/5 and CYP2B6 and suppress CYP2C9. This raises the possibility of interactions between modafinil and drugs that inhibit, induce or are metabolised by CYP enzymes.

Suppression of CYP2C9 was not confirmed clinically. The pharmacokinetics of (S)-warfarin (predominantly metabolised by CYP2C9) were not significantly altered by 4 weeks of pretreatment with modafinil in healthy volunteers.

In healthy women receiving long-term administration of an ethinylestradiol/norgestimate oral con-
traceptive, modafinil (200mg once daily for 1 week then 400mg once daily for 3 weeks) altered the pharmacokinetics of steady-state ethinylestradiol and a single dose of triazolam, both CYP3A4/5 substrates. The addition of modafinil versus placebo resulted in significantly (p < 0.05) greater decreases in the mean AUCτ (−18% vs −4%) and mean Cmax (−11% vs −5%) of ethinylestradiol, and significantly (p < 0.05) greater decreases in the mean AUC∞ (−59% vs +8%) and mean Cmax (−42% vs +7%) of triazolam administered with the final dose of modafinil or placebo. These results also suggest that induction of CYP3A4/5 activity by modafinil was primarily gastrointestinal rather than hepatic. Drugs besides triazolam that undergo significant intestinal metabolism mediated by CYP3A enzymes include ciclosporin, verapamil and lovastatin.

Other drugs that modafinil may interact with include phenytoin (CYP2C9 and CYP2C19 substrate) and diazepam and propranolol (CYP2C19 substrates). Lower dosages of TCAs and SSRIs may be needed in patients deficient in CYP2D6 who are receiving concomitant modafinil, given that the ancillary route of drug elimination via CYP2C19 is more important in these patients.

The potential for interaction between modafinil and other drugs with CNS activity has been examined. Low-dose dexamfetamine (20 mg/day) or methylphenidate (20 mg/day) did not alter the steady-state pharmacokinetics of modafinil (200mg once daily for 1 week then 400mg once daily for 3 weeks). In these studies, dexamfetamine was administered 7 hours and methylphenidate was administered 8 hours after modafinil. However, the tmax of modafinil was significantly prolonged when a single dose of dexamfetamine 10mg or methylphenidate 40mg was administered simultaneously with a single dose of modafinil 200mg (p < 0.05 vs modafinil alone); the median tmax was 3.0 hours with modafinil plus dexamfetamine versus 1.5 hours with modafinil alone, and the tmax range was 1.0–6.0 hours with modafinil plus methylphenidate versus 0.5–3.0 hours with modafinil alone. No other significant alterations in the pharmacokinetics of modafinil occurred.

4. Clinical Efficacy

4.1 In Patients with Obstructive Sleep Apnoea/Hypopnoea Syndrome (OSA/HS) Using Nasal Continuous Positive Airway Pressure Therapy

The efficacy of oral modafinil in patients with residual excessive sleepiness associated with OSA/HS has been examined in three randomised, double-blind, placebo-controlled studies; two studies were of parallel-group multicentre design (n = 30973 and 157531) and one was of crossover single-centre design (n = 30). In these studies, the modafinil dosage was titrated to a final dosage of 200mg or 400mg once daily in the morning, with a treatment duration of 2 or 4 or 12 weeks. Patients were receiving treatment with nCPAP.

Patients had excessive sleepiness (Epworth Sleepiness Scale [ESS] score of ≥1073 or ≥1152 [total ESS scores range from 0–24 points with higher scores indicating greater sleepiness]).

Wakefulness was assessed in these studies using subjective (ESS52,73) and objective (the Multiple Sleep Latency Test [MSLT]52,53, the Maintenance of Wakefulness Test [MWT]52,73) measures. Mild, moderate and severe sleepiness are usually defined as MSLT sleep-onset latencies of 10–15, 5–10 and <5 minutes, Psychomotor Vigilance Task (PVT) testing was used to measure the reaction time of patients to stimuli to assess deficits in attention and performance. Other outcome measures included the Clinical Global Impression of Change (CGI-C), a global evaluation of the patient’s condition, functional status (assessed using the Functional Outcomes of Sleep Questionnaire [FOSQ]) and health-related quality of life (HR-QOL; assessed using the 36-item Short Form Health Survey [SF-36]). Nocturnal polysomnography was also performed. Primary endpoints included the change from baseline in ESS and MWT scores and the CGI-C.
Table II. Effect of modafinil (MOD) on residual excessive sleepiness in patients with obstructive sleep apnoea/hypopnoea syndrome who were receiving nasal continuous positive airway pressure therapy. Results of three randomised, double-blind, placebo (PL)-controlled studies of parallel-group[53,73] or crossover[52] design

