Effects of Modafinil on Cognitive Performance and Alertness During Sleep Deprivation

Nancy J. Wesensten*

Department of Behavioral Biology, Division of Psychiatry and Neuroscience, Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910-7500, USA

Abstract: The performance- and alertness-sustaining/restoring effects of modafinil during sleep deprivation in normal, healthy adults were reviewed. Results indicate that modafinil is efficacious for sustaining/restoring objective performance and alertness during sleep deprivation with few adverse effects. At appropriate dosages, modafinil restores performance and alertness to non-sleep deprived levels. Modafinil also impairs post-sleep deprivation recovery sleep, but from the few studies available addressing this issue, it is unclear whether these sleep impairments translate into post-sleep performance impairments. Further research is needed to determine whether modafinil restores performance on simple cognitive tasks only or whether modafinil additionally restores executive functions (e.g., abstract thought, critical reasoning, planning, decision-making, situational awareness, and effective judgment) which are critical in most modern operational settings. In addition, studies are needed to determine whether modafinil use during sleep deprivation is preferable to that of other available controlled stimulants (such as dextroamphetamine) or non-controlled stimulants (such as caffeine). Such studies would be comprised of direct, head-to-head comparisons among various stimulants across a range of dosages.

Key Words: Stimulants, modafinil, sleep deprivation, reaction time, alertness, executive function.

INTRODUCTION

Modafinil (2-[(diphenyl-methyl)-sulfinyl]acetamide) is a synthetic stimulant currently available under the trade name Modiodal® in Europe and Provigil® in Great Britain (Lafon Laboratories, Maisons-Alfort, France) and the United States (Cephalon, Inc.). It is approved for treatment of the daytime sleepiness associated with narcolepsy. Recently Cephalon, Inc. announced that it received an approvable letter from the U.S. Food and Drug Administration (FDA) to expand the label for modafinil to include improving wakefulness in patients with excessive sleepiness associated with shift work sleep disorder and in patients with obstructive sleep apnea/hypopnea syndrome; approval for the latter indication also was recently granted in the United Kingdom (see www.cephalon.com).

In the present paper, primary focus is given to the effects of modafinil on cognitive performance. Other topics addressed include its effects on objectively/subjectively measured alertness, other subjective effects, recovery sleep effects, and side effects. For the latter topic, only a brief review is provided. Topics covered in this paper are not an exhaustive list of issues relevant to the use of modafinil (or any other stimulant) in the operational environment. Other topics (e.g., cardiovascular and other physiologic effects which may be relevant under certain operational conditions; safety, and abuse potential) are not covered here.

In the United States and Europe, modafinil is available in 100 mg and 200 mg tablets. Following oral administration, peak plasma concentrations are reached in 2-4 hours, and elimination half-life is 13-14 hours [1]. Modafinil is metabolized mainly *via* the CY-P450 enzyme CYP3A4. Its major metabolites are modafinil acid (CRL 40467) and modafinil sulfone (CRL 41056), and the main route of elimination is through urine. Modafinil acid (the main metabolite), is pharmacologically inactive but another metabolite, modafinil sulfone, is pharmacologically active with a half-life of approximately 12 hours.

Modafinil was introduced in the 1980s, and since then different neurochemical/neuroanatomical mechanisms have been proposed for modafinil's effects including either direct or indirect effects on noradrenergic [2], dopaminergic (specifically, the dopamine transporter; [3]), GABAergic [4], and glutaminergic [5] systems. Histaminergic and hypocretin/orexin systems in hypothalamic regions involved in wakefulness have recently been identified as potential modafinil targets [6, 7]. Most recently, modafinil blockade of noradrenaline in the ventrolateral preoptic nucleus (an area of the brain involved in sleep promotion) has been reported [8]. In short, the mechanisms by which modafinil restores/sustains alertness and performance are still under investigation. A detailed review of modafinil's proposed mechanism of action is beyond the scope of this paper. The interested reader is referred to a recent overview of this topic which contains numerous relevant references (see [9]).

Because of its efficacy for restoring alertness and performance in sleep-disordered patients, modafinil's efficacy for reversing (or preventing) the cognitive performance and alertness deficits associated with sleep loss in otherwise normal, healthy adults also is of interest. Relatively few studies (e.g., compared to caffeine or dextroamphetamine) have addressed the effects of modafinil on cognitive per-

*Address correspondence to this author at the Department of Behavioral Biology, Division of Psychiatry and Neuroscience, Walter Reed Army Institute of Research, 503 Robert Grant Avenue, Silver Spring, MD 20910-7500; USA; Tel: 301.319.9248; Fax: 301.319.9979; E-mail: nancy.wesensten@us.army.mil

formance and alertness during sleep deprivation. Therefore, it is possible to review this literature in some detail.

Unless otherwise specified, volunteers in the studies reviewed below were normal, healthy adult (approximately 18-40 years of age) males and females, participating in total sleep deprivation studies. A listing of studies reviewed below is found in Table **1**. For each study, basic methodological details are provided, to include other drugs evaluated in the same study (results for the latter not reviewed here). All references based on the same study are listed together. Side effects are discussed further below (section G).

