

Approved and Investigational Uses of Modafinil

An Evidence-Based Review

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Abstract

Modafinil is a wake-promoting agent that is pharmacologically different from other stimulants. It has been investigated in healthy volunteers, and in individuals with clinical disorders associated with excessive sleepiness, fatigue, impaired cognition and other symptoms. This review examines the use of modafinil in clinical practice based on the results of randomized, double-blind, placebo-controlled clinical trials available in the English language in the MEDLINE database. In sleep-deprived individuals, modafinil improves mood, fatigue, sleepiness and cognition to a similar extent as caffeine but has a longer duration of action. Evidence for improved cognition in non-sleep-deprived healthy volunteers is controversial.

Modafinil improves excessive sleepiness and illness severity in all three disorders for which it has been approved by the US FDA, i.e. narcolepsy, shift-work sleep disorder and obstructive sleep apnoea with residual excessive sleepiness despite optimal use of continuous positive airway pressure (CPAP). However, its effects on safety on the job and on morbidities associated with these disorders have not been ascertained. Continued use of CPAP in obstructive sleep apnoea is essential. Modafinil does not benefit cataplexy.

In very small, short-term trials, modafinil improved excessive sleepiness in patients with myotonic dystrophy. It was efficacious in fairly large studies of attention deficit hyperactivity disorder (ADHD) in children and adolescents, and was as efficacious as methylphenidate in a small trial, but has not been approved by the FDA, in part because of its serious dermatological toxicity. In a trial of 21 non-concurrent subjects, with 2-week treatment periods, modafinil was as effective as dexamfetamine in adult ADHD. Modafinil was helpful for depressive symptoms in bipolar disorder in a trial that excluded patients with stimulant-

induced mania. A single dose of modafinil may hasten recovery from general anaesthesia after day surgery. A single dose of modafinil improved the ability of emergency room physicians to attend didactic lectures after a night shift, but did not improve their ability to drive home and caused sleep disturbances subsequently.

Modafinil had a substantial placebo effect on outcomes such as fatigue, excessive sleepiness and depression in patients with traumatic brain injury, major depressive disorder, schizophrenia, post-polio fatigue and multiple sclerosis; however, it did not provide any benefit greater than placebo.

Trials of modafinil for excessive sleepiness in Parkinson's disease, cocaine addiction and cognition in chronic fatigue syndrome provided inconsistent results; all studies had extremely small sample sizes. Modafinil cannot be recommended for these conditions until definitive data become available.

Modafinil induces and inhibits several cytochrome P450 isoenzymes and has the potential for interacting with drugs from all classes. The modafinil dose should be reduced in the elderly and in patients with hepatic disease. Caution is needed in patients with severe renal insufficiency because of substantial increases in levels of modafinil acid. Common adverse events with modafinil include insomnia, headache, nausea, nervousness and hypertension. Decreased appetite, weight loss and serious dermatological have been reported with greater frequency in children and adolescents, probably due to the higher doses (based on bodyweight) used. Modafinil may have some abuse/addictive potential although no cases have been reported to date.

Excessive daytime sleepiness (EDS) is a pervasive problem, with prevalence rates of 20–43%.^[1,2] The common causes of EDS include: (i) inadequate quantity of sleep as a result of social and/or work-related factors; (ii) poor sleep hygiene; (iii) fragmentation of sleep due to general medical diseases that disrupt sleep as a result of pain or disordered breathing, e.g. obstructive sleep apnoea (OSA); (iv) misalignment of the body's circadian pacemaker with the environment, e.g. shift-work sleep disorder (SWSD); (v) CNS disorders such as narcolepsy, Parkinson's disease, multiple sclerosis (MS) and myotonic dystrophy; (vi) psychiatric disorders such as major depressive disorder; and (vii) drugs that increase sleepiness as a therapeutic or side effect, such as general anaesthetics.

Sleep deprivation can take a heavy toll at both personal and societal levels. On a personal level, patients with sleep deprivation experience EDS, impaired cognitive and motor functioning, poor mood (including symptoms of depression, anxiety and irri-

tability), low energy and decreased libido. All of these can lead to decreased competence at school and work, difficult personal relationships and impaired quality of life (QOL).^[3-5]

At a societal level, sleepiness is an important cause of motor vehicle accidents. According to a US National Highway Traffic Safety Administration report, approximately 0.7% of drivers (an estimated 1.35 million drivers) were involved in motor vehicle accidents attributed to drowsiness over a 5-year period.^[6] It has been estimated that while driving, 30–93% of patients with OSA have fallen asleep and 31–93% have had accidents, whereas 40–48% patients with narcolepsy have fallen asleep and 25% have had accidents.^[7]

Modafinil is a unique oral agent that promotes wakefulness. It has been approved by the US FDA to improve wakefulness in patients with EDS associated with narcolepsy, residual EDS in OSA despite optimal treatment with continuous positive

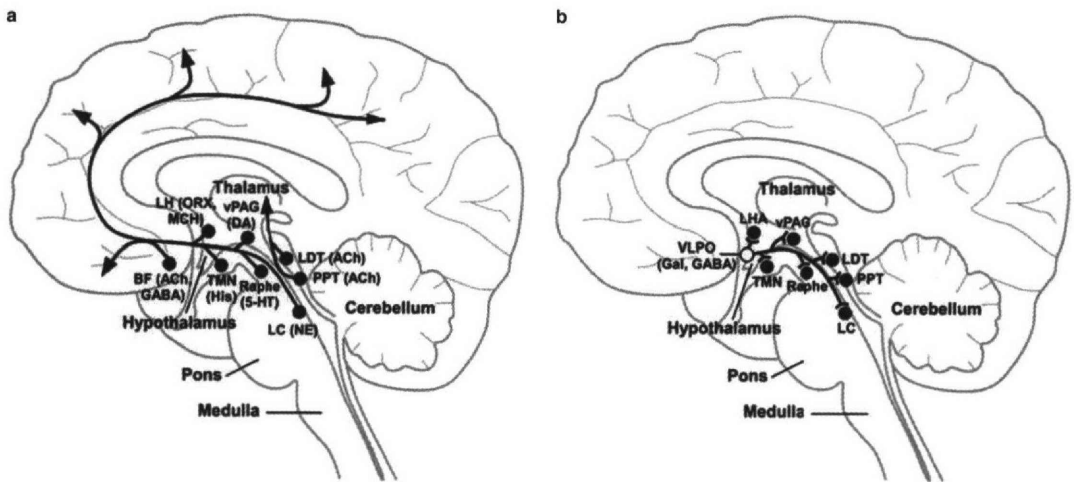


Fig. 1. (a) The ascending arousal system consists of noradrenergic (NE) neurons of the locus coeruleus (LC), cholinergic neurons in the pedunculopontine and laterodorsal tegmental (PPT/LDT) nuclei, serotonergic (5-HT) neurons in the dorsal raphe nucleus, dopaminergic (DA) neurons of the ventral periaqueductal grey matter (vPAG) and histaminergic (His) neurons of the tuberomammillary nucleus (TMN). These systems produce cortical arousal via two pathways: a dorsal route through the thalamus and a ventral route through the hypothalamus and basal forebrain (BF). The latter pathway receives contributions from the orexin (ORX) and melanin-concentrating hormone (MCH) neurons of the lateral hypothalamic (LH) area as well as from GABAergic or acetylcholinergic (ACh) neurons of the BF. (b) A schematic representation of the projections of the ventrolateral preoptic nucleus (VLPO; open circle) to the main components of the ascending arousal system. The VLPO neurons are primarily active during sleep and contain the inhibitory transmitters (reproduced from Fuller et al.,^[9] with permission). Gal = galanin.

airway pressure (CPAP), and excessive sleepiness associated with SWSD.

The aim of this article is to provide an evidence-based review for the approved and investigational uses of modafinil. This review discusses the evidence for usefulness of modafinil based on all available randomized, double-blind, placebo-controlled clinical trials, assessing clinically meaningful efficacy measures, published in the English language and available in the MEDLINE database. Initially, a search was conducted by using search terms 'modafinil' and 'randomized controlled trials' limited to 'humans' and the 'English language'. The search was refined by adding the name of individual disorders such as 'obstructive sleep apnea'. Trials measuring endpoints irrelevant to clinical practice such as 'magnetic resonance imaging' were excluded. Furthermore, case reports, non-randomized, retrospective and open-label studies were not included because of their inherent biases. The last search was performed on 5 July 2008.

1. Pharmacodynamic Properties

The pharmacodynamic properties of modafinil are complex and are described here as they relate to the normal sleep-wake cycle.

1.1 The Normal Sleep-Wake Cycle

The normal sleep-wake cycle is controlled by the sleep- and wake-promoting areas of the brain and the sleep-awake switch; it is regulated by the circadian and homeostatic drives. Many neurotransmitters are involved in this process. This subject has recently been reviewed by Saper et al.^[8] and Fuller et al.,^[9] and is briefly presented here.

1.1.1 The Wake-Promoting Areas

The wake-promoting activity classically described as the 'ascending arousal system' is mediated by distinct neuronal pathways originating in the upper brain stem (figure 1). These pathways activate the cortex via a dorsal route through the thalamus and a ventral route through the hypothalamus and

the basal forebrain (BF). The wake-promoting activity is mediated by multiple neurotransmitters including acetylcholine, noradrenaline (norepinephrine), dopamine, histamine, serotonin and orexin.

The dorsal pathway originates in the cholinergic neurons of the pedunclopontine (PPT) and laterodorsal tegmental (LDT) nuclei located in the dorsal mid-brain and pons, which send projections to the thalamus, specifically to the intralaminar nuclei, the thalamic-relay nuclei and reticular nucleus. The reticular nucleus acts as a gating mechanism and regulates transmission between the thalamic-relay nuclei and the cerebral cortex.

The ventral pathway originates from a group of monoaminergic neurons including: the noradrenergic locus coeruleus (LC), the dopaminergic ventral peri-aqueductal grey matter, the serotonergic dorsal and medial raphe nuclei (DR) and the histaminergic tuberomammillary nucleus (TMN). These neurons send projections to the lateral hypothalamus (LH), the BF and also directly to the cortex. This pathway also receives input from orexin-containing and melatonin-concentrating hormone (MCH) containing neurons of the LH and from cholinergic and GABAergic neurons of the BF. The LH, in turn, sends projections to the cortex, the BF and, reciprocally, to the ascending arousal system.

The cholinergic, the monoaminergic and the orexin neuronal pathways act in collaboration to produce arousal. The monoaminergic neurons fire fastest during wakefulness, decelerate during non-rapid-eye-movement sleep (NREMS) and virtually stop firing during rapid-eye-movement sleep (REMS); orexin neurons amplify the firing rate of TMN, LC and DR during wakefulness, while MCH neurons inhibit the monoaminergic system during REMS. The PPT/LDT and the BF neurons fire rapidly during wakefulness and become less active as the individual goes to sleep but paradoxically fire rapidly again during REMS. Thus, the differences in the firing patterns of the cholinergic and monoaminergic nuclei, in part, regulate the REMS and NREMS states.

1.1.2 The Sleep-Promoting Areas

Sleep is promoted by relatively few neurons of the ventrolateral preoptic (VLPO) area. These neurons contain the neurotransmitters GABA and galanin, which inhibit arousal and thus promote sleep. The VLPO area sends signals to and receives input from each of the arousal regions; these signals are mutually inhibitory. During sleep, the neurons of the VLPO area are active and inhibit the arousal systems, thus disinhibiting and augmenting their own firing; the reverse happens during wakefulness.

1.1.3 The Sleep/Awake Switch

Because of their reciprocal relationship, the arousal and the sleep promoting circuits work as a 'flip-flop' switch, which allows one to fall asleep or awaken without prolonged transition periods. Mathematical modelling shows that when either side of the circuit is damaged, the switch operates closer to the conversion point and leads to abrupt and unintended transitions. Strengthening of either side of this circuit fortifies the whole switch. It is postulated that the orexin neurons, by reinforcing the monoaminergic arousal arm of the circuit, hold the switch in the arousal position during wakefulness and thus stabilize the switch. This is borne out by the fact that patients with narcolepsy, who have low levels of orexin, maintain both the awake and sleep states poorly and experience abrupt and unintended transitions.

1.1.4 Regulation of Sleep

The homeostatic and circadian drives regulate sleep: the homeostatic drive for sleep builds during wakefulness and is depleted by sleep. The cellular basis of this drive is unclear.

The circadian drive of the sleep-wake cycle is regulated by the supra-chiasmatic nucleus (SCN), which is entrained to a 24-hour cycle. This rhythm is mediated by an initial projection from the SCN to the ventral sub-paraventricular zone followed by a secondary projection to the dorsomedial nucleus of the thalamus (DMH); the DMH has major inputs to the VLPO area and to the orexin and MCH neurons in LH that probably regulate the circadian sleep-wake cycle. The homeostatic and circadian drives

can be overridden by cognitive, emotional, social and other cues.

1.2 Mechanism of Action of Modafinil

The exact mechanism of action of modafinil is unclear. Its neurochemical effects have been reviewed recently.^[10] Briefly, in animal studies, modafinil has been shown to interact with dopaminergic, noradrenergic, glutamatergic, GABAergic, serotonergic, orexinergic, and histaminergic pathways.

1.2.1 Effects of Modafinil on the Dopaminergic Pathways

The evidence regarding modafinil and dopaminergic pathway interactions is contradictory. Initial studies showed modafinil had only a weak affinity for dopamine receptors;^[11] it did not stimulate release of dopamine in the mouse caudate nucleus,^[12] or mouse synaptosome preparations preloaded with [³H]dopamine,^[13] and it did not affect the firing rate of the dopaminergic neurons in the rat midbrain.^[14] Various dopamine D₁ and D₂ receptor antagonists did not suppress the modafinil-induced hyperactivity in mice,^[13,15] the modafinil-induced arousal in cats^[16] or the modafinil-induced reduction in stop-signal reaction time in rats.^[17] Furthermore, inhibition of dopamine synthesis did not decrease the hyperactivity associated with modafinil in mice^[13,15] and only slightly reduced the arousal effects of modafinil in cats.^[16]

However, more recent studies show that modafinil administration in different doses and routes leads to increased extracellular levels of dopamine in the rat prefrontal cortex,^[18] the narcoleptic dog caudate nucleus,^[19] rat nucleus accumbens,^[20] and rat striatal slices preloaded with [³H]dopamine.^[21] Conversely, modafinil inhibits the dopaminergic neurons in the ventral tegmental area and the substantia nigra; this inhibition is abolished by sulpiride (a D₂-receptor antagonist) and by nomifensine (a dopamine reuptake inhibitor).^[22] In rhesus monkeys, modafinil occupies the striatal dopamine transporter (DAT) and *in vitro* inhibits dopamine transport.^[23] Furthermore, the wake-promoting effects of modafinil are lost in DAT knockout mice.^[19] Thus, contrary to earlier

literature, new evidence is emerging that indicates a role for dopaminergic pathways in the actions of modafinil. Some of the earlier studies may have been negative because relatively lower doses of modafinil were used.

1.2.2 Effects of Modafinil on Noradrenergic Pathways

The evidence for modafinil action being mediated by noradrenergic pathways is also controversial. Modafinil does not bind to adrenergic receptors at physiological doses,^[11] it does not affect the firing rate of the rat pontine noradrenergic neurons^[14] and it does little to reduce cataplexy that normally responds to α_1 -receptor agonists or to agents that block the reuptake of noradrenaline (norepinephrine) by noradrenaline transporter (NAT).^[24,25]

On the other hand, modafinil use leads to increased levels of noradrenaline in the rat prefrontal cortex and medial hypothalamus.^[18] In rat brain slices, modafinil increases the inhibitory effects of noradrenaline on VLPO neurons.^[26] Various α -adrenoceptor antagonists attenuate the modafinil-induced arousal in cats,^[16] and locomotor activity in mice^[15,27] and monkeys.^[15] The modafinil response is significantly reduced in genetically α_{1B} -adrenoceptor-deficient mice.^[27] Furthermore, modafinil occupies NAT sites in the thalamus of rhesus monkeys *in vivo* and blocks noradrenaline transport via NAT *in vitro*.^[23]

Thus, it appears that noradrenergic pathways are also important for the action of modafinil.

1.2.3 Interactions of Modafinil, Dopaminergic and Adrenergic Signalling

The action of modafinil is not blocked in mice treated with N-(2-chloroethyl)-N-ethyl 2-bromobenzylamine, a toxin that destroys all NAT-bearing forebrain noradrenergic projections, suggesting that forebrain NAT is not important in the action of modafinil. However, pretreatment with quinpirole (a dopamine autoreceptor agonist which suppresses dopamine release) or terazosin (an α -adrenoceptor antagonist) blocked the action of modafinil in these mice. This suggests that non-noradrenergic, dopamine-dependent adrenergic stimulation is essential

for action of modafinil and implies that dopamine may directly stimulate adrenergic receptors.^[28]

1.2.4 Effects of Modafinil on GABAergic, Glutamatergic and Serotonergic Pathways

Ferraro et al.^[29-31] have conducted several studies looking at GABA and/or glutamate levels in various areas of the brain in response to modafinil. In general, the two neurotransmitters have an inverse relationship. With modafinil administration, levels of the activating neurotransmitter glutamate are increased in the thalamus, hippocampus,^[29] striatum,^[30] medial pre-optic area (MPA) and the posterior hypothalamus^[31,32] of the rat brain. The GABA_A-receptor agonist muscimol decreased, whereas the GABA_A-receptor antagonist bicuculline augmented the levels of glutamate in the posterior hypothalamus and MPA; thus, it appears that the glutamate levels in these areas increase when the inhibitory GABAergic tone decreases and glutamate levels decrease when GABAergic tone increases.^[32]

GABA levels decrease with modafinil in the guinea-pig^[33-35] and rat cortex,^[34] the rat MPA and posterior hypothalamus,^[31,32] hippocampus,^[29] nucleus accumbens,^[36,37] striatum, globus pallidus and substantia nigra.^[30] The effects of modafinil on GABA and glutamate levels may be region specific. An intact catecholamine system is important for these changes because pretreatment with dopaminergic neurotoxin and an α_1 -adrenoceptor antagonist reversed the modafinil effects on GABA.^[34,35]

Serotonin and GABA also seem to have an inverse relationship. In many brain areas, including the frontal cortex, central nucleus of amygdala, DR, MPA and posterior hypothalamus, modafinil decreases levels of GABA, but increases levels of serotonin.^[18,38,39] Moreover, the effects of modafinil on GABA release are abolished by serotonergic inhibitors^[31,33] and serotonin selective neurotoxins.^[35] Serotonin reuptake inhibitors (SRIs) enhance the effect of modafinil on serotonin levels.^[38,40]

Thus, modafinil seems to lower the levels of the inhibitory neurotransmitter GABA, and increase glutamate and serotonin levels in several areas of the brain; intact catecholamine and serotonin systems are essential for effects on GABA.