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment regimen (mg) [duration of treatment; weeks]</th>
<th>No. of randomised patients</th>
<th>Mean ESS score baseline</th>
<th>Mean MSLT SOL (min) study end</th>
<th>Mean MWT SOL (min) study end</th>
</tr>
</thead>
<tbody>
<tr>
<td>Black and Hirshkowitz[73]</td>
<td>MOD 200 od [12]</td>
<td>104</td>
<td>–4.5***b</td>
<td>16.5</td>
<td>18.3*</td>
</tr>
<tr>
<td></td>
<td>MOD 400 od [12]</td>
<td>101</td>
<td>–4.5***b</td>
<td>10.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PL [12]</td>
<td>104</td>
<td>–1.8b</td>
<td>9.0</td>
<td></td>
</tr>
</tbody>
</table>

a MOD was titrated to the stated dosage.
b Mean change from baseline.
c Primary endpoint.
d Total no. of patients who completed the study.

ESS = Epworth Sleepiness Scale; MSLT = Multiple Sleep Latency Test; MWT = Maintenance of Wakefulness Test; od = once daily; SOL = sleep-onset latency; * p < 0.05, ** p < 0.001, *** p < 0.0001 vs PL.

4.1.1 Effects on Wakefulness

Subjective Measure

In patients with residual excessive sleepiness associated with OSA/HS, modafinil 200 or 400 mg/day improved wakefulness, as assessed using the ESS, to a significantly greater extent than placebo in the parallel-group studies,[53,73] but not in the smaller crossover study.[52]

In the parallel-group studies, reductions in ESS scores from baseline to end of therapy were significantly greater with modafinil 200 or 400 mg/day than with placebo (table II).[53,73] Significant reductions with modafinil versus placebo were also seen at week 1 (p < 0.001) in the 4-week study[53] and at weeks 4 and 8 (p < 0.0001) in the 12-week study.[73] In the 4-week study, ESS scores were normalised to <10 points in a significantly greater proportion of modafinil than placebo recipients (51% vs 27%; p < 0.01).[53]

In the crossover study, there was no significant difference between modafinil and placebo in ESS score after 2 weeks of treatment (table II).[52]

Patients (n = 266) from the 12-week parallel-group study[73] continued in a 12-month noncomparative extension phase (available as an abstract) during which they received modafinil 200, 300 or 400 mg/day.[75] ESS scores were significantly reduced from a baseline score of 14.5 points at months 3 (by 5.7 points), 6 (5.3), 9 (5.4) and 12 (4.5) with modafinil (all p < 0.0001 vs baseline).[75]

In a 12-week noncomparative extension[76] of the 4-week parallel-group study,[53] patients (n = 125) had an ESS score of 7.8 points at week 12 (patients received modafinil 200, 300 or 400 mg/day).

Objective Measures

At study end, the ability to sustain wakefulness, as assessed by MWT, improved to a significantly greater extent with modafinil 200 or 400 mg/day versus placebo in the 12-week parallel-group study[73] and the crossover study[52] (table II). In the parallel-group study, significantly greater improvements in the ability to sustain wakefulness, as assessed by mean MWT, were also seen with modafinil 200 or 400 mg/day than with placebo at weeks 4 and 8 (p ≤ 0.0001).[73]

In the 4-week parallel-group study, MSLT sleep-onset latency had increased by a significantly greater extent with modafinil than placebo at study end (table II).[53] However, the improvement in MSLT sleep-onset latency did not significantly differ between modafinil and placebo administration in the crossover study (table II).[52]

Additional analysis[74] of the 4-week parallel-group study[53] found that sustained attention on
PVT testing was improved to a significantly greater extent with modafinil than with placebo. Compared with placebo recipients, modafinil recipients had a significant decrease in the number of attention lapses ($p = 0.01$), and significant improvements in the median ($p = 0.01$) and the reciprocal of the 10% slowest ($p = 0.023$) reaction times.