A. MODAFINIL'S EFFECTS ON COGNITIVE PERFORMANCE

In the studies reviewed in this section, a variety of tasks were used to evaluate cognitive performance. There are no universally agreed-upon metrics by which to measure sleep deprivation (and stimulant) effects on cognitive performance; however it is well known that relatively uninteresting, long-duration tasks (for example, 10-30 minute reaction time tasks with infrequently occurring targets) are especially impaired by sleep loss [10, 11]. In most published studies on modafinil's cognitive-enhancing effects during sleep deprivation, at least one task approximating these characteristics was included, as described below.

In the bulk of published studies, a single dosage of modafinil was administered during sleep deprivation, either repeatedly or once over the course of the sleep deprivation period. These studies are reviewed first (and in chronological order, where feasible).

1. Single-Dose Studies

In the first published report of modafinil's effects on cognitive performance during sleep deprivation [12] (earlier published studies [13, 14] did not involve sleep deprivation), young adult volunteers (N=12) were administered modafinil 200 mg or placebo once at 2200 hours (after approximately 14 hours of wakefulness) over the course of a 36-hour sleep deprivation period. A double-blind crossover design with a 2-week washout period was utilized. Effects on critical flicker fusion (CFF), 6-choice reaction time, paired-associates memory, and a 30-minute delayed free recall task were evaluated. Under placebo conditions, sleep deprivation impaired CFF threshold, total reaction time, recognition reaction time, motor reaction time, paired-associates memory recall, and long-term visual memory recall. One-tailed t-tests revealed that modafinil reduced impairments on all measures except long-term visual memory recall at 6 hours post-administration (0400 hours); and its effects on CFF threshold were still evident at 18 hours post-administration (1600 hours).

Defense Research and Development – Canada (DRDC; formerly DCIEM) Studies

In the DRDC studies, modafinil was administered multiple times over the sleep deprivation period. These studies simulated a realistic scenario under which stimulants might be used, i.e., repeated dosing to sustain/restore performance during extended wakefulness.

The first study from that group was a double-blind, placebo-controlled, parallel groups study (N = 41; approximately 13 volunteers per drug group) in which the effects of modafinil 300 mg, dextroamphetamine 20 mg, and placebo were compared [15]. Drug or placebo was administered at 17.5, 47.5 and 57.5 hours of wakefulness; thus, total doses administered were modafinil 900 mg or dextroamphetamine 60 mg. In the first publication from the first study [15], it was reported that modafinil 300 mg improved performance on four-choice serial reaction time, logical reasoning, and digit-span compared to placebo (performance on all tasks was degraded by sleep deprivation). However, post-hoc comparisons of the modafinil vs. placebo groups failed to reveal statistically significant differences on some of the measures, including logical reasoning and short-term memory tasks; and not all of the effects on cognitive performance were positive.

A subsequent publication from the same group [16] compared results from the first study [15] to two similar studies of sleep deprivation, except that a nap was allowed from 2200 to 0000 hours Day 1 (Study 1, early nap; n = 16) or from 0400 to 0600 hours Day 3 (Study 2, late nap; n = 12). These nap times corresponded roughly to the first two drug administrations in the original study [15] (drug administrations at 2330 Day 1 and 0530 Day 3). Subjects who were allowed naps did not receive drug, and vice versa. Performance measures common to all three studies included correct responses per minute on logical reasoning and 4-choice serial reaction time tasks (all of which appeared to be degraded by sleep deprivation). Results presented in graphical form (no statistics provided) suggested that both naps were as effective as modafinil (and dextroamphetamine) for restoring and maintaining performance for several hours, although the duration of effectiveness appeared to be longer following administration of either drug than it was following the first nap.

In another study from the DRDC group, the effects of modafinil 100 mg administered every 8 hours across 40 hours of sleep deprivation (at 0700 hrs and 1300 hrs on Day 1, and again at 0100 hrs, 0700 hrs, and 1300 hrs on Day 2; total dose = modafinil 600 mg) were evaluated in a warm environment (30 degrees C and 50% humidity) in six healthy adults, using a double-blind, placebo-controlled, crossover design with a 5-day washout period [17]. Tasks included 4-choice reaction time (RT), mental addition, detection of repeated numbers (vigilance), logical reasoning, visual perception (line length estimation), and a 4-component synthetic work task (SYNWORK). Modafinil improved performance on several of these tasks (4-choice RT, vigilance, logical reasoning, and SYNWORK) relative to placebo (under the placebo condition, performance was degraded by sleep loss); however, it did not appear that modafinil completely restored performance to baseline levels (an early morning circadian trough in performance was apparent even under modafinil).