1.2.5 Effects of Modafinil on Orexinergic Pathways

Modafinil also interacts with orexin neurons in the brain; patients with narcolepsy deficient in orexin benefit from modafinil.^[41] Also, modafinil activates rat orexin neurons.^[42,43] However, modafinil is more effective in producing wakefulness in orexin knockout mice than in wild-type litter mates.^[44] Therefore, the interactions of modafinil with orexin neurons seem complicated and unclear at present.

1.2.6 Effects of Modafinil on Histaminergic Pathways

Modafinil increases Fos immunoreactivity in the histaminergic TMN,^[43] and histamine levels in the anterior hypothalamus in rats are increased with intraperitoneal and intracerebroventricular injections of modafinil, although direct injection into the TMN does not produce this effect.^[45,46] The locomotor activity of rats is also increased with intraperitoneal administration of modafinil, which is reversed with depletion of neuronal histamine in mice.^[46] Therefore, histamine seems to be important for the locomotion effects of modafinil.

1.2.7 Summary

In summary, modafinil actions seem to be related to decreased GABA and increased glutamate levels; intact catecholamine (including dopamine) and serotonin systems are essential for modafinil effects on GABA. Histaminergic and adrenergic systems seem to be important for modafinil effects on locomotion. Effects of modafinil on orexin seem complicated and controversial at present.

1.3 Effects of Modafinil on Wakefulness in Experimental Models

Modafinil has been shown to cause wakefulness in multiple animal models, such as the Rhesus monkey,^[47] cats,^[26] narcoleptic dogs,^[48] Sprague-Dawley and Wistar rats,^[49,50] English bull dogs (a natural model of sleep-disordered breathing)^[51] and sleep-deprived cats.^[52] In contrast with amphetamine, the wakefulness induced by modafinil is not accompanied by behavioural excitation^[26,47,52] or rebound hypersomnolence.^[49,50,52]

1.4 Effects of Modafinil in Healthy Volunteers

Effects of modafinil have been studied in healthy volunteers under differing conditions.

1.4.1 Effects in Non-Sleep-Deprived Subjects

Several randomized, double-blind studies have investigated the effect of modafinil (in doses of 100 mg, 200 mg or 4 mg/kg) on cognition in non-sleep-deprived, healthy young and elderly volunteers with conflicting results. Some studies found improved cognition,^[53-56] while others did not.^[57-59] One study had 20 subjects in each arm and involved 30 separate endpoints.^[53] It is likely that some of the positive findings in this study may be due to chance alone (type I error). It was also postulated that the conflicting conclusions of the studies may have been due to use of different tests, dissimilar test orders, and disparate lengths of testing (some of which might have led to test fatigue) or small sample sizes. As a result, a study with a larger sample size was conducted,^[59] which included some of the tests used by an earlier study.^[53] The authors concluded that the results did not vary because of test order or test fatigue. However, modafinil was found to improve performance on very specific and somewhat simple tasks. In a more recent trial, modafinil increased ratings on several measures of wakefulness and enhanced performance on cognitive tasks to the same extent as dexamfetamine.^[56] In another trial, modafinil augmented positive affect (evidenced by increased ratings on adjectives measuring positive affect such as 'energized', 'quick-witted', 'over-alert' and 'concentrated'), as well as negative affect (evidenced by decreased ratings on the adjective 'calm'). However, some of these results may have occurred by chance alone because the study had only 12 subjects and the two instruments used to assess mood collectively had 30 test adjectives.^[60] Overall, the evidence that modafinil increases cognition in non-sleep-deprived healthy individuals is controversial.

1.4.2 Effects in Sleep-Deprived Individuals

Multiple studies have compared the effects of modafinil versus those of placebo and caffeine in sleep-deprived healthy volunteers.^[61-68] The dose of

modafinil varied from a single dose of 100 mg just prior to testing to 200 mg three times a day. The duration of sleep deprivation varied from 2.5^[67] to 85 hours.^[66] Compared with placebo, modafinil led to improved subjective measures such as mood and fatigue,^[62] sleepiness,^[62,64,66] vigilance,^[68] and improved objective measures such as reaction times,^[62,64,66] logical reasoning and short-term memory,^[62] vigilance,^[61,64,66,67] and the maintenance of wakefulness test (MWT).^[64,66,67] Compared with placebo, modafinil also attenuated several measures of cognitive impairment associated with sleep deprivation.^[63,64,66] However, the effects of modafinil 400 mg were similar to those of caffeine 600 mg.^[64,66] Beneficial effects of both modafinil and caffeine were especially prominent during the circadian nadir (6:00am through to 10:00am).^[65] The duration of action was longer with modafinil, which is likely to be due its longer half-life ($t_{1/2}$) [the $t_{1/2}$ of caffeine and modafinil are 4–6 hours and 14–17 hours, respectively]. No adverse effects on recovery sleep were noted with modafinil.^[66] Thus, in healthy sleep-deprived subjects, modafinil improved mood, fatigue, sleepiness and cognitive functioning. However, the effects of modafinil 400 mg were similar to those of caffeine 600 mg, but the duration of action of modafinil was longer due to its longer $t_{1/2}$.

1.4.3 Effects in Simulated Night Shifts

In a study of four consecutive simulated night shifts, modafinil 200 mg improved alertness as measured by MWT, vigilance and some but not all executive-function tasks compared with placebo. There were no consistent differences in subjective measures of sleepiness between the two groups. Total sleep time during the day was also not different in the two groups.^[69]

1.4.4 Effects in Simulated Rotating Shifts

In a study of simulated rotating shifts, subjects on placebo had greater impairments in cognition and mood on the night shifts compared with the day shifts. Modafinil, in doses of 200 and 400 mg given 1 hour after waking, ameliorated the cognitive, psychomotor and mood impairments seen on night shifts in a dose-related manner. Modafinil also im-

proved performance during the day shift, but to a lesser extent. Modafinil 400 mg caused significant sleep disturbances (increased sleep onset latency [SOL] and decreased sleep time and sleep efficiency) following day shifts.^[70]

1.4.5 Other Effects

In two double-blind, placebo-controlled studies involving ten young healthy volunteers (mean age 30 years) and ten healthy elderly volunteers (mean age 68 years), modafinil 100 or 200 mg given before bed time did not affect sleep initiation, quality or architecture, or sense of well-being in the morning compared with placebo.^[71,72] No effect was seen in the pulse rate, or evening and morning blood pressure (BP) in these two studies.

However, other studies in non-sleep-deprived subjects have reported increases in diastolic and/or systolic BP and pulse rate with modafinil treatment.^[53,55,58] Therefore, modafinil should be used with caution in patients with hypertension and/or heart disease. BP should be monitored in normotensive individuals receiving modafinil therapy.

2. Pharmacokinetics of Modafinil

The pharmacokinetic profile of modafinil has recently been reviewed,^[73] and is briefly discussed here. Modafinil is a crystalline solid racemic compound with two enantiomers, l-modafinil and d-modafinil, which are pharmacologically equipotent but have different pharmacokinetics. The molecular formula is $C_{15}H_{15}NO_2S$ and the molecular weight is 273.4 Da.^[73]

Modafinil is somewhat soluble in methanol and acetone but virtually insoluble in water and cyclohexane. Therefore, an intravenous form of the drug is not available and the absolute bioavailability of modafinil is unknown. However, it is estimated that at a minimum, 40–65% of the dose is absorbed and peak plasma concentrations (C_{max}) are reached at 2–3 hours.^[74,75] The presence of food in the gastrointestinal tract may delay the absorption of the drug by 0.5–1 hour but the total amount absorbed is not affected.^[76] The pharmacokinetics of a single dose and multiple doses are similar. The pharmacokinetics of modafinil, l-modafinil and d-modafinil

were studied after multiple doses in 32 male volunteers randomly assigned to receive 200, 400, 600 or 800 mg/day for 7 days.^[74] The 800 mg/day dose was discontinued after 3 days because of the development of intolerable hypertension and tachycardia. Two subjects (one on modafinil 400 mg/day and one on 800 mg/day) had serious adverse events (moderate ECG abnormalities and moderate anxiety/tachycardia, respectively). One subject on modafinil 800 mg/day developed tachycardia (pulse increased from a baseline of 77/98 [supine/standing] to 160/170 beats/min) and an increase in BP from a baseline supine BP of 125/89 mmHg and standing BP of 122/91 mmHg to 160/115 mmHg; the BP and pulse rate returned to normal 2 days after stopping the drug. Some increase in BP and pulse rate was observed at one or more assessments with all modafinil doses.^[74]

The C_{max} , area under the plasma concentration-time curve from time zero to infinity (AUC_{∞}) and the area under the plasma concentration-time curve for one dose administration interval (AUC_{0-t}) for modafinil and its enantiomers are dose dependent. The time to C_{max} (t_{max}) for modafinil, d-modafinil and l-modafinil is similar at 1.7–2.7, 1.8–2.5 and 2.0–2.9 hours, respectively. The C_{max} for the two enantiomers was also similar, indicating similar absorption of the two compounds. The $t_{1/2}$ of d-modafinil and l-modafinil is around 4–5 hours and 13–16 hours, respectively. Therefore, the moderately long $t_{1/2}$ of modafinil (14–17 hours) is due primarily to the kinetics of its l-enantiomer. Trough plasma concentration reached a steady state within 4 days for all dose levels given for 7 days. By comparing results at days 1 and 7 the accumulation factor is approximately 1.5. As a result of its short $t_{1/2}$, the d-enantiomer reached steady state on day 1, whereas it took several days for the l-enantiomer to reach steady state. At steady state, l-modafinil constitutes 90% of the trough concentrations of modafinil.

The approximate volume of distribution (V_d) of modafinil is 0.8 L/kg, which is larger than total body water, suggesting that it is able to penetrate into tissues. In the blood, approximately 60% is bound to plasma proteins, mainly to albumin.^[77] The approxi-

mate Vd for both d-modafinil and l-modafinil is 0.5 L/kg. The renal clearance accounted for approximately 5% of the plasma clearance; the liver is the primary site of metabolism, with two principal circulating metabolites – modafinil acid and modafinil sulfone – which are excreted by the kidneys. Cytochrome P450 (CYP) enzyme CYP3A4 is implicated in the generation of modafinil sulfone.^[73]

2.1 Pharmacokinetics in Females and Elderly Males

In a study of pharmacokinetics in young males, young females and elderly males, the pharmacokinetics in females differed as follows: the C_{max} and apparent oral clearance (CL/F) of modafinil were significantly higher than in young males (CL/F was 22% higher); and the $t_{1/2}$ was shorter than in young or elderly males. Since renal clearance was similar in females and young males, the higher CL/F was thought to be because of increased metabolic clearance.^[75] However, these disparities seem to be more related to bodyweight than any real pharmacokinetic differences between the two genders.^[76]

Elderly males had a significantly higher AUC_{∞} and lower CL/F than young males. They also had 20% reduction in clearance of modafinil, d-modafinil and l-modafinil. Since renal clearance did not change with age, the lower CL/F indicates a lower metabolic clearance.^[75]

2.2 Pharmacokinetics in Patients with Renal or Hepatic Impairment

In hepatic insufficiency the absorption of modafinil is delayed, causing a slight increase in t_{max} . The C_{max} and AUC are also increased after acute as well as chronic administration, the C_{max} of modafinil acid is decreased and the $t_{1/2}$ of modafinil is doubled. Therefore, the dose of modafinil should be halved in such patients. In severe renal impairment (creatinine clearance 16.6 ± 0.7 mL/min), plasma modafinil concentrations are increased slightly but plasma concentrations of modafinil acid (due to impaired renal clearance) are considerably higher ($C_{max} = 5.4$ vs 2 mg/mL).^[76] The safety of such a modafinil acid

concentration is unknown. Dosage recommendations in such patients cannot be made.

3. US FDA-Approved Indications of Modafinil

The use of modafinil has been approved for ameliorating the excessive sleepiness associated with narcolepsy, SWSD and residual sleepiness in OSA despite optimal use of CPAP.^[77]

3.1 Narcolepsy

Narcolepsy affects 1 in 2000 people in North America. The main symptoms of narcolepsy are EDS, cataplexy (an abrupt loss of muscle tone triggered by emotion), hypnagogic hallucinations and sleep paralysis. Patients are liable to fall asleep throughout the day, sometimes with little warning and frequently at inappropriate times. Exclusion of other concomitant sleep disorders, such as OSA, periodic limb movements of sleep and REMS behaviour disorders, is important because these occur with higher than expected incidence in patients with narcolepsy; treatment of these disorders may relieve EDS.

Four randomized, double-blind, placebo-controlled trials have assessed the usefulness of modafinil in treatment of EDS in narcolepsy.^[78-81] Two trials with 50 and 75 subjects, respectively, used a crossover design,^[78,81] while two larger studies with 283 and 271 subjects, respectively, had parallel groups.^[79,80] Anti-cataplectic medicines were continued in two trials,^[78,81] while in the larger trials, patients unable to discontinue anti-cataplectic medicines were excluded.^[79,80] In one crossover trial, subjects received modafinil 300 mg/day in two divided doses or placebo for 4-week periods with a 2-week washout interval.^[78] In the other three trials, two daily doses of modafinil (200 and 400 mg) were compared with placebo.^[79-81] Modafinil was given as a single daily dose in the parallel group studies that lasted for 9 weeks each;^[79,80] in the second crossover trial, the treatment phases lasted for 2 weeks with no washout period; modafinil was given in two divided doses.^[81]

Treatment with modafinil 200–400 mg/day improved EDS by the objective MWT in all four studies, and improvement by the subjective Epworth Sleepiness Scale (ESS) was seen in all three studies that used this measure.^[79-81] However, the mean ESS scores were not normalized with modafinil in any of these studies. In the two crossover trials, daily sleep log/diary also showed improvement in EDS, while in the parallel group trials improvement was found on Multiple Sleep Latency (MSLT). The overall level of illness by Clinical Global Impression of Change (CGI-C) improved in the two larger trials but did not improve by CGI in the smaller crossover trial.^[78] The two doses of modafinil were equally effective in all three trials. There was no disruption of night-time sleep in any of the studies. Modafinil did not improve cataplexy in one trial that assessed it.^[78] The larger trials excluded patients with severe cataplexy.

In one parallel group trial, 80% of the subjects receiving modafinil were randomly crossed over to placebo to assess the effects of abrupt discontinuation of modafinil. Patients who were receiving modafinil (both doses) had a return of sleepiness by MWT. However, no symptoms resembling those of amphetamine withdrawal were seen.^[80]

In patients with residual late evening sleepiness despite a positive response to modafinil, use of split doses of modafinil was assessed in two small randomized, double-blind studies.^[82,83] In the first trial, 32 patients with residual late day sleepiness despite modafinil treatment were randomized (after a 1-week washout period) to receive modafinil 200 mg ($n = 11$) or 400 mg ($n = 11$) as a single dose at 7:00am or 400 mg as a split dose ($n = 10$) with 200 mg given at 7:00am and 200 mg at noon. All patients received modafinil 200 mg at 7:00am for 1 week; the dose was gradually increased in the two modafinil 400 mg/day groups over the next 7 days, which was then continued for another week. The outcome measures included SOL on a modified MWT (conducted every 2 hours from 9:00am to 7:00pm), ESS and CGI-C. The study was designed to be a three-way crossover study with each treatment period lasting 3 weeks, but there was a signifi-

cant treatment-by-period interaction in SOL on MWT; therefore, the efficacy was assessed using data of the first treatment period only, essentially converting the trial to a parallel group design and substantially reducing the sample size. Also, it is unclear whether all groups were similar at baseline. The mean SOL times on MWT were significantly better than baseline with both 400 mg doses than the 200 mg dose. This is not surprising because the patients were receiving, on average, modafinil 350 mg/day prior to the study. However, there was significantly greater improvement from baseline in the evening SOL (average of 5:00pm and 7:00pm tests) with the split 400 mg dose than the single modafinil doses. On the other hand, the proportion of patients who were 'much improved' or 'very much improved' on CGI-C were similar with the two 400 mg doses (82% with the single dose and 80% on the split dose); there was also no significant difference in mean ESS score improvement between the three regimens. Thus, one of three endpoints was significantly better with the modafinil 400 mg/day split dose. The results of this study must be interpreted with caution because the design of the study was altered after completion, resulting in a very small sample size. It is possible that with the small sample size and multiple comparisons, the positive results are a consequence of random variation.^[82]

In the second randomized, double-blind, placebo-controlled, parallel group trial, 24 subjects (who were receiving modafinil 400 mg/day [$n = 23$] or 600 mg/day [$n = 1$]) were randomized (after a 2-week washout period) to receive modafinil 400 mg at 7:00am followed by either placebo or modafinil 200 mg at 12 noon for 3 weeks. Compared with baseline, significantly greater improvement in SOL on the evening MWT (average of the 5:00pm and 7:00pm tests) was seen with the 600 mg split dose (mean \pm standard error of the mean [SEM]; 12.0 ± 2.2 minutes) than with the single 400 mg dose (3.8 ± 2.4 minutes; $p < 0.05$). Fifty-eight percent of patients were rated as 'much improved' or 'very much improved' on CGI-C in the 400 mg once-daily group compared with 92% of patients in the 600 mg/day split dose group. These results are not surprising

because this was more of a 'dose escalation' trial because all of these patients were experiencing residual late day sleepiness while receiving at least 400 mg/day of modafinil.^[83]

Thus, based on data from two very small studies with experience in a total of 22 subjects receiving split doses, a split-dose schedule may provide additional benefit to patients with residual late day sleepiness despite use of relatively large single doses of modafinil (up to 400 mg/day). The rationale for this is unclear in view of the rather long $t_{1/2}$ of modafinil (14–17 hours). Effects on sleep by nocturnal polysomnography or subjective measures were not assessed in either study.^[82,83]

Modafinil in doses of 200 or 400 mg is effective in combating EDS in narcolepsy. Patients with a positive response to the higher dose but experiencing residual late day sleepiness may benefit from split 400 or 600 mg/day modafinil. Modafinil does not benefit cataplexy. Abrupt discontinuation of modafinil caused rebound sleepiness but did not cause any amphetamine-like withdrawal symptoms.

3.2 Obstructive Sleep Apnoea

OSA is a major public health problem that is estimated to affect 2% of women and 4% of men aged 30–60 years. Two of the cardinal symptoms of OSA are sleep-disordered breathing and EDS: it is also associated with increased risk of systemic and pulmonary hypertension, stroke, congestive heart failure, myocardial ischaemia and arrhythmias. Rates of occupational and automobile accidents are also increased. In addition to weight loss – and avoidance of sleep deprivation, alcohol, nicotine and sedatives – nasal CPAP is the treatment of choice in management of OSA. CPAP effectively manages apnoeac and hypopnoeac episodes, eliminates arterial desaturation, and improves QOL, EDS, neurocognitive and driving performance, and perceived health status. Adverse cardiovascular endpoints, such as hypertension, arrhythmias, nocturnal ischaemia, left ventricular function and mortality, may also improve with CPAP.^[84]

In some patients, EDS persists despite optimal use of CPAP. The role of modafinil in such patients

was investigated in three randomized, double-blind, placebo-controlled trials;^[85-87] results of one trial are described in two separate reports.^[86,88] One single-centre, crossover trial compared modafinil 400 mg/day with placebo in 30 subjects. The treatment periods lasted 2 weeks with a 1-week washout period.^[85] The other two trials were multicentre, had parallel groups, lasted for 4^[86,88] or 12 weeks^[87] and included 157 and 309 subjects, respectively. The dose of modafinil in the 4-week trial was 200 mg/day in the first week and 400 mg/day thereafter. In the 12-week trial, two doses of modafinil (200 and 400 mg/day) were compared with placebo.