### 4.1.2 Other Outcomes

At study end, significantly greater proportions of modafinil 200 or 400 mg/day recipients than placebo recipients experienced clinical improvement (assessed by CGI-C ratings) in the 12-week parallel-group study (61% and 68% vs 37%; $p < 0.001$).[73] The 4-week parallel-group study yielded a similar result with 71% of modafinil recipients versus 35% of placebo recipients ($p = 0.035$) experiencing clinical improvement at study end.[53] In a 12-week noncomparative extension of the latter study, 71% of modafinil recipients were rated as much or very much improved at week 12.[76] In the crossover study, there was no significant between-treatment difference in the proportion of patients whose condition was rated as ‘better’. [52]

Given its benefits, a reduction in nCPAP use is not considered desirable in patients with OSA/HS. Modafinil did not reduce nCPAP use in the large parallel-group studies,[53,73] although nCPAP use was slightly, but statistically significantly, lower with modafinil than with placebo in the crossover study (6.3 vs 6.5 hours per night; $p = 0.03$).[52] Moreover, during a 12-week noncomparative extension of the 4-week parallel-group study, mean nCPAP use was significantly reduced compared with baseline use in the double-blind portion of the study (5.9 vs 6.3 hours per night; $p = 0.004$).[76]

Modafinil did not have an adverse impact on night-time sleep.[52,53,73] There were no significant differences between modafinil and placebo administration in various nocturnal polysomnography parameters (e.g. arousal frequency,[52,73] sleep efficiency,[52,53,73] sleep duration,[53,73] respiratory events,[52] respiratory disturbance index,[53] and the percentage of time spent in stages 1–4 and REM sleep.[53,73]). However, in the 4-week parallel-group study, the mean arousal index was significantly higher with modafinil than with placebo (14.3 vs 11.8; $p = 0.018$).[53]

### 4.1.3 Health-Related Quality-of-Life (HR-QOL) Considerations

Modafinil improved functional status and HR-QOL to a significantly greater extent than placebo in the parallel-group studies.[73,74]

In the 12-week study, the improvement at study end in the total FOSQ score was significantly greater with modafinil 200 and 400 mg/day than with placebo (mean change of +1.92 and +2.13 vs +0.84; $p = 0.001$), as were improvements in domain scores for vigilance, general productivity and activity level (figure 1).[73] In the extension phase, the total FOSQ score and the mental and physical component scores of the SF-36 were significantly improved from baseline with modafinil ($p < 0.01$).[75]

An additional analysis[74] of the 4-week study[53] found significant improvements in the total FOSQ score and domain scores for vigilance and activity level with modafinil versus placebo ($p < 0.05$) after 4 weeks of therapy. Changes from baseline in domain scores for general productivity, social outcome

![Fig. 1. Effect of modafinil (MOD) on functional outcome in patients with residual excessive sleepiness associated with obstructive sleep apnoea/hypopnoea syndrome. Mean change from baseline to week 12 in Functional Outcomes of Sleep Questionnaire (FOSQ) domain scores. Patients in this randomised, double-blind, parallel-group, multicentre study received oral MOD 200 or 400 mg once daily or placebo (PL) for 12 weeks.[73]](image-url)
and intimacy did not significantly differ between treatment groups.

In the crossover study, there were no significant differences between modafinil and placebo with regard to changes in FOSQ domain scores or SF-36 domain, or physical and mental component scores. Because of the small sample size (n = 30), this study may not have been adequately powered to detect a difference between treatments.

4.2 In Patients with Shift Work Sleep Disorder (SWSD)

The efficacy of modafinil in night-shift workers with chronic SWSD has been examined in two randomised, double-blind, parallel-group, placebo-controlled, multicentre, 12-week trials (n = 204 and 278). One study is available as an abstract and only reported HR-QOL outcomes. The diagnosis of SWSD requires a primary complaint of insomnia or excessive sleepiness that is temporally associated with a work period occurring during the habitual sleep phase. Other diagnostic criteria include loss of a normal sleep-wake pattern (as shown by polysomnography and the MSLT), lack of a medical or mental disorder to account for the symptoms, and symptoms not meeting criteria for any other sleep disorder associated with insomnia or excessive sleepiness.