Institut de Medecine Aerospatiale (Imassa-Cerma) - France Studies

A series of studies was conducted at the Institut de Medicine Aerspatiale (France) to evaluate modafinil's efficacy for restoring/sustaining performance during sleep deprivation. In these studies, a 40-minute performance task battery was used

Table 1.   Studies of Cognitive Performance Effects of Modafinil Reviewed in Text. References Based on the Same Study are Listed Together

Study (References)	Drug / Dose	Total hrs sleep dep	Side effects noted and method used to query for side effects
Saletu *et al*. (1986)	Placebo Modafinil (CRL 40476) 200 mg Modafinil (CRL 40476) 400 mg Modafinil (CRL 40476) 600 mg Adrafinil (CRL 40028) 900 mg	No sleep dep.	Method: spontaneously reported complaints and side effects Placebo = none noted Modafinil 200 mg = moderate elation, moderate talkativeness, slight or moderate activation Modafinil 400 mg = slight nausea, moderate headache, activation (slight and marked) and euphoria; Modafinil 600 mg = sleep disturbances the night after participation; moderate elation; marked overtalkativeness; increased sexuality; moderate activation; marked euphoria, marked pressure to speech; next-morning moderate dizziness.
Saletu *et al*. (1989b)	Placebo Modafinil 100 mg Modafinil 200 mg Dextroamphetamine 10 mg Dextroamphetamine 20 mg	No sleep dep.	Note: modafinil was administered just prior to a nighttime sleep period; upon awakening the next morning, subjective sleep, awakening quality, and daytime well-being were assessed (post-sleep assessments not relevant to this review)
Saletu *et al*. (1989a)	Placebo Modafinil 100 mg Modafinil 200 mg Dextroamphetamine 10 mg Dextroamphetamine 20 mg	No sleep dep.	Note: modafinil was administered just prior to a nighttime sleep period; upon awakening the next morning, subjective sleep, awakening quality, and daytime well-being were assessed (post-sleep assessments not relevant to this review)
Bensimon *et al*. (1991)	Placebo Modafinil 200 mg	36 hours	Method: none indicated (no side effects noted)
Warot *et al*. (1993)	Placebo Modafinil 300 mg Caffeine 300 mg Dextroamphetamine 15 mg	No sleep dep.	Method: open-ended interviews Placebo = none noted Modafinil = Intellectual efficiency; sensation of awakening; sensation of internal tension; sensation of loss of appetite; moderate transient headache
Pigeau *et al*. (1995) Buguet *et al*. (1995) Bard *et al*. (1996) Baranski and Pigeau (1997) Chapotot *et al*. (2003)	Placebo Modafinil 900 mg (300 mg x 3) Dextroamphetamine 60 mg (20 mg x 3)	64 hours	Method: symptoms reported by subjects during post-experiment debrief (not clear whether queried or open-ended) Placebo = increased frequency of urination (subjective self-appraisal); hallucinations; headaches Modafinil = increased frequency of urination (subjective self-appraisal); hallucinations, headaches
Lagarde and Batejat (1995); Lagarde *et al*. (1995)	Placebo Modafinil 1200 mg (200 mg x 6)	61 hours	Method: none indicated (no side effects noted)
Brun *et al*. (1998)	Placebo Modafinil 600 mg (300 mg x 2)	40 Hours	Method: none indicated (no side effects noted)

(Table 1) contd….

Study (References)	Drug / Dose	Total hrs sleep dep	Side effects noted and method used to query for side effects
Stivalet *et al.* (1998)	Placebo Modafinil 700 mg 100 mg x 7)	60 hours	Method: none indicated (no side effects noted)
Baranski *et al.* (1998)	Placebo Modafinil 100 mg (16.7 mg x 6) Modafinil 300 mg (50 mg x 6) Modafinil 600 mg (100 mg x 6)	64 hours	Method: none indicated (no side effects noted)
Batejat and Lagarde (1999)	Placebo Modafinil 400 mg (200 mg x 2)	61 hours	Method: none indicated (no side effects noted)
Pigeau and Angus (2000) (modafinil and dextroamphetamine data were from Pigeau *et al.*, 1995)	Placebo Nap 2200-0000 Day 1 Nap 0400-0600 Day 3 Modafinil 900 mg (300 mg x 3) Dextroamphetamine 60mg (20 mg x 3)	64 hours	No additional side effects noted for nap data
Caldwell *et al.* (2000)	Placebo Modafinil 600 mg (200 mg x 3)	40 hours	Method: spontaneous replies to experimenter query of "how are you feeling?" Modafinil = (effects reported in discussion) nausea, vertigo, jitteriness or nervousness, dizziness, heartburn, headache
Wesensten *et al.* (2002)	Placebo Modafinil 100 mg Modafinil 200 mg Modafinil 400 mg Caffeine 600 mg	54.5 hours	Method: Symptom Questionnaire* Modafinil 100 mg – none significant from placebo Modafinil 200 mg – none significant from placebo Modafinil 400 mg – heart pounding, nausea (compared to placebo); extreme jitteriness/shakiness (observed by experimenter)
Baranski *et al.* (2002)	Placebo Modafinil 600 mg (100 mg X 6)	40 hours	Method: none indicated (no side effects noted)
Randall *et al.* (2003)	Placebo Modafinil 100 mg Modafinil 200 mg	No sleep dep.	Method: none indicated (no side effects noted)
Turner *et al.* (2003)	Placebo Modafinil 100 mg Modafinil 200 mg	No sleep dep.	Method: none indicated (no side effects noted)
Baranski *et al.* (2004)	Placebo Modafinil 4 mg/kg (300 mg on average)	No sleep dep.	Method: none indicated (no side effects noted)
Caldwell *et al.* (2004)	Placebo Modafinil 300 mg (100 mg X 3)	40 hours	Method: Side Effects Questionnaire Placebo = Drugged feeling, loss of coordination, vertigo, confusion, headache Modafinil = Drugged feeling, light-headed, loss of coordination, nausea, vertigo, confusion, headache

(Table 1) contd….