3.2.1 Effects on Excessive Daytime Sleepiness

The effectiveness of modafinil was assessed by subjective measures such as ESS^[85-87] and objective measures such as SOL on MSLT^[85,86] and MWT.^[86,87] SOLs on MSLT of 10–15, 5–10 and <5 minutes indicate mild, moderate and severe sleepiness, respectively.

No improvement in the ESS scores was seen with modafinil in the small ($n = 30$) crossover trial.^[85] In the 4-week trial, the mean ESS scores at baseline, week 1 and week 4 were 14.4, 13.2 and 12.4 with placebo, and 14.2, 10.1 and 9.6 with modafinil, respectively. The mean changes in the ESS scores from baseline to weeks 1 and 4 were significantly better with modafinil compared with the placebo group ($p < 0.001$). Furthermore, by 4 weeks, 51% of modafinil patients had normalized the ESS score to <10 compared with 27% of placebo patients ($p < 0.01$).^[86] In the 12-week parallel group trial, significant improvement was seen in the ESS in both modafinil groups (200 mg and 400 mg) compared with placebo at 4, 8 and 12 weeks ($p < 0.0001$ for all periods).^[87] At the end of the study, 38% of the modafinil 200 mg group, 45% of modafinil 400 mg group and 17% of the placebo group had a normal ESS score. The difference between the two modafinil groups was not significant.

No significant improvement in SOL of MSLT was seen in the small crossover study.^[85] In the 4-week parallel group study, the mean SOL on MSLT with modafinil increased from a baseline of 7.4 minutes to 8.6 minutes, whereas it decreased

from 7.5 minutes to 7.2 minutes in the placebo group ($p = 0.021$).^[86]

Significant improvement in the ability to maintain wakefulness by MWT was seen in both studies that used this measure.^[85,87] In the crossover trial, the mean MWT (\pm SD) was 16.5 ± 4.9 minutes at baseline, 16.6 ± 5.0 minutes with placebo and 18.3 ± 3.9 minutes with modafinil at the end of the 2-week treatment period ($p = 0.02$ for comparison between placebo and modafinil). In the 12-week study, MWT improved significantly with both doses of modafinil at 4, 8 and 12 weeks compared with placebo ($p \leq 0.0001$ for all intervals). At study end, the mean MWT increased in patients receiving modafinil 200 mg and 400 mg by 1.6 minutes and 1.5 minutes, respectively, while it decreased by 1.1 minutes with placebo ($p < 0.0001$). There was no significant difference between the modafinil 200 mg and 400 mg groups at any interval.

3.2.2 Effects on Quality of Life

QOL was evaluated by the 36-item Short-Form Health Survey (SF36) in one trial^[85] and Functional Outcomes of Sleep Questionnaire (FOSQ) in two trials.^[85,87] FOSQ is a 30-item, self-administered, validated questionnaire that assesses the impact of excessive sleepiness on QOL and five domains of everyday life including activity level, vigilance, intimacy and sexual relationships, general productivity, and social outcomes. The small crossover trial showed no improvement with modafinil in either measure.^[85] However, in the 12-week trial, modafinil (200 and 400 mg groups combined), compared with placebo, significantly improved total FOSQ scores at 8 ($p < 0.01$) and 12 weeks ($p < 0.001$).^[87]

3.2.3 Effects on Cognitive Performance

Cognitive performance by using the Steer Clear (a computerized driving simulator with road obstacles which can be avoided by pressing a key) and simple unprepared response time showed no significant change with modafinil in the small crossover trial.^[85] In the 4-week parallel study, alertness measured by prespecified 3 (of 14) variables of the psychomotor vigilance task (PVT) showed significant improvement in number of attention lapses ($p = 0.01$), median reaction time ($p = 0.01$) and the

reciprocal of the 10% slowest reaction time ($p = 0.023$).^[88]

3.2.4 Effects on Illness Severity

A global evaluation of the patient's condition showed no significant improvement with modafinil compared with placebo in the small crossover trial.^[85] However, the overall condition of the patients as measured by CGI-C improved significantly in more patients receiving modafinil than those receiving placebo in the larger parallel group studies. In the 4-week trial, 71% patients receiving modafinil improved compared with 35% receiving placebo at the end of the study ($p = 0.035$).^[86] In the second parallel group trial, 61% and 68% of patients receiving modafinil 200 and 400 mg, respectively, had improved at 12 weeks compared with 37% of patients receiving placebo ($p < 0.001$).^[87] The extent of improvement was similar at 4 and 8 weeks.

3.2.5 Effects on Continuous Positive Airway Pressure Use

All studies monitored the use of CPAP. In the crossover trial the use of CPAP was reduced by 12 minutes in the modafinil group. The use of CPAP was (mean \pm SD) 6.3 ± 1 hours per night in the CPAP plus modafinil group compared with 6.5 ± 1 hours with the CPAP plus placebo group ($p = 0.03$); there was no difference in the two larger studies.

3.2.6 Effects on Sleep

Overnight polysomnography was performed in all three studies: sleep efficiency was not affected by modafinil in any trial, no significant difference was seen in the architecture of the sleep in the two larger trials^[86,87] and the number of arousals was not significantly changed by modafinil in two trials.^[85,87] However, at study end in the third trial, the mean arousal index (arousals per hour of sleep) was higher with modafinil (14.3) than with placebo (11.8) [$p = 0.018$].^[86] The numbers of respiratory events was not significantly altered by modafinil in the two trials that assessed this.^[85,86]

Thus, modafinil seems to be effective as adjunctive treatment for OSA patients who have residual EDS despite optimal therapy with CPAP in short-

term studies. It is important to continue CPAP in these patients because modafinil does not reverse the associated adverse cardiovascular effects. The long-term benefit of modafinil has not been assessed in placebo-controlled trials.

3.3 Shift-Work Sleep Disorder

It is estimated that more than 15 million or 16.8% of full-time employees work alternative shifts including evening, night, rotating, irregular and split shifts.^[89] Shift workers' sleep and wake cycles are misaligned with the circadian rhythm. Using minimum criteria of SWSD (either insomnia or excessive sleepiness), it is estimated that ≈10% of night or rotating shift workers have SWSD.^[90] SWSD is associated with higher rates of ulcers, absenteeism, missed social and family activities, depression and accidents related to sleepiness.^[90]

Two randomized, double-blind, placebo-controlled, parallel group, multicentre trials have evaluated the usefulness of modafinil in SWSD with different measures of efficacy.^[91,92] The trials included 209 and 278 subjects (90% and 77% permanent night-shift workers, respectively) and lasted 3 months and 12 weeks, respectively.^[91,92] Modafinil or placebo was given 30–60 minutes before the start of the night shift. In the first trial, modafinil 200 mg was used,^[91] while in the second trial, two doses of modafinil (200 and 300 mg) were compared with placebo.^[92]

In the first trial,^[91] the primary efficacy measures included the rating on CGI-C test for sleepiness during night shift and during the commute to and from home, and the mean SOL on night-time MSLT. Other efficacy measures included the Karolinska Sleepiness Scale (KSS), ranging from 1 (very alert) to 9 (very sleepy), and the frequency and duration of lapses on PVT. Patients also kept electronic diaries regarding sleepiness, accidents and caffeine use. Polysomnography was performed for 8 hours after the baseline and final night shifts.

A minimal improvement on CGI-C was seen in 74% of patients with modafinil compared with 36% with placebo ($p < 0.001$). The mean SOL (\pm SEM) on MSLT improved with modafinil from a baseline

of 2.1 minutes to 3.8 minutes at the final visit (change 1.7 ± 0.4 minutes; $p < 0.001$) but not with placebo (baseline 2.04 vs 2.37 minutes at final visit; change 0.3 ± 0.3 ; $p = 0.24$). The SOLs were significantly greater with modafinil than with placebo at 2:00am ($p = 0.02$) and 4:00am ($p < 0.001$), but not at 6:00am or 8:00am. However, the average SOL remained below the daytime normal values of 6 minutes throughout the night. The mean KSS scores decreased significantly from baseline to final visit in both groups: modafinil from 7.3 to 5.8 (change $-1.5 \pm$ SD 0.2; $p < 0.001$) and placebo from 7.1 to 6.7 (change -0.4 ± 0.2 ; $p < 0.01$). The change from baseline to final visit was significantly greater for modafinil than placebo ($p < 0.001$). According to the electronic diaries, modafinil significantly reduced the maximum level of sleepiness during the night shift ($p < 0.001$), although it produced no significant improvement in intentional or unintentional sleep episodes; there was a significant decrease in the level of sleepiness during the commute home ($p = 0.012$) but no difference in number of unintentional sleep episodes.

On the PVT, the median number of lapses decreased with modafinil from baseline to final visit (12.5 to 10.25; median change -2.6 ; $p = 0.012$) but an increase was seen in the placebo group (16.3 to 23.75; median change 3.8; $p = 0.008$). The number of lapses at the final visit was significantly less with modafinil than placebo ($p = 0.005$). The duration of lapses also decreased with modafinil from baseline to final visit (780 to 669 msec), while it increased with placebo (from 852 to 1235 msec). At the final visit the difference between modafinil and placebo was significant ($p = 0.004$). However, from the electronic diaries no improvement was seen in mistakes, accidents or near accidents during the night shift; conversely, 25% fewer patients had accidents or near accidents on the commute home (54% with placebo vs 29% with modafinil; $p < 0.001$). The limitations of the study include the enrolment of <10% (209 of 2765) of eligible subjects and that 90% of the patients were on permanent night shifts. Thus, the results of this study may not be applicable

to all patients with SWSD. Furthermore, the MSLT is not validated for use at night.

In the second trial,^[92] outcome measures included patient functioning and health-related QOL (HR-QOL) measured by FOSQ and SF36, respectively. Neither tool has been validated for SWSD. There was a statistically significant greater increase in the mean FOSQ score (2.3) from baseline to final visit in patients receiving the 300 mg dose of modafinil compared with placebo (1.6; $p < 0.05$). Significant improvements were seen in the activity domain scores with both doses of modafinil (200 and 300 mg), and in the vigilance and productivity domain scores with the 300 mg dose of modafinil.

Both doses of modafinil significantly improved the SF36 mental component scores; mean scores changed from baseline by 3.2, 3.7 and 0.7 with modafinil 300 mg, modafinil 200 mg and placebo, respectively ($p < 0.05$ for both doses of modafinil compared with placebo). Both doses of modafinil improved vitality domain scores compared with placebo (14.8 vs 5.3; $p < 0.0001$ with modafinil 300 mg; 15.0 vs 5.3; $p < 0.001$ with modafinil 200 mg). Furthermore, modafinil 300 mg also showed improvement in the role emotional domain score compared with placebo (4.3 vs -2.9; $p < 0.05$).

Night-time and daytime sleep was not altered by modafinil, and caffeine use remained unchanged. One patient developed abnormal liver function test values which returned to normal upon discontinuation of modafinil. Other common adverse events were headache, nausea and nervousness.

Sleepiness was improved in patients with SWSD receiving modafinil 200 mg given 30–60 minutes before the start of the night shift, although the SOLs on MSLT remained below the daytime normal values of <6 minutes throughout the night. Modafinil also improved patient functioning and HR-QOL: greater improvement occurred with modafinil 300 mg than with a 200 mg dose. However, the effects of modafinil on the productivity and safety on the job, and on principal morbidities of SWSD were not assessed in either study. In the second trial, a 7% incidence of accidental injuries was reported in the modafinil 300 mg group compared with none in

the placebo or modafinil 200 mg groups. Furthermore, the long-term usefulness and safety of modafinil in reducing sleepiness in this chronic disorder has not been evaluated in placebo-controlled trials.

4. Investigational Uses (Not Approved by the FDA)

The use of modafinil has been investigated for treatment of EDS, fatigue and impaired cognition, and other symptoms in a number of other disorders.

4.1 Neurological Disorders

Several neurological disorders are associated with EDS. Use of modafinil has been studied in some of these disorders. All these studies had small numbers of patients and therefore must be interpreted cautiously.

4.1.1 Parkinson's Disease

EDS affects up to 50% of patients with Parkinson's disease.^[93] Three small, randomized, double-blind, placebo-controlled studies have evaluated the use of modafinil for EDS in Parkinson's disease including 37, 12 and 21 subjects, respectively.^[93-95] One was a parallel group study lasting 4 weeks,^[93] while two were crossover studies.^[94,95] The first crossover study had 2-week treatment periods with a 2-week washout period,^[94] while the second had 3-week treatment periods with a 1-week washout period.^[95] Modafinil dosage ranged from 100–400 mg/day. Baseline ESS scores were ≥ 10 in all studies. Efficacy was assessed by using multiple instruments. All three studies assessed ESS (ESS was the primary efficacy measure in two studies)^[93,95] and Unified Parkinson's disease Rating Scale (UPDRS), which is a tool that follows the longitudinal course of Parkinson's disease. It includes (i) mentation, behaviour and mood; (ii) Activities of Daily Living; and (iii) motor sections that are evaluated by interview. A total of 199 points are possible, with 199 indicating worst disability and 0 indicating no disability.

Significant improvement in ESS scores were seen in both crossover trials but not in the parallel group trial. In the first crossover trial, the ESS scores

improved in the placebo and modafinil groups by (mean \pm SD) 0.83 ± 1.99 and 3.42 ± 3.9 from baseline scores of 11.8 ± 3.8 and 13.2 ± 2.2 , respectively ($p = 0.011$).^[94] In the second crossover trial, the ESS scores were compared only for the first treatment period, since there was a significant carry-over effect; the scores increased by 1.09 and decreased by 3.4 from a baseline of (mean \pm SD) 16.0 ± 4.2 and 17.8 ± 5.1 with placebo and modafinil, respectively ($p = 0.039$).^[95] None of the studies showed improvement in UPDRS. No significant effect of modafinil was seen in any of secondary efficacy measures, which included Fatigue Severity Scale (FSS), Hamilton Depression Scale (HAM-D), Global Impression Score, SF36, MSLT,^[93] the Beck Depression Scale and MWT,^[94] CGI-C, Excessive Daytime Sleep Rating Scale, and Fatigue Assessment Inventory.^[95]

Thus, in one parallel group study ($n = 37$) no improvement was seen in EDS as measured by ESS; in one crossover trial ($n = 21$), significant improvement in ESS scores was seen with modafinil.^[95] However, in the third trial ($n = 12$), the ESS improved significantly but the MWT did not.^[94] Hence, there is no consistent evidence at present that modafinil is effective for EDS in patients with Parkinson's disease.

4.1.2 Myotonic Dystrophy

It is estimated that more than one-third of patients with myotonic dystrophy experience EDS.^[96] Three randomized, double-blind, placebo-controlled, crossover trials have assessed the efficacy of modafinil for EDS in myotonic dystrophy,^[97-99] in 36, 19 and 13 subjects, respectively.^[97-99] The first and the third studies had 2-week active treatment periods with a 1-week washout period;^[97,99] the second trial had 4-week active treatment periods with a 2-week washout period.^[98] The doses of modafinil were as follows: 100 mg at breakfast and at noon for 1 week and doubled for the second week in the first trial;^[97] 100 mg once a day for 5 days and 200 mg once a day for days 6–28 in the second trial;^[98] 200 mg once a day, which was increased to 400 mg for perceived inadequate effect in the third trial.^[99] The primary efficacy measures were a change in mean modified

ESS scores in the first trial,^[97] changes in median ESS scores and MWT in the second study,^[98] and an increase in spontaneous activity assessed by a new (unvalidated) structured interview in the third trial.^[99]

Improvements in the primary efficacy measures were seen in two trials. Compared with placebo, modafinil lowered the mean total modified ESS scores by 20% in the first trial ($p < 0.001$).^[97] In the second trial, modafinil produced no significant change in median ESS. However, median MWT increased from 31.7 to 40 minutes ($p = 0.026$) with modafinil and decreased from 33.3 to 28.7 minutes with placebo ($p = 0.334$). The post-treatment value for MWT was significantly higher with modafinil than placebo ($p = 0.006$). No significant improvement was seen in the activity level of the patients in the third trial.^[99] However, in this trial the mean ESS scores (a secondary outcome) decreased from a baseline of 10.5 (range 3–18) to 6.8 (1–15) with modafinil, while it increased slightly from 10.5 (3–18) to 10.7 (2–17) with placebo ($p = 0.015$ for improvement with modafinil vs placebo).^[99]

Thus, three very small and short-term studies including a total of 68 subjects suggest that modafinil improves EDS in patients with myotonic dystrophy. Larger studies with longer duration are needed to confirm these results.

4.1.3 Traumatic Brain Injury

Millions of people with traumatic brain injury face multiple challenges, including fatigue and EDS. The role of modafinil in treatment of fatigue and EDS was evaluated in a randomized, blinded, placebo-controlled, crossover trial.^[100] The patients received one 100 mg tablet of modafinil or matching placebo at noon for 3 days; the dose was then increased to one tablet twice a day for 11 days followed by two tablets twice a day for 8 weeks. In patients who were unable to tolerate modafinil 400 mg/day, the dose was scaled back to 200 mg/day. A 4-week washout period intervened between the two treatment periods. Of 51 patients enrolled, 46 completed the study and were included in a per protocol analysis. Primary efficacy measures included FSS, ESS and Modified Fatigue Impact Scale

(MFIS). Secondary measures included: (i) HR-QOL measured by using the physical and mental summary scores from the Medical Outcome Study 12-Item Short Form Survey (SF-12); (ii) assessment of cognitive functioning by measuring reaction time, visual motor speed and memory with the Immediate Post Concussion Assessment Cognitive Testing (ImPACT); (iii) vigilance by using Conners' Continuous Performance Test II (CPT II); and (iv) presence of depression by using the Beck Depression Inventory (BDI). ImPACT consists of six cognitive testing modules; results from these are combined to yield four composite scores: verbal memory, visual memory, visual motor speed and reaction time.

Improvements due to a placebo effect were seen in raw scores of several efficacy measures of fatigue and EDS including FSS, ESS and MFIS, with both modafinil and placebo. After adjustment for baseline values and period effect there were no significant differences in FSS, MFIS, BDI and SF-12 physical and mental scores at any time between the two groups. However, a significantly greater decline (mean \pm SEM) [1.15 ± 0.49] in ESS scores was seen with modafinil at week 4 ($p \leq 0.03$), which did not carry through to week 10. On the other hand, significant worsening in the ImPACT Verbal Memory score occurred with modafinil at week 4 ($p = 0.03$) but not at week 10. On CPT II, significantly more omission (at week 4; $p \leq 0.03$) and commission errors (at week 10; $p \leq 0.05$) were seen with modafinil. Since multiple comparisons were made in this small study without use of a correction factor, it is very likely that the isolated differences that appear to be statistically significant occurred as a result of random variation. Thus, there was a considerable placebo effect on measures of EDS and fatigue with no benefit from modafinil. Insomnia was seen with greater frequency with modafinil (19.6%) than with placebo (3.9%; $\chi^2 = 0.03$).^[100]

4.2 Psychiatric Disorders

Use of modafinil has been investigated in many psychiatric disorders. Some of these studies are relatively large (e.g. Attention Deficit Hyperactivity Disorder [ADHD]) but most involve very small

numbers of patients; all studies are of relatively short duration.