In these studies, patients diagnosed with SWSD received modafinil 60–30 minutes prior to the start of each night-shift. Patients received modafinil 200mg once daily or placebo in one study and modafinil 200 or 300mg once daily or placebo in the other.

Measures of night-time wakefulness included the MSLT, the KSS (with scores ranging from 1 [very alert] to 9 [very sleepy]) and CGI-C ratings. MSLT and KSS were assessed during a laboratory night-shift. PVT testing was also performed during a laboratory night-shift, and polysomnography was used to assess the quality of daytime sleep.

Patient diary data were recorded, and functional status and HR-QOL were assessed using FOSQ and SF-36. Where specified, primary endpoints included the change from baseline in MSLT and the CGI.C. For final visit assessments, data from the last visit on or before month 3 were used.

4.2.1 Effects on Wakefulness and Sleep

Night-time wakefulness was significantly improved with modafinil 200 mg/day compared with placebo in patients with SWSD. Improvement in the ability of patients to sustain wakefulness, as shown by the increase in the mean MSLT from baseline to the final visit, was significantly greater with modafinil than with placebo (table III). Significant differences favouring modafinil were also seen after 1 and 3 months of treatment (both p = 0.01 vs placebo). Although these between-group differences in MSLT were statistically significant, the mean MSLT sleep-onset latency after 3 months’ therapy was still <5 minutes in modafinil recipients, indicating marked sleepiness.

Table III. Effect of modafinil (MOD) on night-time wakefulness and alertness during a laboratory night shift. In this randomised, double-blind, multicentre trial, patients with chronic shift work sleep disorder received MOD 200mg once daily (n = 96) or placebo (PL; n = 108) for 12 weeks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment</th>
<th>Baseline</th>
<th>Final visit</th>
<th>Change from baseline to final visit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean MSLT sleep-onset latency (min)</td>
<td>MOD</td>
<td>2.1</td>
<td>3.8</td>
<td>+1.7a</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>2.0</td>
<td>2.4</td>
<td>+0.3a</td>
</tr>
<tr>
<td>Median number of attention lapses</td>
<td>MOD</td>
<td>12.5</td>
<td>10.3</td>
<td>−2.6**</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>16.1</td>
<td>23.8</td>
<td>+3.8</td>
</tr>
<tr>
<td>Mean Karolinska Sleepiness Scale scores</td>
<td>MOD</td>
<td>7.3</td>
<td>5.8</td>
<td>−1.5**</td>
</tr>
<tr>
<td></td>
<td>PL</td>
<td>7.1</td>
<td>6.7</td>
<td>−0.4</td>
</tr>
</tbody>
</table>

a Primary endpoint.

b Assessed using Psychomotor Vigilance Task testing.

c Karolinska Sleepiness Scale scores range from 1 (very alert) to 9 (very sleepy).

MSLT = Multiple Sleep Latency Test; * p = 0.002, ** p < 0.001 vs PL.
At the final visit, a significantly greater proportion of modafinil than placebo recipients experienced clinical improvement according to the CGI-C (74% vs 36%; p < 0.001). The median number of attention lapses was reduced from baseline to a significantly greater extent with modafinil than with placebo at the final visit (table III). Improvements from baseline in mean KSS scores were significantly greater with modafinil than with placebo at the final visit (table III), and at months 1, 2 and 3 (all p < 0.001 vs placebo).

Comparison of baseline and postbaseline mean KSS scores from patient diary data demonstrated that maximum sleepiness during the night-shift was reduced to a significantly (p < 0.001) greater extent with modafinil (from 7.3 to 5.4 points) than with placebo (from 7.4 to 6.6 points). Similarly, modafinil recipients reported a significantly (p = 0.01) greater reduction from baseline in the level of sleepiness during the commute home (from 5.5 to 4.4 points) compared with placebo recipients (from 5.9 to 5.4 points) [assessed using KSS scores]. Moreover, the proportion of patients reporting accidents or near misses during the commute home was significantly lower in modafinil than placebo recipients (29% vs 54%; p < 0.001).