Study (References)	Drug / Dose	Total hrs sleep dep	Side effects noted and method used to query for side effects
Muller *et al*. (2004)	Placebo Modafinil 200 mg	No sleep dep.	Method: not specified Authors reported that no unpleasant side effects were observed with modafinil 200 mg
Randall *et al*. (2004)	Placebo Modafinil 100 mg Modafinil 200 mg	No sleep dep.	Method: none indicated (no side effects noted)
Walsh *et al*. (2004)	Placebo Modafinil 200 mg per night for 4 nights	No sleep dep. (simulated night shift with 8-hr daytime sleep period)	Method: none indicated (no side effects noted)
Wesensten *et al*. (2005)	Placebo Caffeine 600 mg Modafinil 400 mg Dextroamphetamine 20 mg	85 hours	Method: Symptom Questionnaire* Modafinil 400 mg – excitation, nausea (compared to placebo)

* = side effects listed had a statistically significantly greater frequency for drug v. placebo

that included: (1) a reaction time (RT) task; (2) mathematical processing (MP); (3) memory search (MS); (4) spatial processing (SP); (5) unstable tracking (UT); (6) grammatical reasoning (GR); and (7) concurrent tracking/memory search (TMS) task [18, 19]. Modafinil was administered repeatedly across the sleep deprivation period in a double-blind, placebo-controlled, crossover design with a 2-week washout interval [18, 20] or a 3-day washout [19]. In the first study [18, 20], modafinil 200 mg or placebo was administered 6 times across 60 hours of total sleep deprivation (at 2200 hrs on Day 1; 0600 hrs, 1400 hrs and 2200 hrs on Day 2; and 0600 hrs and 1400 hrs on Day 3; total modafinil dose = 1200 mg) to seven healthy male Air Force participants. In the second study [19], the combined performance and alertness effects of naps + modafinil 200 mg versus naps + placebo were evaluated in eight healthy males during 61 hours of sleep deprivation, with modafinil or placebo administered at 1200 Day 1 (after 6 hours awake) and again at 0900 Day 2 (after 27 hours awake) (total modafinil dose = 400 mg). In both studies, sleep deprivation impaired performance on the above-indicated tasks; and in both studies it was found that, compared to placebo, modafinil improved *average* performance (response time and percent errors) across the sleep deprivation period. However, specific comparisons between modafinil and placebo at each test session for each task and dependent measure revealed few statistically significant differences—perhaps due to small sample size. Most statistically significant differences emerged after the second night of sleep deprivation, and many of these were for a composite "deviation index" calculated from the results of the UT and TMS tasks [18]. Although it was suggested that the 6-hour nap + modafinil condition improved performance more than the 6-hour nap + placebo condition (especially when testing occurred immediately after the nap) [19], this effect was not consistent across dependent measures. Also, since the nap condition was not counterbalanced across placebo and modafinil conditions (and total sleep times in the placebo versus modafinil conditions were not reported) the extent to which sleep (and possibly sleep inertia) vs. modafinil affected performance is not clear in these studies.

Other Single-Dose Studies

In another single-dose study, the effects of modafinil 300 mg on cognitive performance were evaluated across 36 hours of wakefulness in eight healthy male subjects using a double-blind, placebo-controlled, crossover design with a 2-week washout and preceded by a 24-hour non-sleep deprivation "control" session [21]. Modafinil 300 mg or placebo was administered at 2200 Day 1 and again at 0800 Day 2, corresponding to 15 and 24 hours of sleep deprivation (total modafinil dose = 600 mg). Performance on reaction time (RT - key press to a number on a computer screen) and "grammatical reasoning" (GR - comparison of successions of symbols to a reference--similar to a digit symbol substitution task) was evaluated every three hours. Performance on the RT test was unaffected by sleep deprivation (analysis of variance results not provided). For the GR test, a significant Drug x Time was reported, but not enough details were provided to determine whether this effect was due to modafinil versus placebo and/or at what post-drug time points modafinil differed from placebo. An inspection of mean response time on the GR test appeared to indicate that modafinil improved response time and suppressed the early morning drop in performance seen in the placebo group. However, the authors only analyzed the first three minutes of each GR test session [21]. By doing so, they may have actually decreased the sensitivity of their measure since they did report that GR response times for the first three minutes of a session were faster than response times for the second three minutes (regardless of drug condition or sleep deprivation).