4.2.1 Attention Deficit Hyperactivity Disorder (ADHD) in Children and Adolescents

ADHD is a common neurobehavioural disorder in children estimated to affect 2–18% of school-aged children.^[101] In addition to behavioural, psychological and educational interventions, stimulant medications are the mainstay for therapy of ADHD. Current medications approved for treatment of ADHD include methylphenidate and amphetamines; use of these drugs may be limited in some patients as a result of adverse events, lack of effect or addictive potential. Modafinil differs from these drugs structurally and pharmacologically, and may reduce symptoms of ADHD with fewer adverse events.

Three large randomized, double-blind, placebo-controlled, parallel group trials including 248, 190 and 200 children and adolescents (aged 6–17 years) evaluated the use of modafinil administered as a single dose in ADHD.^[102–104] Patients were randomized in a ratio of 2:1 to receive modafinil (170–425 mg once daily, depending on efficacy, tolerability and bodyweight) or placebo. The duration of the studies varied from 7–9 weeks. The primary efficacy measure in all studies was a change in mean score of the School version of ADHD Rating Scale-IV (ADHD-RS-IV)^[105] from baseline to the last visit. The scale was completed by the investigator based on a semi-structured interview with the patient's primary teacher. ADHD-RS-IV is a tool used to evaluate the 18 symptoms of ADHD defined by the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition (DSM-IV)^[102,103] or by DSM-IV-Text Revision (DSM-IV-TR).^[104] The symptoms are evaluated by using a four-point Likert scale (0 = never or rarely, 1 = sometimes, 2 = often and 3 = very often). Thus, higher scores indicate greater severity of illness. The results in all studies were remarkably consistent.^[102–104] At the final visit the mean total scores of the primary efficacy measure, ADHD-RS-IV (school version), decreased significantly more with modafinil than with placebo compared with baseline. The mean (\pm SD) decrease in the ADHD-RS-IV score was 15 ± 11.8 , $17.2 \pm$

12.8 and 17.5 ± 13.1 points with modafinil compared with 7.3 ± 9.7 , 8.2 ± 10.3 and 9.7 ± 10.3 points with placebo, respectively, in the three studies ($p < 0.0001$ for difference between modafinil and placebo for all studies).

All studies also assessed several secondary efficacy measures, which included (i) the scores on the inattention (I) and hyperactivity-impulsivity (H-I) subscales of ADHD-RS-IV School Version; (ii) the total, I and H-I subscale scores on ADHD-RS-IV Home Version obtained by an investigator after an interview with a parent and, if appropriate, with the patient; (iii) CGI-Improvement (CGI-I); (iv) Conners' Parent Rating Scale-Revised, Short Form (CPRS-R-S), which has four subscales (oppositional, cognitive problems/inattention, hyperactivity and ADHD index);^[106] (v) Social Skills Rating Questionnaire (SSRQ);^[107] and (vi) the Child Health Questionnaire (CHQ).^[108] In all studies, significant improvements were seen with modafinil in the I and H-I subscale scores of ADHD-RS-IV School Version, total, I and H-I scores of ADHD-RS-IV Home Version, CGI-I, and the ADHD index subscale of CPRS-R-S. Improvements were also seen in the cognitive/inattention and hyperactivity subscale scores of CPRS-R-S in two studies.^[102,103] Significant improvements were seen in some but not all aspects of SSRQ and CHQ in all three studies.

In one study, at the end of the 7-week double-blind phase, subjects receiving modafinil were further randomized in a double-blind manner to continue receiving modafinil or abruptly convert to placebo for a period of 2 weeks. No abrupt withdrawal symptoms or rebound symptoms of ADHD were seen.^[103]

However, in these studies, modafinil was associated with a very high rate of serious adverse dermatological reactions: two patients developed erythema multiforme/Stevens Johnson syndrome (EM/SJS), three patients had early prodromal EM/SJS and seven patients had symptoms suggestive of prodromal EM/SJS. This constituted a rate of 1.25%, which is hundreds of times higher than the background rate of 1–2/million/year.^[109]

Modafinil in split doses was investigated in one multicentre, randomized, double-blind, placebo-controlled 4-week trial in 248 stimulant-naive or stimulant-unresponsive children aged 6–13 years meeting the DSM-IV criteria for ADHD.^[110] Patients weighing <30 kg were randomized by equal chance to one of four groups, receiving either placebo, modafinil 300, 200 or 100 mg in the morning to be followed by placebo, placebo, modafinil 100 or 200 mg, respectively, at midday. Patients weighing >30 kg could be randomized to one of five groups, i.e. the four groups described here and a fifth group receiving modafinil 200 mg in the morning and another 200 mg at midday.

The efficacy was determined by using ADHD-RS-IV Home and School Version Scales, the 26-item Parent Version of the Conners' ADHD/DSM-IV Scales (CADS-P)^[111] and the CGI-I. The CADS-P specialty scales include a 12-item ADHD Index, an 18-item DSM-IV symptom scale and two 9-item inattentive and hyperactivity/impulsivity subscales. Of 248 randomized subjects, 223 completed the study and 196 subjects received a total dose of modafinil 300 mg or placebo. The results of treatment outcomes in these children as well as those receiving total of modafinil 400 mg/day are shown in table I. Only the modafinil 300 mg once daily dose produced consistent improvement across all scales and subscales in this relatively short 4-week study.

Significantly more insomnia occurred with the 200/100 mg dose (14%) than the placebo group (2%; $p = 0.03$). Overall, 22 (11%) modafinil patients withdrew from the study. Nine patients stopped because of adverse events (four developed rash and two developed decreased appetite) and three (6%) subjects discontinued the placebo group (none for adverse events).

In this small study, split doses of modafinil were not superior to a single 300 mg dose and in fact greater insomnia was seen with one of the split doses of modafinil.

In a 6-week, parallel group, randomized, double-blind, controlled trial, the use of modafinil was compared with methylphenidate in 60 children (two

Table 1. Results of single vs split dosages of modafinil in attention deficit hyperactivity disorder (ADHD)

Regimen for modafinil (mg)	ADHD-RS-IV school version (p-value)		ADHD-RS-IV home version (p-value)		CADSP (p-value)		CGI-I	
	In	H/I	In	H/I	total score	mean ADHD index score	In	H/I
300 once a day (n = 50) ^a	SI (0.006)	SI (0.02)	SI (0.002)	SI (0.001)	SI (0.01)	SI (0.04)	SI (0.02)	SI (0.02)
200 am/100 midday (n = 49) ^a	SI (0.03)	SI (0.04)	NS	SI (0.048)	NS	NS	NS	SI (0.03)
100 am/200 midday (n = 48) ^a	NS	NS	NS	NS	SI (0.01)	NS	SI (0.049)	SI (0.01)
200 am/200 midday (n = 49) ^b	NS	NS	SI (0.01)	SI (0.03)	SI (0.02)	NS	NS	SI (0.02)

a Placebo, n = 51.

b Placebo, n = 27.

am = morning; **CADS-P** = 26-item Parent Version of the Conners' ADHD/DSM-IV Scales; **CGI-I** = Clinical Global Impressions-Improvement; **DSM-IV** = Diagnostic and Statistical Manual of Mental Disorders; **H/I** = hyperactivity/impulsivity subscale; **In** = inattention subscale; **NR** = not reported; **NS** = not significant; **RS** = rating scale; **SI** = significant improvement compared with placebo.

and three patients withdrew from the modafinil and methylphenidate groups, respectively) aged 6–15 years with DSM-IV-TR diagnosis of ADHD. Subjects were randomized to receive modafinil 200–300 mg/day or methylphenidate 20–30 mg/day; those weighing <30 kg received modafinil 200 mg once daily or methylphenidate 20 mg in two split doses (morning and midday) and those weighing >30 kg received modafinil 300 mg once daily or methylphenidate 30 mg in three split doses (morning, midday and 4:00pm). The doses were gradually titrated up from modafinil 100 to 300 mg and from methylphenidate 10 to 30 mg over 3 weeks. The primary endpoints were the decrease from baseline in parent and teacher ADHD-RS-IV scores. At 6 weeks, the parent ADHD-RS-IV scores decreased by (mean ± SD) 24.36 ± 11.66 and 22.66 ± 14.88 in the modafinil and methylphenidate groups, respectively (p < 0.001 for both groups compared with baseline) with no significant difference between the two groups at study end (p = 0.94) or in the degree of reduction from baseline (p = 0.62). The teacher ADHD-RS-IV scores also decreased at 6 weeks compared with baseline by (mean ± SD) 20.53 ± 6.99 and 21 ± 12.21 with modafinil and methylphenidate, respectively (p-value for change from baseline not provided). There was no significant difference between the two groups at study end (p = 0.87) or in the degree of score reduction from baseline (p = 0.75). The proportion of responders (defined as at least 40% decrease in the scores) by parent and teacher ADHD-RS-IV scores was also similar in the two groups (73% in the modafinil group and 70% in the methylphenidate group [p-value not provided] by parent ADHD-RS-IV scores, and 73% in each group by teacher ADHD-RS-IV scores). Significantly more patients in the methylphenidate group had decreased appetite (18 in the modafinil group and 26 in the methylphenidate group; p = 0.03) and difficulty falling asleep (2 in the modafinil group and 8 in the methylphenidate group; p = 0.05). The latter may, in part, be due to the last dose of methylphenidate being given at 4:00pm.¹¹¹²¹

Modafinil appears to be efficacious in children and adolescents with ADHD. However, approval by

the FDA has been unsuccessful, in part, because of severe dermatological reactions.

4.2.2 ADHD in Adults

ADHD frequently persists into adult life; a recent meta-analysis estimated that 15% of patients at age 25 years meet full ADHD criteria and 40–60% meet criteria of ADHD in partial remission.^[113] This translates into a prevalence of 1.25% of full threshold diagnosis of ADHD and 3.2% for ADHD in partial remission.^[113] Adults with ADHD experience poor organizational skills, lack of prioritization, limited time-management, poor attention to detail and careless mistakes. These result in poor work performance, under-achievement, low self-esteem, and strained relationships with family and friends.^[114]

In a small study, 21 (non-concurrent) patients with adult ADHD, aged 18–59 years (median age 43 years) completed a randomized, double-blind, placebo-controlled, three-phase crossover study comparing the efficacy of modafinil with dexamfetamine and placebo.^[115] The patients had been diagnosed with ADHD by age 7 years and currently met full DSM-IV criteria for ADHD with corroboration from one parent or an older sibling. The treatment phases lasted 2 weeks with a 4-day washout period. Modafinil and dexamfetamine were given in two divided doses, one given upon awakening and the second 5 hours later. The dose was titrated up to 400 mg of modafinil and up to 40 mg of dexamfetamine over the first week and maintained for another 7–10 days. Primary efficacy measures included the self-rated DSM-IV ADHD Behavior Checklist for Adults (BCA),^[116] and the 21-item BDI and the 14-item Hamilton Anxiety Scale (HAS) to look for drug effects on mood that could influence ADHD scales. Evaluations also included a 17-item checklist to screen for stimulant side effects,^[117] and the following three tests of cognition: (i) the Controlled Oral Word Association Test (COWAT), which assesses executive function and asks the subjects to recite as many words as possible that begin with three specific letters; (ii) the Wechsler Adult Intelligence Scale-Revised digit span forwards and backwards subtests; and (iii) the Stroop Color-Word Interference Test.^[118] To minimize a type 1 error, a

Bonferroni correction to the p-values was used, which resulted in a significance level of 0.002.

The mean \pm SD doses of modafinil and dexamfetamine were 206 ± 84.9 mg and 21.8 ± 8.9 mg, respectively. Compared with placebo, both dexamfetamine and modafinil significantly reduced the ADHD symptoms by DSM-IV ADHD BCA ($p < 0.001$ for both). There were no significant effects of the drugs on BDI, HAS or tests of cognition and mood. No significant adverse effects were seen with either drug compared with placebo.

Thus, in a very short-term study including only 21 non-concurrent subjects (which raises questions about bias and validity of the study), modafinil was as effective as dexamfetamine in adult ADHD. Therapeutic decisions cannot be made from a study with such a small sample size. Larger and more long-term studies are needed to establish the role of modafinil in adult ADHD.

4.2.3 Major Depressive Disorder

Depression is a very common disorder, with a life-time prevalence of 15–20%.^[119] It is estimated that 29–46% of patients have a partial or no response to treatment with a single antidepressant.^[120] As a result, several drugs have been used to augment the effect of SRIs. Two large, multicentre, randomized, double-blind, placebo-controlled, parallel group trials assessed the use of modafinil in patients with major depressive disorder with residual symptoms of fatigue and sleepiness despite treatment with antidepressants.

The first study conducted by DeBattista et al.^[121] lasted 6 weeks and enrolled 136 patients with major depressive disorder with partial response to a minimum of 6 weeks of antidepressant therapy; 93% of patients were taking a single antidepressant, while 7% were taking two or more. Depending on efficacy and tolerability, the dose of modafinil varied from 100 to 400 mg/day. In a second study, Fava et al.^[120] enrolled 314 patients with major depressive disorder who did not have complete response to monotherapy with minimally effective doses of SRIs for ≥ 8 weeks and at a stable dose for ≥ 4 weeks. The active treatment group received modafinil 200 mg/day and the study lasted 8 weeks.

Efficacy in the two studies was assessed by using different combinations of instruments, including (i) FSS and Brief Fatigue Inventory (BFI) to assess fatigue; (ii) ESS for sleepiness; (iii) HAM-D-17, HAM-D-21, HAM-D-31 and Montgomery-Asberg Depression Rating Scale (MADRS) for overall level of depression; (iv) CGI-Severity of Illness (CGI-S), CGI-C, CGI-I for overall condition; and (v) SF36 for QOL. FSS has nine items measured on a 7-point scale; BFI has nine items measured on a 10-item scale, with lower levels indicating less fatigue on both instruments.

The two studies showed considerable placebo effect, with reductions in ESS and FSS scores with both modafinil and placebo. Significantly greater reductions were seen in the DeBattista et al.^[121] study in ESS scores at week 1 ($p < 0.01$) and FSS scores at week 2 ($p < 0.05$) with modafinil; in the Fava et al.^[120] study, significantly greater reductions with modafinil were seen both in ESS ($p = 0.02$) and in FSS ($p = 0.04$) at week 1. However, no significant differences between modafinil and placebo were seen at any other time interval in either study. Thus, any improvements seen in ESS and FSS beyond the first couple of weeks were likely to be because of a placebo effect.

Substantial placebo effect was also seen in measures of depression. In the DeBattista study, reductions in HAM-D-21 and HAM-D-17 scores and in the Fava study, reductions in HAM-D31, HAM-D17 and BFI scores were seen with both placebo and modafinil with no significant differences between the two at any interval. DeBattista et al.^[121] also reported no significant improvement in CGI-C or SF36 with modafinil.

In the study by Fava et al.,^[120] overall CGI-I scores improved significantly with modafinil compared with placebo at week 1 ($p = 0.049$) and at final visit ($p = 0.01$). More patients in the modafinil group showed minimal improvement (70%) compared with placebo (53%; $p = 0.006$); however, the number of responders (much or very much improved) was not significantly different in the two groups (41% with modafinil and 32% with placebo; $p < 0.09$). No significant difference was seen in

MADRS with modafinil. In a subgroup analysis performed in patients with baseline HAM-D-17 scores ≥ 14 , a significant reduction in ESS scores was seen: mean \pm SD reduction of 4.0 ± 4.9 with modafinil compared with 3.0 ± 4.1 with placebo ($p = 0.03$). However, this subgroup analysis was not prespecified; also, since multiple comparisons were made without use of a correction factor, the difference in this subgroup may be fortuitous. Hence, this finding needs to be confirmed in an independent study before these results can be applied to clinical practice

More patients in the modafinil group compared with placebo had headaches (22% vs 12%) and nervousness (20% vs 4%) in the DeBattista et al.^[121] study. In the Fava et al.^[120] study, more patients with modafinil compared with placebo had nausea (9% vs 2%; $p = 0.01$) and felt jittery (4% vs 1%; $p = 0.03$); there was a mean \pm SD weight loss of 0.6 ± 2.9 kg in the modafinil group and 0.4 ± 2.2 kg in the placebo group ($p < 0.0001$).

Since many patients have a lag period from initiation of antidepressant treatment to improvement, and fatigue and EDS can occur as adverse effects of antidepressants, a multisite, double-blind, placebo-controlled trial was conducted to see if addition of modafinil to an SRI at treatment onset would hasten its effect and ameliorate fatigue and EDS. Of 73 patients enrolled, 51 completed the study. Subjects received an open-label SRI and were randomized to receive one tablet per day of modafinil 100 mg or a matching placebo for the first week, and two tablets per day for the next 5 weeks. The ESS scores decreased with both modafinil and placebo (showing a substantial placebo effect), with no significant difference in the primary efficacy measure of the rate of change in ESS scores from baseline to week 6 ($p = 0.73$). The mean (\pm SD) study-end ESS scores were also similar (modafinil = 7.3 ± 4.9 , placebo = 8.1 ± 3.1 ; $p = 0.69$). There were also no significant differences in the secondary efficacy measures of proportion of patients with 50% reduction in the HAM-D-31 or MADRS scores (modafinil = 78%, placebo = 69%, $\chi^2 = 0.50$; and modafinil = 75%, placebo = 86%, $\chi^2 = 0.14$, respectively), or final

visit ESS score <10 (modafinil = 61%, placebo = 75%, $\chi^2 = 0.51$) or FSS score <4 (modafinil = 61%, placebo = 53%, $\chi^2 = 0.51$). Remission rates defined by a HAM-D-21 score of ≤ 7 were also not different in the two arms (modafinil = 50%, placebo = 47%, $\chi^2 = 0.86$).^[122] More patients receiving modafinil did not complete the study because of adverse events than the placebo recipients ($\chi^2 = 0.03$). The entire study was terminated early because two patients in the modafinil arm developed suicidal ideation; one patient developed suicidal ideation requiring hospitalization during the second week when doses of sertraline and modafinil were raised from 50 and 100 mg/day to 100 and 200 mg/day, respectively. The second patient receiving fluoxetine developed suicidal ideation when modafinil was increased from 100 to 200 mg/day in the second week of therapy.^[122]

Thus, currently, there is no evidence that modafinil is beneficial for augmentation or adjunctive treatment of depression.