Modafinil did not have a deleterious effect on daytime sleep. There were no significant differences between modafinil 200 mg/day and placebo recipients with regard to changes in daytime sleep parameters such as sleep duration, sleep-onset latency, sleep efficiency or sleep architecture. Modafinil improved functional status and HR-QOL to a significantly greater extent than placebo in patients with SWSD. At week 12, FOSQ total scores and domain scores for vigilance and general productivity were improved from baseline to a greater extent with modafinil 300 mg/day than with placebo, and FOSQ activity level scores were improved from baseline to a significantly greater extent with modafinil 200 or 300 mg/day versus placebo (all p < 0.05) [quantitative data not reported].

Moreover, the improvement in the mental component of SF-36 was significantly greater with modafinil 200 or 300 mg/day than with placebo (p < 0.05) at 12 weeks (quantitative data not reported).

Twelve-month open-label extension studies (n = 166 and 125; both available as abstracts) of the two SWSD trials have also been conducted. At 12 months, modafinil recipients had significant improvements in the total FOSQ score and domain scores for activity, general productivity, intimacy, social outcome and vigilance (p-values not reported) in the extension of one of the SWSD trials, but not in the extension of the other trial.

5. Tolerability

Tolerability data were obtained from three randomised, double-blind, placebo-controlled studies in patients with OSA/HS (section 5.1) and in two randomised, double-blind, placebo-controlled, multicentre studies in patients with SWSD (section 5.2) [see sections 4.1 and 4.2 for further study details]. One of the SWSD studies is available as an abstract and did not report statistical analyses.

5.1 In Patients with OSA/HS

Modafinil was generally well tolerated in patients with OSA/HS using nCPAP. Adverse events were mostly of mild-to-moderate severity. With modafinil, the most commonly reported adverse events (i.e. occurring in ≥5% of patients) were headache, infection, nausea, anxiety, accidental injury, diarrhoea, hypertension, nervousness, dizziness, insomnia, rhinitis and dry mouth (table IV). In the parallel-group studies, headache, nausea and nervousness occurred significantly more frequently in modafinil than in placebo recipients (table IV).

In the crossover study, the overall incidence of adverse events was significantly higher with modafinil than with placebo (74% vs 45%; p = 0.04), although there were no significant between-treatment differences in the incidence of the most commonly reported adverse events (table IV).
Table IV. Incidence of adverse events in patients with obstructive sleep apnoea/hypopnoea syndrome who received modafinil (MOD).

Results of three randomised, double-blind studies of parallel-group\cite{53,73} or crossover\cite{52} design. Treatment duration was 2,\cite{52} 4\cite{53} or 12\cite{73} weeks.

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Black and Hirshkowitz\cite{73}</th>
<th>Pack et al.\cite{53}</th>
<th>Kingshott et al.\cite{52}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MOD 200mg (n = 103)</td>
<td>MOD 400mg (n = 99)</td>
<td>PL (n = 103)</td>
</tr>
<tr>
<td>Headache</td>
<td>23 26 13*</td>
<td>23 11*</td>
<td>16 16</td>
</tr>
<tr>
<td>Infection</td>
<td>19 10 22</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10 10 22</td>
<td>6 4</td>
<td>16 0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 8 2</td>
<td>6 1</td>
<td></td>
</tr>
<tr>
<td>Accidental injury</td>
<td>8 5 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>8 5 8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 8 2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervousness</td>
<td>6 6 2</td>
<td>12 3*</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>6 5 3</td>
<td>6 3</td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>7 4 1</td>
<td>5 1</td>
<td></td>
</tr>
<tr>
<td>Rhinitis</td>
<td>6 5 8</td>
<td>8 3</td>
<td></td>
</tr>
<tr>
<td>Dry mouth</td>
<td></td>
<td></td>
<td>10 0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>% of patients</th>
<th>MOD 400mg (n = 77)</th>
<th>PL (n = 80)</th>
<th>MOD 400mg (n = 31)b</th>
<th>PL (n = 31)b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>23 11*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>19 10</td>
<td>6 4</td>
<td>16 0</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>10 22</td>
<td>6 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anxiety</td>
<td>6 2</td>
<td>6 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accident injury</td>
<td>8 8</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Diarrhoea</td>
<td>8 8</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>4 2</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nervousness</td>
<td>6 2</td>
<td>12 3*</td>
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<tr>
<td>Dizziness</td>
<td>6 3</td>
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<tr>
<td>Insomnia</td>
<td>7 1</td>
<td>5 1</td>
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<tr>
<td>Rhinitis</td>
<td>6 8</td>
<td>8 3</td>
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</tr>
<tr>
<td>Dry mouth</td>
<td>10 0</td>
<td></td>
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</tr>
</tbody>
</table>

a Adverse events experienced by ≥5% of patients.
b Total no. of patients receiving ≥1 dose of study drug.