The effects of modafinil 100 mg on a visual search task was evaluated in six adult male volunteers across 60 hours of sleep deprivation using a double-blind, placebo-controlled, crossover design with a 15-day washout [22]. Modafinil 100 mg (or placebo) was administered every 8 hours during the sleep deprivation period (2000 Day 1, 0400, 1200, and 2000 Day 2; 0400, 1200 and 2000 Day 3; total modafinil dose = 700 mg). Volunteers detected the letter "Q" among a varying number of "O" distracter letters ("parallel processing" condition in which RT is unaffected by the number of distracters); or they detected the letter "O" among a varying number of "Q" distracters ("serial processing" condition in which RT increases as a function of number of distracters). Under the "O" target condition, with placebo speed of searching decreased and errors increased from baseline through sleep deprivation; in contrast, with modafinil, performance remained unchanged from baseline through sleep deprivation.

The effects of modafinil 200 mg versus placebo were evaluated in six UH-60 helicopter pilots deprived of sleep for 40 hours in a double-blind, placebo-controlled, crossover design with an 8-hour recovery sleep washout [23]. Modafinil 200 mg or placebo was administered at 16, 20, and 24 hours of sleep deprivation (total modafinil dose = 600 mg), and was found to improve some aspects of flight simulator performance that had degraded with sleep deprivation. These effects were statistically significant during three of five post-drug sessions for the "left standard rate turn" and during one of five post-drug sessions for "straight-and-level" and "descent" maneuvers. In addition, a marginal effect of modafinil was found for the "left descending turn," which the authors indicated is a "composite of turn-rate, airspeed, slip, roll, and vertical-speed control accuracy." In a similarly designed study [24], qualitatively similar simulator-based performance-improving effects of modafinil 100 mg were reported in ten F-117 pilots (total modafinil dose = 300 mg), although these effects with the lower dose of modafinil appeared to be less robust than those seen in the previous study using modafinil 200 mg [23]. The extent to which simulator-based findings generalize to non-pilot performance is not clear; however, the results do indicate that even presumably well-learned aspects of performance are not resistant to sleep loss (as previously thought) – and are improved by modafinil [23, 24].

Modafinil 200 mg was evaluated in a double-blind, placebo-controlled, parallel groups study simulating shift work [25]. Modafinil or placebo (n = 16 per group) was administered at 2200 hours for four consecutive "night shifts" (2300 to 0730 hours) followed by daytime sleep (6 to 8 hours time in bed commencing at 0800 hours). During the simulated night shift, psychomotor vigilance (PVT) and digit-symbol substitution tests were administered approximately bihourly. Under placebo conditions, PVT performance (as indexed by number of lapses [responses $\geq$ 500 ms] and slowest 10% reaction times) degraded within night shifts and across nights; modafinil 200 mg sustained PVT performance near baseline levels. Digit-symbol substitution performance decreased across the night shift under placebo conditions, an effect that was not improved by modafinil 200 mg; however, on that task performance improved across nights in both groups, suggesting learning effects.

The effects of a single administration of modafinil 400 mg versus placebo, caffeine 600 mg, and dextroamphetamine 20 mg (parallel groups; N = 48; n = 12 per drug group) were evaluated during an 85-hour sleep deprivation period [26]. Drug or placebo was administered double-blind at 64 hours of sleep deprivation, just prior to midnight (such studies have been referred to as "recuperation studies" [27] because sleep deprivation continues until performance is substantially degraded, then the efficacy of a compound to restore or "recuperate" performance is evaluated). Rather than simulating real-world operations (in which the goal would be to prevent performance/alertness degradation in the first place), the aim of recuperation studies is to evaluate absolute degree of performance restoration under worst-case scenario conditions. In the 85-hour sleep deprivation study, PVT response speed decreased across the sleep deprivation period. Modafinil 400 mg improved PVT response speed for the entire 20-hour post-drug period (however, performance in the placebo group also improved across the last 6 hours of the post-drug period, presumably as a function of circadian rhythmicity). Although post-drug data were not statistically compared to baseline, it did appear that modafinil 400 restored PVT performance to non-sleep-deprived levels [26].

In sum, modafinil doses ranging from 100 to 400 mg improves performance on tasks of reaction time, logical/grammatical reasoning, digit span, visual search, and a synthetic work task. However, different doses of modafinil were not directly compared in the above-reviewed studies. Thus, failures to find statistically significant differences between modafinil and placebo may have been a function of modafinil dose used rather than a lack of modafinil efficacy per se. Dose-response studies more adequately address the latter concern, and are reviewed next.

2. Dose-Response Studies

In several published studies, the effects of different doses of modafinil have been directly compared. In the first such study to be published [13], the effects of a single administration of modafinil 200, 400, or 600 mg on tests of reaction time and attention (administered at 0, 2, 4, 6, and 8 hours post-administration) was examined in a non-sleep deprived, elderly subject sample (range 56-76 years of age; mean = 66 years) using a double-blind, placebo-controlled, counterbalanced design. All doses of modafinil improved reaction time and attention task performance, with positive effects evident as early as two hours post-administration. Although the effects appeared to be dose-dependent, it is unclear whether dose-response effects were actually statistically evaluated.