4.2.4 Bipolar Depression

The efficacy of modafinil as adjunctive treatment for bipolar I or II depression has been evaluated in a single, 6-week, randomized, double-blind, placebo-controlled, parallel group study in 85 subjects (58 completed the trial) with inadequate response to mood stabilizers with or without antidepressants.^[123] The trial subjects received modafinil 100–200 mg/day or placebo for 6 weeks. The primary outcome measure was a change in the scores of Inventory of Depressive Symptoms (IDS).^[124] The scores of IDS ranged from 0–84; scores of <12 are considered normal. The mean (\pm SD) baseline scores were 30.1 ± 9.7 and 31 ± 8.7 in the modafinil and placebo groups, respectively. Controlling for baseline scores, the endpoint scores on IDS improved significantly with modafinil. Significant improvement was also seen in the secondary endpoints, i.e. CGI-Bipolar Depression Severity, and 44% of modafinil patients had >50% reduction in IDS scores and 39% achieved remission compared with placebo rates of 23% and 18%, respectively ($p = 0.038$ and 0.033 , respectively). Treatment-related hypomania or mania defined as a score of >13 on Young Mania

Rating Scale was not different in the two groups. However, 19 patients in the modafinil group were receiving sedative hypnotics compared with seven in the placebo group ($p = 0.002$); also, patients with stimulant-induced mania were excluded from the trial.

This small study suggests that modafinil in dosages of 100–200 mg/day may be helpful in bipolar depression. However, these results need to be interpreted with caution since the withdrawal rate (32%) was considerable; larger studies are required to settle the question. Since stimulants can precipitate mania in patients with bipolar disorder, caution is required if using modafinil for this condition.

4.2.5 Schizophrenia

Four small, randomized, controlled trials have addressed the use of modafinil in the treatment of schizophrenia.^[125–128] Three studies assessed cognitive functioning^[125–127] (with cognitive function being the sole focus in two studies).^[125,127] Two studies assessed the negative symptoms,^[126,128] and only one study assessed the positive symptoms^[126] of schizophrenia. Two trials tested only a single dose of modafinil,^[125,127] while the others lasted for 8 weeks. All studies had ≤ 20 subjects who completed the trial.

Turner et al.^[125] randomized 20 patients to receive a single 200 mg modafinil dose or placebo in a double-blind, crossover design. Efficacy outcomes included subjective visual analogue rating of feelings of 16 dimensions examined four times during the testing session, and a battery of neuropsychological tests from the Cambridge Neuropsychological Test Automated Battery (CANTAB®).^[129] These included (i) tests of visual memory, e.g. pattern recognition memory, and the delayed matching to sample (DMTS); (ii) tests of working memory and planning such as the spatial working memory (SWM) and spatial span tasks; (iii) tests of decision-making and response control, e.g. the stop-signal task; and (iv) a three-dimensional version of attentional set-shifting task (IDED) and the One-Touch Tower of London spatial planning task (NTOL). The Wechsler Adult Intelligence Scale digit span (a test of short-term memory) was also assessed. Mo-

modafinil had no significant effects on any of the subjective measures. Significant improvement with modafinil compared with placebo were seen in the accuracy of forward and backward digit spans ($p = 0.018$ and 0.006 , respectively); increase in the NTOL latency ($p = 0.003$); and a decrease in total extra-dimension shift errors on the IDED ($p = 0.039$).

In another small study, Spence et al.^[127] randomized 19 patients with schizophrenia with predominantly negative symptoms to receive a single dose of modafinil 100 mg or placebo for two separate days, 1 week apart, in a double-blind, crossover design. Patients with predominantly positive symptoms were excluded. Subjects had functional MRI scan 2 hours after the drug or placebo while performing the 2-back working memory task (WMT).^[130] No significant improvement in the WMT was seen with modafinil compared with placebo. One patient developed psychosis 4 days after receiving modafinil.

Sevy et al.^[126] enrolled 24 patients (20 completed) with schizophrenia or schizoaffective disorder into an 8-week randomized, double-blind, placebo-controlled, parallel group trial. Subjects received up to 200 mg of modafinil per day or placebo as adjunct therapy. Efficacy measures included (i) fatigue measured by CGI-S and CGI-I subscales, FSS and a 10 cm visual analogue fatigue scale (VAFS) with global rating of fatigue ranging from 0 (worst) to 10 (no fatigue); (ii) other symptoms assessed by CGI-S and CGI-I; (iii) Brief Psychiatric Rating Scale (BPRS),^[131] which is an 18-item scale measuring positive symptoms, general psychopathology and affective symptoms; (iv) BPRS-anchored version; (v) Scale for Assessment of Negative Symptoms (SANS: modified version);^[132] and (vi) HAM-D. Adverse effects were evaluated with the Abbreviated Treatment Emergent Symptom Scale,^[133] the Modified Simpson Dyskinesia Scale^[134] and the Modified Simpson-Angus Scale (to assess for akathisia).^[135] Neuropsychological testing included (i) the Identical Pairs version of the Continuous Performance Test (CPT-IP), a test of sustained attention and vigilance;^[136,137] (ii) the letter number span, a measure of attention and concentration;^[138]

(iii) the Oculomotor Delayed Response Test (ODRT),^[139] which is a computerized version of a spatial working memory task; (iv) DMTS; (v) COWAT and the Rey Auditory Verbal Learning Test (RAVLT), which assesses immediate and delayed recall of a 15-word list.^[140]

At baseline, the placebo group had significantly more fatigue both by FSS and VAFS ($p < 0.01$), and also had significantly higher scores for ODRT and immediate recall on RAVLT ($p < 0.05$). Both modafinil and placebo produced a significant reduction of similar extent in FSS scores from baseline to week 8 ($p < 0.01$). At 8 weeks, both placebo and modafinil produced significant improvements in CGI-I and its fatigue subscale, VAFS and SANS alogia subscale; both increased akathisia with no significant differences between the two groups in any measure, testifying to a sizeable placebo effect. There was no improvement in positive or negative symptoms or cognition with modafinil. The most common adverse effects with modafinil were agitation ($n = 4$), insomnia ($n = 3$) and dry mouth ($n = 2$). One patient developed psychosis with modafinil in the first week and discontinued participation.

Over a period of 4 years, Pierre et al.^[128] randomized 20 patients with schizophrenia or schizoaffective disorder to receive either 100–200 mg of modafinil per day or placebo for 8 weeks. Modest improvements were seen in the primary efficacy measure, i.e. the total score on the 18-item version of SANS and its subscale scores with modafinil as well as placebo with no significant difference between the two groups.^[141]

Thus, in four small studies (combined patient total <80) that assessed the effect of modafinil on clinical measures in schizophrenia, modafinil was found to be ineffective for positive and negative symptoms of schizophrenia. Of three studies that looked at cognitive tasks, only one study using one single dose of modafinil showed improvements in a few specific tasks.^[125] However, since multiple tests were done in a small number of subjects in this study, with some tests having multiple outcome measures (e.g. DMTS and SWM have 19 and 24 outcome measures, respectively), a type I error is

highly likely. Furthermore, it is unclear whether these small differences in very specific tasks produced by one single dose of modafinil will translate into clinically meaningful improvement in patients with schizophrenia.

Currently, there is no evidence that modafinil is beneficial in patients with schizophrenia. Furthermore, since psychosis was reported in 2 of 62 patients who received modafinil, it should be used with great caution in this condition.

4.2.6 Cocaine Addiction

Two double-blind, randomized trials have assessed the usefulness of modafinil for treatment of cocaine addiction.^[142,143] One was a parallel group trial, in which 62 treatment-seeking cocaine-dependent subjects, without significant medical or psychiatric problems, were randomized to receive modafinil 200–400 mg/day or placebo for 8 weeks.^[142] All subjects also received cognitive behavioural therapy twice a week. The primary efficacy measure was benzoylecgonine-negative urine samples calculated as a percentage of the 24 (three times a week) requested samples, although only 74.5% and 63% of expected urine samples in the modafinil and placebo groups, respectively, were collected. By this method, 42% and 24% of urine samples from the modafinil and placebo groups, respectively, were benzoylecgonine-negative ($p = 0.03$) over the duration of the study; 27% and 22% of urine samples in the modafinil and the placebo groups, respectively, were benzoylecgonine negative at baseline. Conversely, no improvement with modafinil was seen in several secondary outcomes that included self-reported cocaine use on Timeline Follow-Back Interview,^[144] and several measures of cocaine craving/withdrawal such as the Cocaine Selective Severity Assessment,^[145] Brief Substance Craving Scale^[146] and Cocaine Craving Questionnaire.^[147] The findings of this study are hard to interpret because a significant proportion of patients had benzoylecgonine-negative urine levels at baseline. Furthermore, even though significantly more negative urine results were turned in by patients taking modafinil, the subjective reporting of cocaine use, dollars spent and cocaine craving was unchanged.

In the second trial with a double-blind, placebo-controlled, crossover design, 8 of 13 non-treatment-seeking, long-term users of smoked cocaine completed the study.^[143] The effects of two doses of modafinil (200 and 400 mg) on response to smoked cocaine were compared with placebo. The study lasted 48 days and was conducted in combined inpatient and outpatient settings.

Patients received placebo or modafinil for about 10 days followed by assessment of the effects of smoked cocaine over a 3- to 4-day period; all patients were tested with four doses of cocaine: 0, 12, 25 and 50 mg. After cocaine testing, the drug or placebo was crossed over. The modafinil 200 mg dose always preceded the 400 mg dose. The efficacy measures included (i) the opportunity to buy the same dose of cocaine that had been tested or keep \$US5.00 out of the subjects' earnings; (ii) Subjective Effects Questionnaire which had five clusters, i.e. Bad Drug Effects, Self-Esteem, Calm, Good Drug Effects and Drug Quality; and (iii) urine was tested for cocaine. At testing, active cocaine was bought significantly more frequently than placebo cocaine ($p < 0.001$). However, both doses of modafinil significantly reduced the interest in buying ($p < 0.03$), the amount willing to pay, and ratings on the 'Drug Quality' cluster ($p < 0.05$) following the two largest doses (25 and 50 mg) of cocaine. However, cocaine-positive urine tests in the outpatient setting did not change.

Thus, in one study, although more patients in the modafinil group had cocaine-negative urine results (a significant proportion of patients had negative urine results at baseline), the cocaine craving and use, and dollars spent on cocaine did not change. In the second trial, the willingness to buy, the amount willing to pay and drug-quality of 25 and 50 mg doses of cocaine declined with modafinil treatment, but the use of cocaine as assessed by urine testing did not decrease.

Therefore, at present there is no consistent evidence that modafinil is beneficial for treatment of cocaine addiction.

4.3 Disorders Associated with Excessive Fatigue

Modafinil has also been investigated in small numbers of patients with disorders associated with chronic excessive fatigue.

4.3.1 Chronic Fatigue Syndrome

In a single randomized, double-blind, placebo-controlled, crossover study involving 14 patients treated for 20 days in each arm with a 2-week washout period, modafinil in doses of 200 mg/day and 400 mg/day had inconsistent effects on the primary efficacy measure of cognition. No improvement was seen in the secondary efficacy measures of fatigue, QOL or mood. However, the small sample size limits the statistical power of the study.^[148]

4.3.2 Fatigue in Post-Polio Syndrome

Two small, randomized, double-blind, placebo-controlled, crossover trials have assessed the use of modafinil in management of post-polio fatigue.

In the first study, which enrolled 14 patients who received modafinil (starting with 100 mg once daily and increasing to 200 mg twice daily) or placebo for 5 weeks in each treatment phase with a 1-week washout period, a considerable placebo effect was seen. At treatment end, fatigue as measured by the Piper Fatigue Scale improved by (mean \pm SD) 27 \pm 40% with modafinil and by 43 \pm 36% with placebo, with no significant difference between the two treatments. The ESS scores also improved with both treatments with no significant difference from baseline or between the two treatments. There were also no differences with modafinil in other secondary efficacy measures such as backward and forward aural digit span (a measure of short-term memory) and reaction time (an indirect measure of fatigue).^[149]

In the second trial, 36 patients were randomized to receive either modafinil or placebo.^[150] Treatment phases lasted 6 weeks with a 2-week washout period. Modafinil 200 mg/day was given in two equally split doses at breakfast and lunch for the first 3 weeks and was subsequently increased to 400 mg/day still as split doses. Improvements were seen in primary efficacy measures of ESS, VAFS and fa-

tigue impact scale with both placebo and modafinil without significant differences between the two treatments. No improvement was seen in SF36, a secondary outcome measure. Three patients assigned to modafinil withdrew shortly after initiating treatment; one developed acute psychosis requiring hospitalization.

Thus, in two small studies, substantial placebo effects on fatigue and excessive sleepiness were seen; modafinil did not provide any additional benefits in post-polio fatigue. One of 32 patients who received modafinil developed acute psychosis requiring hospitalization.

4.3.3 Fatigue in Multiple Sclerosis

More than 50% of patients with MS experience fatigue, which is often the most troublesome symptom. A single randomized, double-blind, placebo-controlled, parallel group, 5-week trial including 115 patients assessed the effectiveness of modafinil compared with placebo.^[151] Modafinil 200 mg/day was given for 1 week and then increased by 100 mg each week to a maximum of 400 mg/day. The primary efficacy measure was the MFIS. Compared with baseline, the mean MFIS scores improved significantly both in the placebo and modafinil groups ($p < 0.001$ for both), with no significant difference between the two groups. Thus, in this single study a substantial placebo effect was seen with no additional benefit with modafinil.

4.4 Other Investigational Uses

Modafinil use has been investigated in recovery from general anaesthesia and sleep-deprived emergency room (ER) physicians as well.

4.4.1 Recovery from General Anaesthesia

In a randomized, double-blind, placebo-controlled, parallel group study of 34 patients, the effects of a single modafinil 200 mg dose given at discharge to patients (all were American Society of Anesthesiologists' [ASA] class I or II) after same-day surgery under general anaesthesia was compared with placebo. Patients were contacted 24 hours later and assessed by a verbal analogue scale for the following variables: energy, appetite, nausea, restlessness, ten-

sion, feeling worn out, fatigue, exhaustion, relaxation, dizziness, reading ability, pain, ease of sleep and mental limitation to resume activity. Significantly fewer patients receiving modafinil were worn out and exhausted ($p < 0.01$ for both); patients given modafinil also had less fatigue ($p < 0.05$) and were more alert and energetic. However, the study had a small sample size and used multiple comparisons, which raises the likelihood of type I error.^[152]

4.4.2 Sleep-Deprived Emergency Room Physicians

A single randomized, double-blind, placebo-controlled, crossover trial evaluated the effect of modafinil or placebo on cognition and sleep in 25 ER physicians after night shifts in two single-day phases, which were separated by a 7-week washout period. Subjects received either a single dose of modafinil 200 mg or matching placebo between 6:30am and 7:30am after a night shift, and then attended interactive didactic sessions and workshops until 10:00am, 11:30am or 1:00pm. The primary efficacy measures were assessed on a visual analogue scale (VAS); the modafinil group found it easier to attend didactic sessions ($p < 0.001$), had no improvement in the ability to drive home and had more difficulty falling asleep ($p < 0.05$). Eleven subjects developed adverse effects with modafinil, which included headache, anxiety, nervousness, nausea, euphoria, abnormal vision, lightheadedness and diuresis compared with one with placebo.^[153]

5. Abuse/Addictive Potential

There is no injectable form of modafinil available and no withdrawal symptoms have been reported after abrupt discontinuation of the drug;^[80,103] therefore, the abuse potential of the drug is thought to be low. However, patients with a history of substance abuse were excluded from one of these studies.^[103]

The abuse potential of modafinil was compared with methylphenidate in a study of 24 subjects with history of polysubstance abuse.^[154] Subjects were randomized to receive a single dose of methylphenidate (45 or 90 mg) or modafinil (200, 400 or 800 mg) on days 1, 4, 7, 10, 13 and 16 with 2 days of washout period between various dosages. Both drugs, compared with placebo, caused a decrease in

kilocalories consumed at the noon meal and estimated sleep. The effects produced on the caloric intake by modafinil 200 and 400 mg were lesser than with methylphenidate 45 and 90 mg, but the effects of modafinil 800 mg were similar to methylphenidate 90 mg. The subjective and objective effects on duration of sleep with modafinil 200 and 400 mg were similar to methylphenidate 45 and 90 mg; duration was significantly reduced with modafinil 800 mg compared with other doses of modafinil and both doses of methylphenidate. Both drugs produced a dose-related increase in 6-hour AUC scores for supine and standing BP and pulse rate; also, significant orthostatic increases in BP and pulse rate were seen with both drugs compared with placebo. The effect of modafinil on orthostatic tachycardia was significantly less than with methylphenidate.

On the Drug Rating Questionnaire, the two drugs in various doses, compared with placebo, had significant increases in 'feel the drug', 'like the drug' and 'high now' responses both by subjective and by objective ratings. The effects tended to be dose related. The Drug Identification Questionnaire showed that subjects were able to differentiate all doses of both drugs from placebo, albeit significant stimulant effects were seen only with methylphenidate and 800 mg of modafinil. Although significant increases in the Amphetamine Scale score of the Addiction Research Center Inventory (ARCI)^[155] were seen with methylphenidate only, significant increases on the lysergic acid diethylamide group scale scores were seen with both drugs. Compared with placebo, significantly greater responses were produced by both drugs on several items of the Drug Response Questionnaire and included: 'nervous', 'stomach turning', 'hearing changed' and 'body feels different, changed or unreal'. Scores for the 'sleepy' item were significantly lower with all doses of modafinil compared with placebo and methylphenidate 45 mg. On the Observer's Specific Drug Response Questionnaire, responses on 'sleepy' and 'nodding' were lower than placebo with both drugs. Overall, the responses were similar with the two drugs; however, responses were lower with modafinil on the 'sleepy', 'relaxed' and 'tremulous' items.

Thus, in this one study in subjects with a history of drug abuse, modafinil seems to have a profile very similar to methylphenidate and therefore may have some addictive potential.^[154]

The abuse potential of modafinil has also been compared with dexamfetamine in 11 healthy adults with no history of drug abuse in a randomized, double-blind trial. Three different doses of the two drugs (modafinil 1.75, 3.5 and 7mg/kg, and dexamfetamine 0.035, 0.07 and 0.14 mg/kg) were tested. Assessments were performed 30 minutes and every hour for 5 hours after drug administration and included (i) verbal reports of drug effects on several feelings such as 'stimulated', 'sleepy', 'liking the drug effect' by using 100-unit VASs; (ii) the five subscales of ARCI; and (iii) the Profile of Mood States (POMS). Both drugs significantly increased ratings on several measures of abuse potential such as the POMS Elation scale, VAS for feeling high and the Morphine Benzadrine Group scale (a measure of euphoria) of the ARCI. Modafinil also increased ratings on the POMS Total Positive scale, while dexamfetamine increased VAS ratings for liking the drug. Thus, there was considerable overlap between the two drugs on measures of abuse potential.^[156]

Modafinil, therefore, may have some abuse/addictive potential in non-drug abusers as well, although no such cases have been reported to date.