do = once daily; PL = placebo; * p < 0.05, ** p = 0.01 vs MOD.

Treatment discontinuation because of adverse events occurred significantly more frequently with modafinil than with placebo in the parallel-group studies (10% [200mg] and 11% [400mg] vs 3%; p < 0.05\cite{73} and 10% vs 1%; p = 0.016\cite{53}) but not in the crossover study (3% vs 0%).\cite{52}

Serious adverse events, none of which were considered related to the study drug, occurred in four modafinil recipients (cellulitis, hernia, accidental overdose of methanol de-icer, vomiting) in the 12-week parallel-group study\cite{73} and in one modafinil recipient (chest pain) in the 4-week parallel-group study;\cite{53} no serious adverse events were reported in the crossover study.\cite{52}

No clinically meaningful differences between modafinil and placebo administration were observed with regards to laboratory parameters, physical examination findings, ECG recordings or vital signs (see also section 2.4).\cite{52,53,73}

In a 12-month extension study, the most commonly reported treatment-emergent adverse events in modafinil 200–400 mg/day recipients included infection, nervousness, headache, accidental injury, sinusitis, rhinitis, depression, anxiety, insomnia and dizziness (5–11% of patients).\cite{75}

5.2 In Patients with SWSD

Modafinil was generally well tolerated in patients with SWSD.\cite{77,78} Adverse events were generally of mild-to-moderate severity.\cite{77,78}

The most commonly reported treatment-emergent adverse events (i.e. occurring in ≥5% of patients in either treatment arm) in modafinil and placebo recipients included headache (26% vs 19%), nausea (9% vs 3%), infection (6% vs 10%), accidental injury (6% vs 8%), abdominal pain (6% vs 2%), nervousness (6% vs <1%), insomnia (6% vs 0%), dry mouth (5% vs 4%), tooth disorder (5% vs <1%) and rhinitis (3% vs 6%).\cite{77} Only insomnia occurred in significantly more modafinil than placebo recipients (p = 0.01). No serious adverse events occurred in modafinil recipients.

In the study available as an abstract, modafinil 200 and 300 mg/day and placebo recipients reported headache (17%, 26% and 16%), nausea (6%, 19% and 5%) and nervousness (3%, 10% and 2%).\cite{78}

No clinically meaningful differences between modafinil and placebo recipients were seen with regards to laboratory parameters, physical examination findings, ECG recordings or vital signs.\cite{77,78}
Modafinil was generally well tolerated in 12-month extension studies in patients with SWSD; the most commonly reported adverse events included headache, infection and pain (11–19% of patients).[79,80]

6. Dosage and Administration

In the US and certain European countries, modafinil is indicated to improve wakefulness in patients who have excessive sleepiness associated with OSA/HS or SWSD, in addition to its original indication in patients with excessive sleepiness associated with narcolepsy.[14,62] Modafinil should be used as an adjunct to standard treatment (e.g., nCPAP) in patients with OSA/HS.[14,62] In the US and the EU, the recommended modafinil dosage is 200mg once daily in OSA/HS (although in the EU it may be titrated to 400mg/day if necessary).[14,62] The recommended modafinil dosage is 200mg once daily in SWSD (taken 1 hour prior to the work shift) in both the US and the EU.[4,62]

Local prescribing information should be consulted for contraindications, warnings and precautions related to modafinil use, for specific dosage recommendations in special patient populations and for information about drug interactions.