Performance effects of modafinil 16.7, 50, or 100 mg administered every 8 hours across 64 hrs of wakefulness (total modafinil doses = 100, 300, or 600 mg, respectively) were evaluated—i.e., after 16, 24, 32, 40, 48, and 54 hours of continuous wakefulness [28]. Six healthy male subjects served as volunteers in a double-blind, placebo-controlled, crossover design with a 2-week washout period. Tests of 4-choice RT, visual perception (line length estimation), mental addition, and digit span were administered at varying intervals six times throughout the sleep deprivation period. Performance on all tests degraded across the sleep deprivation period (most notably during the circadian trough); significant

Drug x Session interactions for 4-choice reaction time and mental addition were followed by planned contrasts suggesting that modafinil 100 mg (300 mg/24 hours) improved performance compared to placebo, and performance was generally reported to be maintained at or near baseline levels with this dose. For low-dose modafinil (16.7 mg every 8 hours or 50 mg per day), performance was comparable to that found with placebo, and the intermediate dose (50 mg every 8 hours or 150 mg per day) accordingly produced intermediate levels of performance, in a dose-dependent manner.

In a study designed similarly to [26], the effects of a single administration of modafinil 100, 200, or 400 mg versus caffeine 600 mg administered at 41 hours of sleep deprivation (just prior to midnight) were evaluated during a 54-hour sleep deprivation period in a double-blind, placebo-controlled, parallel-groups study (N = 50) (i.e., a "recuperation" study") [29]. Testing occurred bihourly prior to drug administration and hourly thereafter. PVT speed was degraded by sleep deprivation; and modafinil 200 and 400 mg effectively maintained response speed on the PVT for 11 hours post-administration. Although it appeared that performance was improved in a dose-dependent fashion, differences between the 200 and 400-mg dose of modafinil were not statistically significant. Although separate analyses were conducted for pre-drug and post-drug data, it appeared that both the 200 and 400 mg doses restored performance to baseline levels.

In sum, results from the above-reviewed studies suggest that modafinil's effects are dose dependent. Previous studies involving multiple administrations of a single dose of modafinil have generally utilized the 200 mg dose [15, 20, 23], a dose selection likely based on a report that higher doses produce no additional improvements in performance [20]. Results presented above suggest that practical (albeit perhaps not statistically significant) benefits can be realized with doses higher than 200 mg (e.g., modafinil 400 mg [29]); especially in those instances in which circadian and homeostatic factors converge to produce especially poor performance—e g., after two or more nights of sleep loss and near the trough of the circadian rhythm of performance [26, 29].

3. Modafinil Effects on Tests of Executive Function

Results from recent studies have shown that performance on tasks of executive function (e.g., abstract thought, critical reasoning, planning, decision-making, situational awareness, and effective judgment) is impaired by sleep deprivation [30, 31] – and results from brain imaging studies indicate that sleep deprivation deactivates those areas of the brain governing executive functions [32]. Executive function tasks appear to tap functions critical in most operational settings (perhaps even more so than psychomotor or simple cognitive tasks). Thus, whether stimulants restore executive functions is of both practical and theoretical relevance.

Modafinil effects on executive function tests were evaluated in the simulated night shift study described above [25]. Tests which were not repeatable (six of the nine different tests administered) were administered a single night only (either the second or fourth night shift), and for those tests

performance with modafinil was compared to performance with placebo. Testing occurred between 0415 and 0530 hours. Compared to placebo, modafinil 200 mg significantly improved performance on verbal fluency, flexibility, and originality as measured by the Torrence Test of Creative Thinking-Verbal. Modafinil also improved performance on the Wisconsin Card Sorting Task (a test of planning, mental flexibility, set-shifting, and concept formation) and Haylings Sentence Completion (which measures the ability to inhibit verbal responses). Performance on other executive function tasks either did not show drug effects (non-repeated tasks including Thurstone's Word Fluency; Anagram Task; Category Test; Letter-Number Sequencing) and/or did not appear to be sensitive to sleep deprivation (repeated tasks including Optimal Telegram and Torrence Test of Creative Thinking-Figural).

In another study described above [26], probe tasks of executive function also were administered post-drug (Tower of Hanoi; Iowa Gambling Task; Stroop; Biber Cognitive Estimation). Results suggested that impairments on these tasks seen in the placebo group (suggesting sleep deprivation effects) were countered by modafinil 400 mg.

In a separate report from the original study outlined above [15], modafinil effects were evaluated in volunteers who were either attempting to instruct another volunteer on drawing a route along a map ("Instruction Givers") or attempting to draw a route along a map based on an Instruction Giver's directions ("Instruction Followers") [33]. Although this task was not a formal task of executive function, it does appear to differ from typical tasks of psychomotor or simple cognitive performance. Modafinil was reported to reduce map-drawing accuracy, "number of turns taken" and "word tokens used to describe a map" compared to placebo; however, the extent to which modafinil differed from placebo was not clear – and whether this task was sensitive to sleep deprivation also was not clear.