6. Drug Interactions

The vast majority of clinically used drugs undergo phase I metabolism mediated by the CYP enzyme system. The most important of these isoenzymes are (with the fraction of drugs metabolized by each in parentheses) CYP3A4 (40–45%), CYP2D6 (20–30%), CYP2C9 (10%), CYP2C19 (5%), CYP1A2 (5%), CYP2B6 and CYP2E1 (2–4% each), CYP2A6 (2%), CYP2C8 (1%) and CYP3A5 (<1%). The substrates for CYP3A4 and CYP3A5 overlap.^[156]

In vitro studies using human hepatocytes show that modafinil induces CYP1A2, CYP2B6 and CYP3A4/5, weakly inhibits CYP2C9 and strongly inhibits CYP2C19.^[157] Coadministration of modafinil

with drugs metabolized by CYP1A2, CYP2B6 and CYP3A4/5 could lead to decreased blood concentrations of these drugs and thus reduced efficacy. Conversely, concentrations of drugs metabolized by isoenzymes CYP2C9 and CYP2C19 may increase when given along with modafinil.

The pharmacokinetics of one single dose (5 mg) of warfarin (a major substrate of CYP2C9) were investigated *in vivo* in a single-blind, single-period study, before and after administration of modafinil 200 mg/day for 1 week and then 400 mg/day for 3 weeks, or placebo for 4 weeks in 28 subjects (14 in each group). No statistically significant changes were found in mean AUC_{∞} of S-warfarin, R-warfarin or in clotting times. However, in two subjects receiving modafinil, the AUC_{∞} of S-warfarin (the pharmacologically more active enantiomer) increased by 43% and 60% each.^[158] Information regarding clotting times in these two patients is not available; therefore, until further data are available, it is prudent to monitor prothrombin time and/or international normalized ratio more frequently when modafinil is added or removed from regimens including warfarin. Other important substrates of CYP2C9 are phenytoin, losartan, sulfamethoxazole, tolbutamide and torasemide; their concentrations may increase when coadministered with modafinil.

A second *in vivo* study evaluated the effect of modafinil on the pharmacokinetics of CYP3A4/5 substrates triazolam and a contraceptive containing ethinylestradiol. Compared with placebo, treatment with modafinil decreased the C_{max} and AUC_{∞} of triazolam by 42% and 59%, respectively ($p < 0.0001$ for both), and the C_{max} and AUC_{0-1} of ethinylestradiol by 11% ($p = 0.032$) and 18%, respectively ($p = 0.0044$).^[159] Therefore, patients receiving oral contraceptives should use other methods of contraception while taking modafinil and for 1 month after its withdrawal. Furthermore, in one patient, coadministration of modafinil 200 mg/day for 1 month caused a 50% decrease in ciclosporin (another substrate of CYP3A4) trough concentrations.^[160] Therefore, modafinil seems to induce CYP3A4/5; the two enzymes combined are responsible for metabolism of almost 50% of all currently used medications,

which come from almost every drug class. Some key CYP3A4/5 substrates that can decrease in concentration when coadministered with modafinil include calcium channel antagonists (diltiazem, felodipine, nifedipine and verapamil), benzodiazepines (alprazolam, midazolam and triazolam), HMG-CoA reductase inhibitors (atorvastatin and lovastatin, but not pravastatin), macrolide antibiotics (clarithromycin and erythromycin), antiretroviral agents (indinavir, nelfinavir, ritonavir and saquinavir), and others such as losartan, sildenafil and tacrolimus.^[161]

Furthermore, in CYP2D6-deficient patients (7.7–10% of Whites of North America and Europe, 2–7% of Black Americans, <1% of Chinese, 1–5% of other Asians, 19% of South Africans, 1–2% of Saudi Arabians and 3–6.6% of Hispanics), blood concentrations of some CYP2D6 substrates such as SRIs and tricyclic antidepressants can increase with coadministration of modafinil as a result of inhibition of CYP2C19, which serves as a secondary metabolic pathway for these drugs.^[162]

Since modafinil is in part metabolized by CYP3A4, agents that inhibit (e.g. diltiazem, verapamil, ketoconazole, itraconazole, clarithromycin, erythromycin, indinavir, ritonavir, saquinavir and grapefruit juice) or induce (e.g. rifamycins, carbamazepine, phenobarbital [phenobarbitone], phenytoin, efavirenz, nevirapine and hypericum [St John's wort]) this enzyme may lead to higher or lower modafinil concentrations, respectively.^[157]

7. Safety and Tolerability of Modafinil

The safety and tolerability of modafinil is described here for healthy individuals and patients with various medical disorders.

7.1 Safety and Tolerability in Healthy Individuals

Many adverse events due to modafinil use in excess of placebo have been reported in healthy volunteer studies. Compared with placebo, healthy volunteers receiving modafinil 100–400 mg had a statistically significant higher systolic BP,^[53,55] diastolic BP and heart rate.^[55,74] However, two other

studies reported no changes in BP (systolic or diastolic) or pulse rate with modafinil 100–200 mg.^[71,72]

Healthy volunteers receiving modafinil 100 mg also had significantly higher ratings for somatic anxiety and several bodily symptoms such as shaking, palpitations, dizziness, restlessness, muscular tension, physical tiredness and irritability compared with placebo.^[57] In a study of simulated shift work, subjects receiving modafinil (200–400 mg/day) had increased sleep disturbances including a significant increase in SOL, decrease in total sleep time and less satisfaction with sleep with modafinil during the simulated shift-work periods. During the day shifts, the subjects also reported diminished sleep efficiency.^[70] However, in two other studies, modafinil (100 or 200 mg) given 30 minutes before bed time did not affect sleep initiation, quality or architecture of sleep.^[71,72] It is likely that the effects on sleep are dose related.

In a study of the pharmacokinetics of modafinil, 83% (20 of 24) of subjects receiving modafinil (doses of 200–800 mg) reported at least one adverse effect compared with 25% (2 of 8) of those receiving placebo. The most common adverse events with modafinil were headaches (34%), and insomnia, anxiety and palpitations (each 21%).^[74] Two subjects (one receiving modafinil 400 mg/day and one receiving 800 mg/day) had serious adverse events (moderate ECG abnormalities and moderate anxiety/tachycardia, respectively). One subject receiving modafinil 800 mg/day developed tachycardia (pulse increased from a baseline of 77/98 [supine/standing] to 160/170 beats/min) and an increase in BP (from a baseline supine BP of 125/89 mmHg and standing BP of 122/91 mmHg to 160/115 mmHg). The subject's BP and pulse rate returned to normal 2 days after discontinuation of the drug. The 800 mg dose was discontinued after 3 days of treatment because of clinically significant cardiovascular events such as hypertension and tachycardia.^[74]

7.2 Safety and Tolerability in Clinical Trials

In clinical trials, several adverse events have been reported with significantly greater frequency with modafinil than with placebo.

Insomnia occurred more often with modafinil in one study of SWSD (modafinil 6%, placebo 0%; $p = 0.01$),^[91] in traumatic brain injury (modafinil 19.6%, placebo 3.9%; $\chi^2 = 0.03$),^[100] and in children and adolescents with ADHD who received modafinil as a single dose (modafinil 29%, placebo 4% [$p < 0.05$]; modafinil 24%, placebo 0% [$p < 0.0001$]; modafinil 28%, placebo 7% [$p < 0.05$] in the three studies, respectively),^[102-104] or one of the split modafinil doses (modafinil 200/100 mg 14%, placebo 2%; $p = 0.03$).^[110] No significant differences in the incidence of insomnia were seen in adults with narcolepsy,^[79] OSA^[86,87] or depression.^[120,121] The higher frequency of insomnia and other adverse effects in children may be because on a bodyweight basis they received a much higher dose than adults (340 mg for children weighing <65 lb [30 kg] and 425 mg for children > 65 lb [30 kg]). At the highest dose, the children received 21 mg/kg of the drug, whereas the adults received closer to 2.6–2.7 mg/kg.^[109] In a safety evaluation of 1500 patients, insomnia was reported by 5% patients receiving modafinil and in 1% receiving placebo.^[160]

Headache was reported more frequently with modafinil in some studies of OSA (modafinil [200 and 400 mg combined] 23%, placebo 11% [$p = 0.044$]; modafinil 200 mg 23%, placebo 13% [$p = 0.02$], respectively),^[86,87] narcolepsy (modafinil 200 mg 52%, modafinil 400 mg 51%, placebo 36%; $p < 0.05$ for both doses of modafinil),^[79] ADHD (modafinil 22%, placebo 9%; $p < 0.05$)^[104] and depression (modafinil 22%, placebo 12% [p-value not available]).^[121] However, no significant increase was reported in other studies of narcolepsy,^[80,81] OSA,^[85] SWSD,^[91] ADHD^[102,103] and depression.^[120] In a safety evaluation of 1500 patients, headache was seen in 34% of modafinil and 23% of placebo recipients; occurrence of headache was dose related.^[160]

Nausea occurred more commonly with modafinil in one trial of OSA (modafinil 10%, placebo 2%; $p = 0.01$),^[87] but not in two others,^[85,86] and in two studies of narcolepsy (modafinil 200 mg 13%, modafinil 400 mg 12% and placebo 2%; $p < 0.05$ for both in one study).^[80] In the second study, more nausea was seen with modafinil 400 mg ($p = 0.039$)

but not with modafinil 200 mg.^[81] No significant increase was seen in the third narcolepsy study.^[79] Nausea was also more frequent in one trial of depression (modafinil 9%, placebo 2%; $p < 0.01$)^[120] but not in the second.^[121] No significant increase in nausea was seen in studies of SWSD^[91] and ADHD.^[104] In a safety evaluation of 1500 patients, nausea was seen in 11% of modafinil and 3% of placebo recipients.^[160]

Nervousness occurred more often with modafinil in one study of OSA (modafinil 12%, placebo 3%; $p = 0.024$),^[86] but not in the second,^[87] in narcolepsy subjects with modafinil 400 mg ($p = 0.007$), but not 200 mg,^[81] and with modafinil 100–400 mg in one study of depression (modafinil 20%, placebo 4%).^[121] In a second study of depression, more modafinil recipients complained of being jittery (modafinil 4%, placebo 1%; $p = 0.03$).^[120] No significant increase in nervousness was seen in other studies of narcolepsy,^[79,80] ADHD^[102,104] and SWSD.^[91] In a safety evaluation of 1500 patients, nervousness was reported in 7% of modafinil versus 3% of placebo recipients.^[160]

Rhinitis occurred more frequently with modafinil 200 mg (11%) than with placebo (3%; $p < 0.05$), but not with modafinil 400 mg in patients with narcolepsy;^[80] however, several other studies reported no significant increase in rhinitis.^[79,86,87,91,102] In a safety evaluation of 1500 patients, rhinitis was seen in 7% of modafinil and 3% of placebo recipients.^[160]

Decreased appetite with modafinil was reported in three studies of ADHD: modafinil 16%, 14% and 18% vs placebo 4%, 2% and 3%, respectively ($p < 0.05$ for all).^[102-104] Weight loss was significantly greater with modafinil in three studies of ADHD, occurring in 7% of modafinil and 1% of placebo recipients ($p < 0.05$ in one trial).^[104] In the two other studies, the mean weight increased by 0.8 and 1 kg, respectively, with placebo, whereas it decreased by 0.8 and 0.6 kg, respectively, with modafinil ($p < 0.0001$ for both studies).^[102,103] A significant decrease in body mass index (BMI) was reported in one study of OSA (modafinil -0.32 , placebo 0; $p = 0.019$).^[86] Mean (\pm SD) loss in weight of 0.6 ± 2.9 kg was seen with modafinil versus 0.4 ± 2.2 kg

with placebo ($p < 0.0001$) in one trial of depression.^[120] No change in weight occurred in one study of narcolepsy.^[79]

Multiple studies reported no significant changes in vital signs^[78-81,85,87,91,95,102-104,120,123,125] or ECG.^[79,85,86,91,95,98,102-104] However, many of these studies excluded patients with hypertension,^[85,102-104,120] tachycardia,^[102-104,120] ECG evidence of ischaemia or ventricular hypertrophy,^[123] any significant clinically active disease^[79,80,86,87] and significant cardiac disease.^[81,85] A small but statistically significant difference in sitting BP was reported in one OSA trial (1 mmHg increase with modafinil, 2.6 mmHg decrease with placebo; $p = 0.035$); this occurred despite a significant decrease in BMI with modafinil.^[86] In the safety evaluation of 1500 patients, 2.4% of patients on modafinil required new or increased antihypertensive therapy compared with 0.7% with placebo; the differences were larger in patients with OSA, with 3.4% patients on modafinil and 1.1% on placebo requiring such a change.^[160]

Significantly more patients receiving modafinil withdrew from studies as a result of adverse events (modafinil 10%, placebo 1% [$p = 0.016$],^[86] modafinil 10%, placebo 3% [$p < 0.05$],^[87] modafinil 300 mg 20%, placebo 4% [p-value not available],^[92] modafinil 11%, placebo 5.6% [$\chi^2 = 0.03$]^[122]). Overall, in placebo-controlled trials, 8% receiving modafinil discontinued therapy compared with 3% with placebo.^[160]

In individuals with ADHD, a large number of adverse dermatological reactions have been reported: 12 patients had serious drug rashes, two had confirmed EM/SJS, three had early prodromal EM/SJS and seven had symptoms suggestive of prodromal EM/SJS. This constituted a rate of 1.25%, which is hundreds of times higher than the background rate of SJS (1–2 million per year).^[109]

Two patients with major depressive disorder developed suicidal ideation in the second week of a trial of combined modafinil and SRIs therapy when the dosage of modafinil was escalated from 100 to 200 mg/day; the sertraline dosage had been simulta-

neously increased from 50 to 100 mg/day in one patient; the other was in the second week of fluoxetine 20 mg/day therapy.^[122]

One patient each in two separate studies of modafinil use in schizophrenia developed psychosis: one during the first week of taking modafinil 100 mg/day required hospitalization^[126] and the other 4 days after taking a single dose of modafinil 100 mg.^[127] Another patient with post-polio fatigue also developed psychosis shortly after starting modafinil 200 mg/day.^[150] Acute psychosis has also been described in one patient with SWSD without any history of psychiatric disorder^[163] while receiving modafinil 400 mg and in another patient with schizophrenia while receiving modafinil 800 mg/day.^[164]

Recently, a single fatal case of multi-organ hypersensitivity reaction was described in a 31-year-old woman who developed periorbital oedema, pruritic facial and scalp rash, and clear conjunctival discharge 1 week after starting modafinil for fatigue associated with MS. Despite hospitalization and treatment with antihistamines, histamine H₂-receptor antagonists and stress dose corticosteroids, she continued to worsen and died from a multi-organ hypersensitivity reaction involving the myocardium, skeletal muscle, liver and spinal cord. This led to modification of the modafinil package insert to include a warning about multi-organ hypersensitivity reactions.^[165] Provigil®[†] labelling also recommends that modafinil not be used in patients with left ventricular hypertrophy (LVH) or in patients with mitral valve prolapse (MVP) who have experienced the MVP syndrome (ECG changes, chest pain or arrhythmia) with other CNS stimulants. Modafinil has not been studied in patients with recent myocardial infarction or unstable angina pectoris, therefore caution is advised in such patients.^[160] Modafinil has a category C for pregnancy.^[160]

8. Dosage and Administration

Modafinil (Provigil®) is available in 100 and 200 mg tablets in the US. The recommended dose for patients with OSA and narcolepsy is 200 mg/day

1 The use of trade names is for product identification purposes only and does not imply endorsement.

given as a single dose in the morning. In patients with narcolepsy experiencing residual late evening sleepiness, a single dose of 400 mg in the morning may be tried, failing which split doses of 400 or 600 mg/day may be beneficial. For patients with SWSD, modafinil 200 mg should be given 1 hour prior to the start of the night shift; a dose of 300 mg improves the QOL more than the 200 mg dose. In patients with hepatic impairment, the dosage should be halved. The dosage should also be decreased in the elderly. Modafinil use in patients with severe renal failure needs careful consideration since modafinil acid levels are markedly increased, with unclear safety implications; no dosage recommendations can be made for such patients. Due consideration should be given to drug interactions with drugs that are metabolized by the CYP isoenzymes, especially CYP3A4/5 and CYP2C9, but also CYP1A2, CYP2B6, CYP2C19 and CYP2D6 in CYP2D6-deficient individuals.

9. Summary and Conclusions

EDS is a pervasive problem with high personal and societal costs. Modafinil is a wake-promoting agent that is pharmacologically different from other CNS stimulants. Its use has been investigated in healthy volunteers and in many disorders associated with excessive sleepiness, fatigue, impaired cognition and other symptoms.

The evidence that modafinil improves cognition in non-sleep-deprived healthy adults is controversial. However, in sleep-deprived healthy adults, modafinil 400 mg/day improves mood, fatigue, sleepiness and cognition to the same extent as caffeine 600 mg/day, although with a longer duration of action because of its longer $t_{1/2}$.

Modafinil has been approved by the FDA for use in patients with narcolepsy, SWSD and OSA with residual EDS despite optimal treatment with CPAP. It improves excessive sleepiness and illness severity in all three disorders, although ESS scores were not normalized in any of the narcolepsy studies and the SOL on MWT remained below the daytime normal value of 6 minutes throughout the night in SWSD. In patients with OSA, the ESS scores normalized in

only 38–51% of subjects with modafinil, the SOLs on MSLT improved by an average of 1.2 minutes and the ability to remain awake on MWT improved by 1.5–1.8 minutes. Modafinil also improved QOL and some measures of PVT in patients with OSA and SWSD. However, the effects of modafinil on productivity, safety on the job and morbidities associated with these disorders have not been ascertained; subjects with SWSD taking modafinil had fewer accidents and near accidents on the commute home but not during the night shifts. In patients with OSA, continued use of CPAP is essential because it may benefit the adverse cardiovascular effects of OSA. Modafinil does not ameliorate cataplexy in patients with narcolepsy and other medications are needed to control it. The long-term safety and efficacy of modafinil, like most drugs, has not been determined in placebo-controlled trials in any of these disorders.

Modafinil has shown some beneficial effect in other disorders, but caution and further trials are necessary. Modafinil improved EDS in three small trials of myotonic dystrophy, which collectively had 68 subjects and treatment periods lasting 2–4 weeks; larger studies with longer duration are needed to confirm these results. Modafinil is efficacious in children and adolescents with ADHD, but its approval by the FDA has been prevented in part due to the occurrence of serious adverse dermatological events including SJS and EM, the rate of which is hundreds of times higher than the background rate. In a very small crossover trial ($n = 21$ non-concurrent subjects, raising concerns about selection bias) in adults with ADHD, with treatment periods lasting only 2 weeks, modafinil was found to be as effective as dexamfetamine. Larger and more long-term studies are needed before these findings can be applied to clinical practice. Modafinil was efficacious for depressive symptoms in bipolar disorder in one trial; patients with stimulant-induced mania were excluded from this trial and there was a very large withdrawal rate (32%), raising questions about the validity of the results. Furthermore, since CNS stimulants can precipitate mania in bipolar disorder, modafinil should be used cautiously in such patients. A single

dose of modafinil seemed to hasten recovery from general anaesthesia after same-day surgery in ASA class I and II patients. However, 14 variables were compared in 34 subjects, raising the likelihood of a type I error. More data are needed before these results can be applied to clinical practice. In ER physicians, modafinil administration after a night shift made it easier for them to attend didactic lectures, but did not improve their ability to drive home and caused sleep disturbances subsequently. More adverse events were seen with modafinil.