7. Place of Modafinil in the Management of Excessive Sleepiness Associated With OSA/HS and SWSD

Excessive sleepiness is a symptom associated with various disorders.[81,82] In patients reporting excessive sleepiness, the underlying cause should be established and sleep hygiene evaluated. For some conditions (e.g., OSA/HS) there are specific measures that can be taken to ameliorate excessive sleepiness.[81,82]

The prevalence of sleep apnoea syndrome was estimated to be 2% among middle-aged women and 4% among middle-aged men in a US study.[83] Excessive sleepiness is one of the symptoms of OSA/HS; the disorder has been linked to hypertension and other cardiovascular morbidities, as well as impaired cognitive function and HR-QOL.[84] Patients with OSA/HS also appear to have an increased risk of sudden death due to cardiac causes during the sleeping hours.[85] OSA/HS has also been linked to an increased risk of motor vehicle and occupational accidents.[84]

The treatment of choice in OSA/HS is nCPAP.[86] As well as eliminating apnoea, this therapy is associated with improvements in sleepiness and cognitive function, as well as improvements in BP.[86] However, some patients with OSA/HS who are receiving nCPAP therapy experience residual excessive sleepiness.[53] Optimising nCPAP use is the first-line treatment strategy in such patients and other treatment options (e.g., oral appliances) may be of benefit.[73,87] Modafinil is a treatment option, in addition to nCPAP, in patients for whom residual excessive sleepiness remains an issue, despite these measures.

In patients with residual excessive sleepiness associated with OSA/HS who were receiving nCPAP, modafinil was associated with significantly greater improvements in subjective and objective measures of wakefulness in two parallel-group studies (section 4.1.1).[53,73] Results were less consistent in a smaller crossover study, with a significant improvement in the MWT sleep-onset latency with modafinil versus placebo, but no significant between-treatment difference in ESS scores or MSLT sleep-onset latency (section 4.1.1).[52] Possible reasons for the discrepancy in results between the parallel-group and crossover studies include a lack of statistical power and a short treatment duration in the crossover study.[52]

In patients with OSA/HS, clinical improvement occurred in significantly more modafinil than placebo recipients[53,73] and modafinil did not have detrimental effects on night-time sleep (section 4.1.2).[52,53,73] In addition, aspects of functional status and HR-QOL improved to a significantly greater extent with modafinil than with placebo in the parallel-group studies,[73,74] but not in the crossover study[52] (section 4.1.3). It should be noted that only one[73] of these three trials included a study arm evaluating modafinil 200mg once daily, the dosage approved in the US for use in OSA/HS (section 6).

Concerns have been raised that the improvement in wakefulness experienced by patients with OSA/HS...
HS who receive modafinil may lead them to reduce their use of nCPAP.\textsuperscript{[88,89]} No reduction in nCPAP use occurred in modafinil recipients in the two parallel-group studies,\textsuperscript{[53,73]} although a statistically significant reduction in nCPAP use was seen in modafinil recipients in the smaller, crossover trial\textsuperscript{[52]} (section 4.1.2). It has been suggested that the small reduction in nCPAP use observed with modafinil was not of clinical significance,\textsuperscript{[53]} although the lower nCPAP use seen in modafinil recipients may have reduced the likelihood of finding improvements in efficacy outcomes (i.e. ESS scores and MSLT sleep-onset latency) with the drug.\textsuperscript{[52]}

As mentioned previously, all appropriate measures should be taken to ensure that patients with OSA/HS are making optimal use of nCPAP before modafinil therapy is started.\textsuperscript{[73,87]} In patients receiving modafinil in conjunction with nCPAP, nCPAP use should be encouraged and compliance with nCPAP therapy should be regularly assessed.\textsuperscript{[4]} The potential role of modafinil in patients with OSA/HS who do not tolerate nCPAP and are refractory to other treatment options is an area for future study.\textsuperscript{[87]}

The results of a 12-month noncomparative extension study indicate that modafinil maintains its wake-promoting effect over the longer term (section 4.1.1),\textsuperscript{[75]} although there is a need for more long-term data on the use of the drug in OSA/HS, particularly concerning any possible effect on nCPAP use.