Modafinil's effects on self-assessment of cognitive performance have been evaluated [17, 34]. Again, although the self-assessment tasks used in those studies are not formal tasks of executive function, self-assessment is likely governed by the same areas of the brain that control executive functions. In both studies, volunteers self-assessed performance on two tasks: in the first task (perceptual comparison) subjects determined which of two parallel horizontal lines was either longer or shorter (depending on instructions provided just before the stimulus). In the second task, subjects mentally added eight numbers that were presented sequentially. Subjects provided an estimate of (a) the percentage of trials they anticipated that they would get correct just prior to performing each task and (b) the percentage of trials they thought they had answered correctly immediately following each task. In one study [34], an overconfidence effect with modafinil 300 mg compared to placebo was reported (i.e., under placebo conditions, even sleep-deprived volunteers accurately self-assessed), an effect that was most evident 2 to 4 hours after each drug administration. However, results from the other study [17] in which a smaller dose of modafinil (100 mg per administration) was used during sleep deprivation failed to indicate overconfidence effects (and self-assessment under placebo conditions remained accurate

across sleep deprivation). Most recently, modafinil effects on self-assessment of performance in non-sleep deprived volunteers was evaluated [27]. In a double-blind crossover design (1-week wash-out), volunteers received a single dose of modafinil 4 mg/kg (modafinil 300 mg, on average) or placebo. Three 50-minute cognitive testing sessions were administered (pre-drug, then again 90 and 180 minutes post-drug). Pre- and post-task self-assessments of performance were obtained for a mental addition task, visual perceptual comparison, logical reasoning, and detection of repeated numbers (a vigilance task) in the same manner as reported previously [34]. In addition, trial-by-trail self-assessments were obtained for the mental addition and visual perceptual comparison tasks. For trial-by-trial self-assessments, upon entering each response, subjects provided a subjective confidence rating reflecting their "subjective probability of a correct response, from 0 (certain of an error) to 100 (certain of a correct response)" [27]. Analysis of trial-by-trial confidence ratings indicated for the addition task, subjects accurately self-assessed performance under both modafinil and placebo conditions. For the perceptual comparison task, subjects over-rated their performance; however, this overconfidence effect was virtually identical under both modafinil and placebo conditions. For the task-level self-assessments, subjects accurately self-assessed pre-task performance under both modafinil and placebo conditions across tasks. For their post-task assessments, subjects overrated their performance with modafinil compared to placebo; however, this effect was only marginally significant ($p = 0.07$) and small (5% difference between estimated and actual performance with modafinil).

In sum, evidence suggests that for the few tasks of executive function which have been evaluated to date -- and which are affected by sleep deprivation -- modafinil improves performance on these tasks relative to placebo. Modafinil may also negatively affect executive functions with a self-assessment component [17, 34]. Although the self-assessment methods used to evaluate judgment [17, 27, 34] were unconventional, the above results warrant further investigation. Given that relatively few tasks of executive function have been evaluated, modafinil's effects on a broader spectrum of these functions remains to be elucidated.

4. Modafinil Effects on Cognitive Performance in Non-Sleep Deprived Volunteers

There is some evidence in non-sleep-deprived volunteers that modafinil generally enhances higher-order cognitive performance. In a double-blind, placebo-controlled parallel groups study (N = 60; 20 subjects per drug group), a single dose of modafinil 100 mg was compared to modafinil 200 mg on tasks of digit span, a battery of eight tasks from the Cambridge Neuropsychological Test Automated Battery (CANTAB) tapping visual memory, working memory/planning and attention; a gambling task; and response inhibition [35]. Of the 30 dependent variables analyzed, 10 showed statistically significant effects of modafinil versus placebo. Several of these included measures tapping executive function, including mean attempts on the New Tower of London; deliberation time on a gambling task, and stop-signal reaction time and number of errors on a Stop-signal task (the latter 2 dependent measures also showed dose-dependent effects of modafinil). The results suggested that some aspects of executive functioning are improved by modafinil. In a double-blind, placebo-controlled parallel groups design (N = 45; n = 15 per group), significant performance-enhancing effects were found with modafinil 200 mg (but not modafinil 100 mg) in middle-aged adults but only for time to complete the color-naming phase of the Stroop test [36]. In that study, modafinil 200 mg also increased the total number of errors made on the Wisconsin Card-Sorting task (WCST) – however, errors were actually lower with modafinil 100 mg compared to placebo, suggesting that this effect was not dose-dependent. In another study, effects of modafinil 200 mg versus placebo were evaluated on tasks of numeric working memory, delayed matching-to-sample, letter cancellation, and trail-making using a double-blind cross-over design (N = 16; one-week wash-out) [37]. Modafinil decreased errors on the numeric working memory task, particularly for the most difficult condition (all 4 digits re-ordered: e.g., 1-2-3-4 to 3-1-4-2); further analyses indicated that subjects who were the poorest performers at baseline benefited most from modafinil. Although modafinil did not improve overall reaction times on this task, it marginally decreased the percentage of long-latency reaction times (again under the most difficult condition). On the delayed matching-to-sample task, modafinil significantly reduced the number of errors for the longest-delay (8 seconds) condition and improved reaction times for all delay conditions (1, 4, and 8-sec delays).