A substantial placebo effect was seen in many disorders associated with fatigue and excessive sleepiness. Modafinil and placebo produced comparable improvement in measures of fatigue, such as FSS, BFI and MFIS, and of EDS, such as ESS, in disorders like traumatic brain injury,^[100] major depressive disorder,^[120-122] schizophrenia,^[126] post-polio syndrome and MS. Similar improvements were seen in multiple depression scales in major depressive disorder,^[120-122] in CGI-I in major depressive disorder and schizophrenia^[120,126] and SANS alogia scale in schizophrenia.^[126] Modafinil did not provide any benefit greater than placebo and is, therefore, not recommended for any of these disorders. These data attest to the need for making clinical decisions based on placebo-controlled trials, especially for subjective symptoms such as fatigue and excessive sleepiness.

Evidence for usefulness of modafinil is contradictory in Parkinson's disease. Three trials gave conflicting results: one parallel group trial showed no improvement in EDS,^[93] a second trial showed significant improvement in EDS^[95] and in the third trial, ESS scores improved but MWT did not.^[94] Thus, at present, there is no consistent evidence that modafinil improves EDS in Parkinson's disease. Contradictory results were also seen in two trials of cocaine addiction; in one trial, more cocaine-negative urine tests were turned in, although self-reported cocaine use, money spent and cocaine cravings were unchanged.^[142] In the second trial, modafinil reduced the interest in buying cocaine and the amount willing to pay for it in the laboratory setting, but cocaine-positive urine tests in the outpatient

setting did not change.^[143] Thus, at present, modafinil cannot be recommended for cocaine use.

Modafinil also produced contradictory results for cognition and did not benefit fatigue, QOL or mood in chronic fatigue syndrome. However, the sample size in this study was too small for adequate statistical power, and larger studies are needed to clarify the utility of modafinil for chronic fatigue syndrome.

In individuals with a history of poly-substance abuse, modafinil had a profile very similar to methylphenidate and in adults without history of substance abuse, modafinil had a profile very similar to dexamfetamine on several measures of abuse potential.^[56] Thus, modafinil may have some abuse/addictive potential. Further studies are needed to delineate this issue.

Modafinil induces and inhibits several CYP isoenzymes *in vitro*. With concomitant administration of modafinil, concentrations of CYP3A4/5 substrates ethinylestradiol, triazolam and ciclosporin decreased, and concentrations of CYP2C9 substrate S-warfarin increased (in some patients). Modafinil has the theoretical potential of interacting with drugs from almost all classes; this issue needs careful consideration when modafinil is added to or removed from drug regimens including these drugs. Modafinil is metabolized in part by CYP3A4; drugs that induce or inhibit this enzyme can change modafinil concentrations when coadministered concurrently.

Metabolism of modafinil is reduced in the elderly and in patients with hepatic disease requiring dosage reductions. Modafinil concentrations are raised slightly in severe renal insufficiency but modafinil acid concentrations are greatly increased, with unclear safety implications. It is unclear whether modafinil can be used safely in such patients.

Common adverse events with modafinil include insomnia, headache, nausea, nervousness and hypertension, some of which are dose related. Decreased appetite, weight loss and serious dermatological reactions were seen with greater frequency in children with ADHD, probably because of the much higher doses on mg/kg basis in these individuals. Isolated

cases of psychosis have been described in patients with schizophrenia and post-polio fatigue as well as in those with no psychiatric disorder; two cases of suicidal ideation occurred when modafinil was used in conjunction with SRIs in patients with major depressive disorder. A single fatal case of multi-organ hypersensitivity has also been described. Modafinil should not be used in patients with LVH or MVP who develop the MVP syndrome with other stimulants. Caution is advised for its use in patients with recent myocardial infarction or unstable angina. Modafinil is category C for pregnancy.

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References

- National Sleep Foundation. Omnibus sleep in America poll. Washington, DC: National Sleep Foundation, 2001
- Hasler G, Buysse DJ, Gamma A, et al. Excessive daytime sleepiness in young adults: a 20-year prospective community study. *J Clin Psychiatry* 2005; 66: 521-9
- Pilcher JJ, Huffcutt AI. Effects of sleep deprivation on performance: a meta-analysis. *Sleep* 1996 May; 19 (4): 318-2
- Dinges DF, Pack F, Williams K, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. *Sleep* 1997 Apr; 20 (4): 267-77
- Van Dongen HP, Maislin G, Mullington JM, et al. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep* 2003 Mar 15; 26 (2): 117-26
- NHTSA. National Highway Traffic Safety Administration report [online]. Available from URL: http://www.nhtsa.gov/people/injury/research/drowsy_driver.html [Accessed 2006 Apr 25]
- Leger D. The cost of sleep-related accidents: a report for the National Commission on Sleep Disorders Research. *Sleep* 1994 Feb; 17 (1): 84-93
- Saper CB, Scammell TE, Lu J. Hypothalamic regulation of sleep and circadian rhythms. *Nature* 2005 Oct 27; 437 (7063): 1257-63
- Fuller PM, Gooley JJ, Saper CB. Neurobiology of the sleep-wake cycle: sleep architecture, circadian regulation, and regulatory feedback. *J Biol Rhythms* 2006 Dec; 21 (6): 482-93
- Minzenberg MJ, Carter CS. Modafinil: a review of neurochemical actions and effects on cognition. *Neuropsychopharmacology* 2008 Jun; 33 (7): 1477-502
- Mignot E, Nishino S, Guilleminault C, et al. Modafinil binds to the dopamine uptake carrier site with low affinity. *Sleep* 1994 Aug; 17: 436-7
- De Séréville JE, Boer C, Rambert FA, et al. Lack of pre-synaptic dopaminergic involvement in modafinil activity in anaesthetized mice: in vivo voltammetry studies. *Neuropharmacology* 1994 Jun; 33: 755-61
- Simon P, Hémet C, Ramassamy C, et al. Non-amphetaminic mechanism of stimulant locomotor effect of modafinil in mice. *Eur Neuropsychopharmacol* 1995 Dec; 5 (4): 509-14
- Akaoka H, Roussel B, Lin JS, et al. Effect of modafinil and amphetamine on the rat catecholaminergic neuron activity. *Neurosci Lett* 1991 Feb 11; 123 (1): 20-2
- Duteil J, Rambert FA, Pessonnier J, et al. Central alpha 1-adrenergic stimulation in relation to the behaviour stimulating effect of modafinil: studies with experimental animals. *Eur J Pharmacol* 1990 May 3; 180 (1): 49-58
- Lin JS, Roussel B, Akaoka H, et al. Role of catecholamines in the modafinil and amphetamine induced wakefulness, a comparative pharmacological study in the cat. *Brain Res* 1992 Sep 25; 591 (2): 319-26
- Eagle DM, Tufft MR, Goodchild HL, et al. Differential effects of modafinil and methylphenidate on stop-signal reaction time task performance in the rat, and interactions with the dopamine receptor antagonist cis-flupenthixol. *Psychopharmacology (Berl)* 2007 Jun; 192 (2): 193-206
- de Saint Hilaire Z, Oroscio M, Rouch C, et al. Variations in extracellular monoamines in the prefrontal cortex and medial hypothalamus after modafinil administration: a microdialysis study in rats. *Neuroreport* 2001 Nov 16; 12 (16): 3533-7
- Wisor JP, Nishino S, Sora I, et al. Dopaminergic role in stimulant-induced wakefulness. *J Neurosci* 2001; 21: 1787-94
- Murillo-Rodriguez E, Haro R, Palomero-Rivero M, et al. Modafinil enhances extracellular levels of dopamine in the nucleus accumbens and increases wakefulness in rats. *Behav Brain Res* 2007 Jan 25; 176 (2): 353-7
- Dopheide MM, Morgan RE, Rodvelt KR, et al. Modafinil evokes striatal [(3)H]dopamine release and alters the subjective properties of stimulants. *Eur J Pharmacol* 2007 Jul 30; 568 (1-3): 112-23
- Korotkova TM, Klyuch BP, Ponomarenko AA, et al. Modafinil inhibits rat midbrain dopaminergic neurons through D2-like receptors. *Neuropharmacology* 2007 Feb; 52 (2): 626-33
- Madras BK, Xie Z, Lin Z, et al. Modafinil occupies dopamine and norepinephrine transporters in vivo and modulates the transporters and trace amine activity in vitro. *J Pharmacol Exp Ther* 2006 Nov; 319 (2): 561-9
- Mignot E, Renaud A, Nishino S, et al. Canine cataplexy is preferentially controlled by adrenergic mechanisms: evidence using monoamine selective uptake inhibitors and release enhancers. *Psychopharmacology (Berl)* 1993; 113 (1): 76-82
- Nishino S, Fruhstorfer B, Arrigoni J, et al. Further characterization of the alpha-1 receptor subtype involved in the control of cataplexy in canine narcolepsy. *J Pharmacol Exp Ther* 1993 Mar; 264 (3): 1079-84
- Gallopin T, Luppi PH, Rambert FA, et al. Effect of the wake-promoting agent modafinil on sleep-promoting neurons from the ventrolateral preoptic nucleus: an in vitro pharmacological study. *Sleep* 2004 Feb 1; 27 (1): 19-25
- Stone EA, Cotecchia S, Lin Y, et al. Role of brain alpha 1B-adrenoceptors in modafinil-induced behavioral activity. *Synapse* 2002 Dec 15; 46 (4): 269-70
- Wisor JP, Eriksson KS. Dopaminergic-adrenergic interactions in the wake promoting mechanism of modafinil. *Neuroscience* 2005; 132: 1027-34
- Ferraro L, Antonelli T, O'Connor WT, et al. The antinarcotic drug modafinil increases glutamate release in thalamic areas and hippocampus. *Neuroreport* 1997 Sep 8; 8 (13): 2883-7

30. Ferraro L, Antonelli T, O'Connor WT, et al. The effects of modafinil on striatal, pallidal and nigral GABA and glutamate release in the conscious rat: evidence for a preferential inhibition of striato-pallidal GABA transmission. *Neurosci Lett* 1998 Sep 4; 253 (2): 135-8
31. Ferraro L, Tanganelli S, O'Connor WT, et al. The vigilance promoting drug modafinil decreases GABA release in the medial preoptic area and in the posterior hypothalamus of the awake rat: possible involvement of the serotonergic 5-HT3 receptor. *Neurosci Lett* 1996 Dec 6; 220: 5-8
32. Ferraro L, Antonelli T, Tanganelli S, et al. The vigilance promoting drug modafinil increases extracellular glutamate levels in the medial preoptic area and the posterior hypothalamus of the conscious rat: prevention by local GABA_A receptor blockade. *Neuropsychopharmacology* 1999 Apr; 20 (4): 346-56
33. Tanganelli S, Fuxe K, Ferraro L, et al. Inhibitory effects of the psychoactive drug modafinil on γ -aminobutyric acid outflow from the cerebral cortex of the awake freely moving guinea pig: possible involvement of 5-hydroxytryptamine mechanisms. *Naunyn Schmiedebergs Arch Pharmacol* 1992; 345: 461-5
34. Tanganelli S, Ferraro L, Bianchi C, et al. 6-Hydroxy-dopamine treatment counteracts the reduction of cortical GABA release produced by the vigilance promoting drug modafinil in the awake freely moving guinea-pig. *Neurosci Lett* 1994 Apr 25; 171 (1-2): 201-4
35. Tanganelli S, Pérez de la Mora M, Ferraro L, et al. Modafinil and cortical gamma-aminobutyric acid outflow: modulation by 5-hydroxytryptamine neurotoxins. *Eur J Pharmacol* 1995 Jan 24; 273 (1-2): 63-71
36. Ferraro L, Tanganelli S, O'Connor WT, et al. The vigilance promoting drug modafinil increases dopamine release in the rat nucleus accumbens via the involvement of a local GABAergic mechanism. *Eur J Pharmacol* 1996 Jun 13; 306: 33-9
37. Ferraro L, Antonelli T, O'Connor WT, et al. Modafinil: an antinarcotic drug with a different neurochemical profile to d-amphetamine and dopamine uptake blockers. *Biol Psychiatry* 1997 Dec 15; 42 (12): 1181-3
38. Ferraro L, Fuxe K, Tanganelli S, et al. Amplification of cortical serotonin release: a further neurochemical action of the vigilance-promoting drug modafinil. *Neuropharmacology* 2000 Aug 23; 39 (11): 1974-83
39. Ferraro L, Fuxe K, Tanganelli S, et al. Differential enhancement of dialysate serotonin levels in distinct brain regions of the awake rat by modafinil: possible relevance for wakefulness and depression. *J Neurosci Res* 2002 Apr 1; 68 (1): 107-12
40. Ferraro L, Fuxe K, Agnati L, et al. Modafinil enhances the increase of extracellular serotonin levels induced by the antidepressant drugs fluoxetine and imipramine: a dual probe microdialysis study in awake rat. *Synapse* 2005 Mar 15; 55 (4): 230-41
41. Nishino S. The hypocretin/orexin system in health and disease. *Biol Psychiatry* 2003 Jul 15; 54 (2): 87-95
42. Chemelli RM, Willie JT, Sinton CM, et al. Narcolepsy in orexin knockout mice: molecular genetics of sleep regulation. *Cell* 1999 Aug 20; 98 (4): 437-51
43. Scammell TE, Estabrooke IV, McCarthy MT, et al. Hypothalamic arousal regions are activated during modafinil-induced wakefulness. *J Neurosci* 2000 Nov 15; 20 (22): 8620-8
44. Willie JT, Renthal W, Chemelli RM, et al. Modafinil more effectively induces wakefulness in orexin-null mice than in wild-type littermates. *Neuroscience* 2005; 130 (4): 983-95
45. Ishizuka T, Sakamoto Y, Sakurai T, et al. Modafinil increases histamine release in the anterior hypothalamus of rats. *Neurosci Lett* 2003 Mar 20; 339 (2): 143-6
46. Ishizuka T, Murakami M, Yamatodani A. Involvement of central histaminergic systems in modafinil-induced but not methylphenidate-induced increases in locomotor activity in rats. *Eur J Pharmacol* 2008 Jan 14; 578 (2-3): 209-15
47. Lagarde D, Milhaud C. Electroencephalographic effects of modafinil, an alpha-1- adrenergic psychostimulant, on the sleep of rhesus monkeys. *Sleep* 1990 Oct; 13: 441-8
48. Shelton J, Nishino S, Vaught J, et al. Comparative effects of modafinil and amphetamine on daytime sleepiness and catalepsy of narcoleptic dogs. *Sleep* 1995 Dec; 18: 817-26
49. Touret M, Sallanon-Moulin M, Jouvet M. Awakening properties of modafinil without paradoxical sleep rebound: comparative study with amphetamine in the rat. *Neurosci Lett* 1995 Apr 7; 189: 43-6
50. Edgar DM, Seidel WF. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence in the rat. *J Pharmacol Exp Ther* 1997 Nov; 283: 757-69
51. Panckeri KA, Schotland HM, Pack AI, et al. Modafinil decreases hypersomnolence in the English bulldog, a natural animal model of sleep-disordered breathing. *Sleep* 1996 Oct; 19: 626-31
52. Lin JS, Gervasoni D, Hou Y, et al. Effects of amphetamine and modafinil on the sleep/wake cycle during experimental hypersomnia induced by sleep deprivation in the cat. *J Sleep Res* 2000 Mar; 9 (1): 89-96
53. Turner DC, Robbins TW, Clark L, et al. Cognitive enhancing effects of modafinil in healthy volunteers. *Psychopharmacology* 2003; 165: 260-9
54. Baranski JV, Pigeau R, Dinich P, et al. Effects of modafinil on cognitive and meta-cognitive performance. *Hum Psychopharmacol* 2004 Jul; 19 (5): 323-32
55. Müller U, Steffenhagen N, Regenthal R, et al. Effects of modafinil on working memory processes in humans. *Psychopharmacology* 2004; 177: 161-9
56. Makris AP, Rush CR, Frederich RC, et al. Behavioral and subjective effects of d-amphetamine and modafinil in healthy adults. *Exp Clin Psychopharmacol* 2007 Apr; 15 (2): 123-33
57. Randall DC, Shneerson JM, Plaha KK, et al. Modafinil affects mood, but not cognitive function, in healthy young volunteers. *Hum Psychopharmacol* 2003; 18: 163-73
58. Randall DC, Fleck NL, Shneerson JM, et al. The cognitive-enhancing properties of modafinil are limited in non-sleep-deprived middle-aged volunteers. *Pharmacol Biochem Behav* 2004; 77: 547-55
59. Randall DC, Viswanath A, Bharania P, et al. Does modafinil enhance cognitive performance in young volunteers who are not sleep-deprived? *J Clin Psychopharmacol* 2005; 25: 175-9
60. Taneja I, Haman K, Shelton RC, et al. A randomized, double-blind, crossover trial of modafinil on mood. *J Clin Psychopharmacol* 2007 Feb; 27 (1): 76-9
61. Lagarde D, Batejat D. Disrupted sleep-wake rhythm and performance: advantages of modafinil. *Mil Psychol* 1995; 7: 165-91
62. Pigeau R, Naitoh P, Buguet A, et al. Modafinil, d-amphetamine and placebo during 64h of sustained mental work. I, effects on mood, fatigue, cognitive performance and body temperature. *J Sleep Res* 1995; 4: 212-28