Circadian rhythm disorders affected almost 25% of night-shift workers in a US/French study\textsuperscript{[90]} and there are almost 6 million full-time workers in the US who work night-shifts on a regular or rotating basis.\textsuperscript{[91]} Night-shift workers have a 6- to 14-fold greater risk of experiencing severe sleepiness than day workers.\textsuperscript{[92]} Moreover, excessive sleepiness in shift workers is associated with numerous deleterious consequences, including an increased risk of errors and accidents.\textsuperscript{[93,94]}

Various strategies to ameliorate the adverse consequences of shift work have been evaluated in night-shift workers including bright light therapy\textsuperscript{[95-97]} and administration of caffeine,\textsuperscript{[98,99]} benzodiazepines,\textsuperscript{[100,101]} metamfetamine\textsuperscript{[102]} and melatonin,\textsuperscript{[103-105]} as well as strategic napping during the night-shift.\textsuperscript{[106]} Whereas some of these modalities (e.g. bright light therapy) have been shown to be beneficial, others (e.g. melatonin) have yielded inconclusive results.

Compared with placebo, modafinil significantly improved subjective and objective measures of wakefulness in patients with SWSD (although patients remained markedly sleepy according to the MSLT), as well as having no adverse impact on daytime sleep (section 4.2.1).\textsuperscript{[77]} Modafinil also improved aspects of functional status and HR-QOL to a significantly greater extent than placebo (section 4.2.2).\textsuperscript{[78]}

While studies to date have demonstrated the efficacy of modafinil in improving wakefulness in patients with excessive sleepiness associated with OSA/HS and SWSD, it would be of interest to establish if the drug also reduces adverse outcomes associated with these disorders (for example, reducing the incidence of motor vehicle accidents in patients with OSA/HS and the incidence of job errors and/or accidents in patients with SWSD).

Modafinil is currently the only wake-promoting drug approved for use in the US in excessive sleepiness associated with OSA/HS and SWSD.\textsuperscript{[107]} Although amfetamines have also been shown to improve daytime sleepiness in patients with OSA/HS,\textsuperscript{[108]} these agents are associated with the drawbacks of abuse potential and cardiovascular adverse effects.\textsuperscript{[109]} Methylphenidate has a long record of clinical efficacy in treating excessive sleepiness, although there is a lack of data from large well designed trials.\textsuperscript{[107]} The development of tolerance is also an issue with the use of amfetamines or methylphenidate.\textsuperscript{[107]} Pemoline was shown to improve alertness during a night shift in a small trial;\textsuperscript{[110]} however, the use of this drug is contraindicated in the US because of the risk of hepatotoxicity.\textsuperscript{[107]}

Although the exact mechanism by which modafinil exerts its wake-promoting effect is unclear, it appears to have a different mechanism of action from that of other CNS stimulants such as amfetamine, dexamfetamine and methylphenidate (section 2.1). Moreover, it seems to have a much
lower abuse potential than these other stimulants (section 2.4).

Modafinil is generally well tolerated in the short-term in patients with OSA/HS and SWSD (section 5). In addition, preliminary data from 12-month extension studies indicate that the good tolerability of modafinil is maintained over the longer term in OSA/HS and SWSD (sections 5.1 and 5.2), although there is a need for additional long-term data. Modafinil has been shown to be generally well tolerated over the longer term in patients with narcolepsy (mean duration of treatment 22.4 months [range 1–114 months]). Trial data indicate that overdoses of modafinil (up to 4500mg) were not associated with unexpected or life-threatening events. In addition, no fatal outcomes associated with overdoses of modafinil alone (up to 12g) have been reported during postmarketing surveillance, although fatal outcomes have been associated with overdoses involving multiple drugs (including modafinil).

Modafinil may also have potential in other disorders which may produce excessive sleepiness (e.g. restless legs syndrome, disrupted sleep due to medical causes such as pain); however, well designed trials evaluating the drug in these conditions are needed.

In conclusion, oral modafinil promotes wakefulness in patients with OSA/HS and SWSD. It is an effective adjunctive therapy in patients with residual excessive sleepiness associated with OSA/HS who are receiving nCPAP. In SWSD, the drug improves night-time wakefulness without disrupting daytime sleep. Modafinil is generally well tolerated in patients with OSA/HS or SWSD and has a low abuse potential. Thus, modafinil is a valuable new treatment option for use in patients with excessive sleepiness associated with OSA/HS (as an adjunct to nCPAP) or SWSD.

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