63. Stivalet P, Esquivie D, Barraud P-A, et al. Effects of modafinil on attentional processes during 60h of sleep deprivation. *Hum Psychopharmacol* 1998; 13: 501-7
64. Wesensten NJ, Belenky G, Kautz MA, et al. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. *Psychopharmacology* 2002; 159: 238-47
65. Wesensten NJ, Belenky G, Thorne DR, et al. Modafinil vs. caffeine: effects on fatigue during sleep deprivation. *Aviat Space Environ Med* 2004 Jun; 75 (6): 520-5
66. Wesensten NJ, Killgore WD, Balkin TJ. Performance and alertness effects of caffeine, dextroamphetamine, and modafinil during sleep deprivation. *J Sleep Res* 2005 Sep; 14 (3): 255-66
67. Dinges DF, Arora S, Darwish M, et al. Pharmacodynamic effects on alertness of single doses of armodafinil in healthy subjects during a nocturnal period of acute sleep loss. *Curr Med Res Opin* 2006 Jan; 22 (1): 159-67
68. Lagarde D, Batejat D, Van Beers P, et al. Interest of modafinil, a new psychostimulant, during a sixty-hour sleep deprivation experiment. *Fundam Clin Pharmacol* 1995; 9 (3): 271-9
69. Walsh JK, Randazzo AC, Stone KL, et al. Modafinil improves alertness, vigilance, and executive function during simulated night shifts. *Sleep* 2004 May 1; 27 (3): 434-9
70. Hart CL, Haney M, Vosburg SK, et al. Modafinil attenuates disruptions in cognitive performance during simulated night-shift work. *Neuropsychopharmacology* 2006 Jul; 31 (7): 1526-36
71. Saletu B, Frey R, Krupka M, et al. Differential effects of a new adrenergic agonist: modafinil and D-amphetamine on sleep and early morning behaviour in young healthy volunteers. *Int J Clin Pharmacol Res* 1989; 9 (3): 183-95
72. Saletu B, Frey R, Krupka M, et al. Differential effects of the new adrenergic agonist modafinil and D-amphetamine on sleep and early morning behaviour in elderlies. *Arzneimittelforschung* 1989; 39 (10): 1268-73
73. Robertson PR, Hellriegel ET. Clinical pharmacokinetic profile of modafinil. *Clin Pharmacokinet* 2003; 42 (2): 123-7
74. Wong YN, Simcoe D, Hartman LN, et al. A double-blind, placebo-controlled, ascending-dose evaluation of the pharmacokinetics and tolerability of modafinil tablets in healthy male volunteers. *J Clin Pharmacol* 1999 Jan; 39 (1): 30-40
75. Wong YN, King SP, Simcoe D, et al. Open-label, single-dose pharmacokinetic study of modafinil tablets: influence of age and gender in normal subjects. *J Clin Pharmacol* 1999 Mar; 39 (3): 281-8
76. Moachon G, Kanmacher I, Clenet M, et al. Pharmacokinetic profile of modafinil. *Drugs Today* 1996; 32: 327-37
77. Cephalon Inc. Provigil (modafinil) tablets: prescribing information [online]. Available from URL: <http://www.provigil.com/> [Accessed 2007 Feb 22]
78. Billiard M, Besset A, Montplaisir J, et al. Modafinil: a double-blind multicentric study. *Sleep* 1994 Dec; 17 (8 Suppl.): S107-12
79. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil for the treatment of pathological somnolence in narcolepsy. *Ann Neurol* 1998 Jan; 43 (1): 88-97
80. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 2000 Mar 14; 54 (5): 1166-75
81. Broughton RJ, Fleming JA, George CF, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of excessive daytime sleepiness in narcolepsy. *Neurology* 1997; 49: 444-51
82. Schwartz JR, Feldman NT, Bogan RK, et al. Dosing regimen effects of modafinil for improving daytime wakefulness in patients with narcolepsy. *Clin Neuropharmacol* 2003 Sep-Oct; 26 (5): 252-7
83. Schwartz JR, Nelson MT, Schwartz ER, et al. Effects of modafinil on wakefulness and executive function in patients with narcolepsy experiencing late-day sleepiness [published erratum appears in *Clin Neuropharmacol* 2004 May-Jun; 27 (3): 152]. *Clin Neuropharmacol* 2004 Mar-Apr; 27 (2): 74-9
84. Guilleminault C, Abad VC. Obstructive sleep apnea syndromes. *Med Clin North Am* 2004 May; 88 (3): 611-30
85. Kingshott RN, Vennelle M, Coleman EL, et al. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual daytime excessive sleepiness in the sleep apnea/hypopnea syndrome. *Am J Respir Crit Care Med* 2001; 163: 918-23
86. Pack AI, Black JE, Schwartz JRL, et al. Modafinil as adjunct therapy for daytime sleepiness in the obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 164: 1675-81
87. Black JE, Hirshkowitz M. Modafinil for treatment of residual excessive sleepiness in nasal continuous positive airway pressure-treated obstructive sleep apnea/hypopnea syndrome. *Sleep* 2005 Apr 1; 28 (4): 464-71
88. Dinges D, Weaver TE. Effects of modafinil on sustained attention performance and quality of life in OSA patients with residual sleepiness while being treated with nCPAP. *Sleep Medicine* 2003; 4: 393-402
89. Beers TM. Flexible schedules and shift work: replacing the '9-to-5' workday? *Monthly Labor Rev* 2000; 123: 33-40
90. Drake CL, Roehrs T, Richardson G, et al. Shift work sleep disorder: prevalence and consequences beyond that of symptomatic day workers. *Sleep* 2004 Dec 15; 27 (8): 1453-62
91. Czeisler CA, Walsh JK, Roth T, et al., for the U.S. Modafinil in Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with shift-work sleep disorder. *N Engl J Med* 2005 Aug 4; 353 (5): 476-86
92. Erman MK, Rosenberg R, for the US Modafinil Shift Work Sleep Disorder Study Group. Modafinil for excessive sleepiness associated with chronic shift work sleep disorder: effects on patient functioning and health-related quality of life. *Prim Care Companion J Clin Psychiatry* 2007; 9 (3): 188-94
93. Ondo WG, Fayle R, Atassi F, et al. Modafinil for daytime somnolence in Parkinson's disease: double blind, placebo controlled parallel trial. *J Neurol Neurosurg Psychiatry* 2005 Dec; 76 (12): 1636-9
94. Hogl B, Saletu M, Brandauer E, et al. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled trial. *Sleep* 2002; 25: 905-9
95. Adler CH, Caviness JN, Hentz JG, et al. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Movement Disorders* 2003; 18: 287-93
96. Laberge L, Bégin P, Montplaisir J, et al. Sleep complaints in patients with myotonic dystrophy. *J Sleep Res* 2004 Mar; 13 (1): 95-100
97. MacDonald JR, Hill JD, Tarnopolsky MA. Modafinil reduces excessive somnolence and enhances mood in patients with myotonic dystrophy. *Neurology* 2002; 59: 1876-80
98. Talbot K, Stradling J, Crosby J, et al. Reduction in excess daytime sleepiness by modafinil in patients with myotonic dystrophy. *Neuromuscul Disord* 2003; 13: 357-64

99. Wintzen AR, Lammers GJ, van Dijk JG. Does modafinil enhance activity of patients with myotonic dystrophy? A double-blind placebo-controlled crossover study. *J Neurol* 2007 Jan; 254 (1): 26-8
100. Jha A, Weintraub A, Allshouse A, et al. A randomized trial of modafinil for the treatment of fatigue and excessive daytime sleepiness in individuals with chronic traumatic brain injury. *J Head Trauma Rehabil* 2008 Jan-Feb; 23 (1): 52-63
101. Visser SN, Lesesne CA. Prevalence of diagnosis and medication treatment for attention-deficit/hyperactivity disorder: United States, 2003. *MMWR Morb Mortal Wkly Rep* 2005; 54 (34): 842-7
102. Biederman J, Swanson JM, Wigal SB, et al. Efficacy and safety of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, flexible-dose study. *Pediatrics* 2005 Dec; 116 (6): e777-84
103. Swanson JM, Greenhill LL, Lopez FA, et al. Modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder: results of a randomized, double-blind, placebo-controlled, fixed-dose study followed by abrupt discontinuation. *J Clin Psychiatry* 2006 Jan; 67 (1): 137-47
104. Greenhill LL, Biederman J, Boellner SW, et al. A randomized, double-blind, placebo-controlled study of modafinil film-coated tablets in children and adolescents with attention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry* 2006 May; 45 (5): 503-11
105. DuPaul G, Power T, Anastopoulos A, et al. *ADHD rating scale-IV: home and school versions*. New York: Guilford Publications, 1998
106. Conners CK. *Conners' parent rating scales-revised: short form (CPRS-R:S)*. North Tonawanda (NY): Multi-Health Systems, 1997
107. Gresham FM, Elliot SN. *Social skills rating scale*. Circle Pines (MN): American Guidance Service, 1990
108. Landgraf JM, Abetz L, Ware JE. *The child health questionnaire (CHQ): a user's manual*. Boston (MA): Health Act, 1999
109. Department of Health and Human Services, Food and Drug Administration. Center for Drug Evaluation and Research. *Psychopharmacologic Drugs Advisory Committee Meeting: March 2006* [online]. Available from URL: <http://www.fda.gov/ohrms/dockets/ac/06/transcripts/2006-4212T1.pdf> [Accessed 2007 Feb 24]
110. Biederman J, Swanson JM, Wigal SB, et al. Modafinil ADHD Study Group. A comparison of once-daily and divided doses of modafinil in children with attention-deficit/hyperactivity disorder: a randomized, double-blind, and placebo-controlled study. *J Clin Psychiatry* 2006 May; 67 (5): 727-35
111. Conners CK, Sitarenios G, Parker JD, et al. The revised Conners' Parent Rating Scale (CPRS-R): factor structure, reliability, and criterion validity. *J Abnorm Child Psychol* 1998 Aug; 26 (4): 257-68
112. Amiri S, Mohammadi MR, Mohammadi M, et al. Modafinil as a treatment for Attention-Deficit/Hyperactivity Disorder in children and adolescents: a double blind, randomized clinical trial. *Prog Neuropsychopharmacol Biol Psychiatry* 2008 Jan 1; 32 (1): 145-9
113. Faraone SV, Biederman J, Mick E. The age-dependent decline of attention deficit hyperactivity disorder: a meta-analysis of follow-up studies. *Psychol Med* 2006 Feb; 36 (2): 159-65
114. Moss SB, Nair R, Vallarino A, et al. Attention deficit/hyperactivity disorder in adults. *Prim Care* 2007 Sep; 34 (3): 445-73
115. Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention deficit hyperactivity disorder in adults. *J Child Adolesc Psychopharmacol* 2000; 10 (4): 311-20
116. Murphy KR, Barkley RA. Updated adult norms for the ADHD Behavior Checklist for Adults. *ADHD Report* 1996; 4: 12-13
117. Barkley RA, Murphy KR. *Attention-deficit hyperactivity disorder: a clinical workbook*. New York (NY): Guilford Press, 1998: 131-3
118. Golden CJ. Identification of brain disorders by the Stroop Color and Word Test. *J Clin Psychol* 1976; 32: 654-8
119. Kessler RC, Berglund P, Demler O, et al. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Arch Gen Psychiatry* 2005; 62: 593-602
120. Fava M, Thase ME, DeBattista C. A multicenter, placebo-controlled study of modafinil augmentation in partial responders to selective serotonin reuptake inhibitors with persistent fatigue and sleepiness. *J Clin Psychiatry* 2005 Jan; 66 (1): 85-93
121. DeBattista C, Dogramji K, Menza MA, et al. Adjunct modafinil for short-term treatment of fatigue and sleepiness in patients with major depressive disorder: a preliminary double-blind, placebo-controlled study. *J Clin Psychiatry* 2003; 64: 1057-64
122. Dunlop BW, Crits-Christoph P, Evans DL, et al. Co-administration of modafinil and a selective serotonin reuptake inhibitor from the initiation of treatment of major depressive disorder with fatigue and sleepiness: a double-blind, placebo-controlled study. *J Clin Psychopharmacol* 2007 Dec; 27 (6): 614-9
123. Frye MA, Grunze H, Suppes T, et al. A placebo-controlled evaluation of adjunctive modafinil in the treatment of bipolar depression. *Am J Psychiatry* 2007 Aug; 164 (8): 1242-9
124. Rush AJ, Giles DE, Schlessner MA. The Inventory of Depressive Symptomatology (IDS): preliminary findings. *Psychiatry Res* 1986; 18: 65-87
125. Turner DC, Clark L, Pomarol-Clotet E, et al. Modafinil improves cognition and attentional set shifting in patients with chronic schizophrenia. *Neuropsychopharmacology* 2004 Jul; 29 (7): 1363-73
126. Sevy S, Rosenthal MH, Alvir J, et al. Double-blind, placebo-controlled study of modafinil for fatigue and cognition in schizophrenia patients treated with psychotropic medications. *J Clin Psychiatry* 2005 Jul; 66 (7): 839-43
127. Spence SA, Green RD, Wilkinson ID, et al. Modafinil modulates anterior cingulate function in chronic schizophrenia. *Br J Psychiatry* 2005 Jul; 187: 55-61
128. Pierre JM, Pelouin JH, Wirshing DA, et al. A randomized, double-blind, placebo-controlled trial of modafinil for negative symptoms in schizophrenia. *J Clin Psychiatry* 2007 May; 68 (5): 705-10
129. Cambridge Neuropsychological Test Automated Battery (CANTAB®) [online]. Available from URL: <http://www.cantab.com> [Accessed 2007 Nov 1]
130. Callicott JH, Ramsey NF, Tallent K, et al. Functional magnetic resonance brain mapping in psychiatry: methodological issues illustrated in a study of working memory in schizophrenia. *Neuropsychopharmacology* 1998; 18: 186-96
131. Overall JE, Gorham DR. The Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. *Psychopharmacol Bull* 1988; 24: 97-9
132. Andreasen NC. Scale for the Assessment of Negative Symptoms (SANS). *Br J Psychiatry* 1989; 155 Suppl. 7: 53-8
133. Guy W, editor. *ECDEU assessment manual for psychopharmacology*. US Dept Health, Education and Welfare publi-

- cation (ADM): Rockville (MD): National Institute of Mental Health. 1976: 76-338
134. Simpson GM, Lee JH, Zoubok B, et al. A rating scale for tardive dyskinesia. *Psychopharmacology (Berl)* 1979; 64: 171-9
 135. Simpson GM, Angus JWS. A rating scale for extrapyramidal side effects. *Acta Psychiatr Scand Suppl* 1970; 212: 11-9
 136. Cornblatt BA, Lenzenweger MF, Erlenmeyer-Kimling L. The continuous performance test, identical pairs version: II, contrasting attentional profiles in schizophrenic and depressed patients. *Psychiatry Res* 1989 Jul; 29 (1): 65-85
 137. Cornblatt BA, Obuchowski M, Roberts S, et al. Cognitive and behavioral precursors of schizophrenia. *Dev Psychopathol* 1999; 11: 487-508
 138. Gold JM, Carpenter C, Randolph C, et al. Auditory working memory and Wisconsin Card Sorting Test performance in schizophrenia. *Arch Gen Psychiatry* 1997 Feb; 54 (2): 159-65
 139. Hershey T, Craft S, Glauser TA, et al. Short-term and long-term memory in early temporal lobe dysfunction. *Neuropsychology* 1998 Jan; 12 (1): 52-64
 140. Lezak MD. *Neuropsychological assessment*. Third edition. New York (NY): Oxford University Press, 1995: 438-45, 544-50
 141. Andreasen NC. Negative symptoms in schizophrenia: definition and reliability. *Arch Gen Psychiatry* 1982 Jul; 39 (7): 784-8
 142. Dackis CA, Kampman KM, Lynch KG, et al. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology* 2005 Jan; 30 (1): 205-11
 143. Hart CL, Haney M, Vosburg SK, et al. Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology* 2008 Mar; 33 (4): 761-8
 144. Sobell LC, Sobell MB. Timeline follow-back: a technique for assessing self-reported alcohol consumption. In: Allen J, Litten RZ, editors. *Measuring alcohol consumption: psychosocial and biological methods*. Totowa (NJ): Humana Press, 1992: 41-72
 145. Kampman KM, Volpicelli JR, McGinnis DE, et al. Reliability and validity of the cocaine selective severity assessment. *Addict Behav* 1998; 23: 449-61
 146. Somoza E, Dyrenforth S, Goldsmith J, et al. In search of a universal drug craving scale. Annual Meeting of the American Psychiatric Association; 1995 May 20-25; Miami (FL)
 147. Tiffany ST, Singleton E, Haertzen CA, et al. The development of a cocaine craving questionnaire. *Drug Alcohol Depend* 1993; 34: 19-28
 148. Randall DC, Cafferty FH, Shneerson JM, et al. Chronic treatment with modafinil may not be beneficial in patients with chronic fatigue syndrome. *J Psychopharmacol* 2005 Nov; 19 (6): 647-60
 149. Chan KM, Strohschein FJ, Rydz D, et al. Randomized controlled trial of modafinil for the treatment of fatigue in post-polio syndrome. *Muscle Nerve* 2006 Jan; 33 (1): 138-41
 150. Vasconcelos OM, Prokhorenko OA, Salajegheh MK, et al. Modafinil for treatment of fatigue in post-polio syndrome: a randomized controlled trial. *Neurology* 2007 May 15; 68 (20): 1680-6
 151. Stankoff B, Waubant E, Confavreux C, et al. Modafinil for fatigue in MS: a randomized placebo-controlled double-blind study. *French Modafinil Study Group. Neurology* 2005 Apr 12; 64 (7): 1139-43
 152. Larijani GE, Goldberg ME, Hojat M, et al. Modafinil improves recovery after general anesthesia. *Anesth Analg* 2004 Apr; 98 (4): 976-81
 153. Gill M, Haerich P, Westcott K, et al. Cognitive performance following modafinil versus placebo in sleep-deprived emergency physicians: a double-blind randomized crossover study. *Acad Emerg Med* 2006 Feb; 13 (2): 158-65
 154. Jasinski DR. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. *J Psychopharmacol* 2000 Mar; 14 (1): 53-60
 155. Martin WR, Sloan JW, Sapira JD, et al. Physiologic, subjective, and behavioral effects of amphetamine, methamphetamine, ephedrine, phenmetrazine, and methylphenidate in man. *Clin Pharmacol Ther* 1971 Mar-Apr; 12 (2): 245-58
 156. Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. *Trends Pharmacol Sci* 2004 Apr; 25 (4): 193-200
 157. Robertson P, DeCory HH, Madan A, et al. In vitro inhibition and induction of human hepatic cytochrome P450 enzymes by modafinil. *Drug Metab Dispos* 2000 Jun; 28 (6): 664-71
 158. Robertson Jr P, Hellriegel ET, Arora S, et al. Effect of modafinil at steady state on the single-dose pharmacokinetic profile of warfarin in healthy volunteers. *J Clin Pharmacol* 2002 Feb; 42 (2): 205-14
 159. Robertson Jr P, Hellriegel ET, Arora S, et al. Effect of modafinil on the pharmacokinetics of ethinyl estradiol and triazolam in healthy volunteers. *Clin Pharmacol Ther* 2002 Jan; 71 (1): 46-56
 160. FDA. Provigil® (modafinil) tablets (C-IV) [online]. Available from URL: http://www.fda.gov/cder/foi/label/2004/20717se1-008_provigil_lbl.pdf [Accessed 2007 Mar 3]
 161. Wilkinson GR. Drug metabolism and variability among patients in drug response. *N Engl J Med* 2005 May 26; 352 (21): 2211-21
 162. Bernard S, Neville KA, Nguyen AT, et al. Interethnic differences in genetic polymorphisms of CYP2D6 in the US population: clinical implications. *Oncologist* 2006 Feb; 11 (2): 126-35
 163. Mariani JJ, Hart CL. Psychosis associated with modafinil and shift work [letter]. *Am J Psychiatry* 2005 Oct; 162 (10): 1983
 164. Narendran R, Young CM, Valenti AM, et al. Is psychosis exacerbated by modafinil? *Arch Gen Psychiatry* 2002 Mar; 59 (3): 292-3
 165. Sabatine MS, Poh KK, Mega JL, et al. Case records of the Massachusetts General Hospital: case 36-2007 - a 31-year-old woman with rash, fever, and hypotension. *N Engl J Med* 2007 Nov 22; 357 (21): 2167

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