Positive effects on cognitive performance have not consistently been found. In the study cited above [37], performance on letter cancellation and trail-making were not affected by modafinil. In a double-blind, placebo-controlled, parallel groups design (N = 30; 10 subjects per drug group, a single dose of modafinil 100 mg versus modafinil 200 mg were compared using a battery of five tasks from the CANTAB [38]. Two of the tasks were the same as those used in another study of modafinil cited above [35], i.e., delayed matching to sample (DMTS) and rapid visual information processing (RVIP). In the latter study [38], results failed to show significant effects of either modafinil dose on any of the cognitive performance measures (including the DMTS, for which the previous study [35] reported a significant modafinil effect for response latency). The failure to find significant effects in one study [38] may have been due, in part, to relatively small number of subjects (n = 10 per group versus n = 20 per group in [35]). Also, on some tasks ceiling effects may have precluded performance improvements with modafinil.

In sum, the evidence regarding modafinil's cognitive-enhancing effects in non-sleep deprived volunteers is mixed (which may be due in part to lack of statistical power in those studies in which modafinil had no effect). In above-reviewed studies in which modafinil effects were found, even though the volunteers were purportedly non-sleep deprived, their pre-study sleep/wake history was not objectively verified. Thus, it is possible that some volunteers entered the study partially sleep deprived – and reported performance improvements with modafinil [35, 36] were actually due to a reversal of sleep deprivation effects. An addi-

tional consideration is time of day at which modafinil was administered and subsequent performance tested. Cognitive performance is at its lowest in the morning and improves across the day (as a function of circadian rhythms); thus, improvements with modafinil would be more evident in studies in which modafinil administration and testing occurred in the morning versus afternoon or evening (for example, results of one study [38] failed to show cognitive-enhancing effects of modafinil in young, healthy, non-sleep deprived volunteers who were tested in the afternoon).

5. Summary - Modafinil's Effects on Cognitive Performance

Modafinil, when administered as a single dose ranging from 100 to 400 mg, either repeatedly [15—24] or once [12, 26] and over sleep deprivation periods ranging from 36 to 85 hours (as well as across nights, [25]), improves performance on tasks of reaction time, logical/grammatical reasoning, digit span, visual search, and a synthetic work task. In some studies it was unclear whether effects of modafinil significantly differed from those of placebo. In other studies comparisons between modafinil and placebo failed to reveal statistically significant differences. Return-to-baseline (pre-sleep deprivation) performance was not always noted. However, overall the bulk of studies indicate that modafinil improves psychomotor and cognitive performance during sleep deprivation, most notably during the circadian nadir in performance.

Modafinil's effects also appear to be dose-dependent (albeit nonsignificantly so in at least one study in which different doses were evaluated). Whether dose-dependent effects (statistically significant or not) translate into real-world gains in performance also remains to be determined.

In most studies reviewed above, short-duration tasks that purportedly tap some specific cognitive function (e.g., memory, grammatical reasoning) were used, and the effects of modafinil on reaction time and/or accuracy were reported. To date, few studies have employed tasks that are thought to reflect higher-order mental processes (i.e., "executive functions") or employed tasks with apparent face validity in combination with sleep deprivation. Exceptions include studies in which simulators (UH-60 helicopter, [23]; F-117, [24]) were utilized. Although the efficacy of modafinil for reversing sleep deprivation induced deficits in pilot-relevant higher-order mental abilities such as navigation were not explored, in the simulator studies pilots' ability to perform specific, well-practiced flight maneuvers was evaluated [23, 24]. Even these well-practiced flight maneuvers were affected by sleep loss, an effect that was reversed by modafinil [23, 24]. Subjects' ability to verbally describe a map for reconstruction by another subject was evaluated in one study [34], and results showed that that modafinil negatively affected performance on this task. More recently, results of two studies [25, 26] showed that modafinil improved some aspects of executive function. Although tasks of executive function also were included in at least two additional studies [35, 36], volunteers in these latter studies were not sleep deprived – nonetheless, some evidence for improved executive functioning with modafinil was found [35, 36].

B. MODAFINIL REVERSAL OF ALERTNESS IMPAIRMENTS DURING SLEEP LOSS

1. Objective Tests of Alertness: Sleep Latency Tests

Results of numerous studies have documented the sensitivity of sleep latency tests to sleep deprivation (e.g., see [39] for a recent review). During such tests, volunteers are placed in a quiet, darkened room. They are instructed either to try to fall asleep (Multiple Sleep Latency Test or MSLT [40]) or to try to stay awake [41]; (Maintenance of Wakefulness Test [42]). Sleep/wake is objectively monitored on-line. The test is terminated as soon as the subject falls asleep (or after a predetermined amount of time if the volunteer remains awake, e.g., 20 minutes for the MSLT), and the time taken for the volunteer to fall asleep serves as the dependent measure. Because sleep latencies decrease with increasing sleep loss [43], sleep latency is considered an objective index of alertness; sleep latency has been widely validated and thus is recognized by most sleep researchers as the "gold standard" for objectively measuring alertness [44]. Although other objective measures of alertness exist (e.g., the alpha attenuation task [45]) such metrics are not widely used (compared to the MWT and MSLT) and results will not be reported here.

In several of the above-reviewed studies, modafinil's effects on objective measures of alertness (as measured by the MSLT or MWT) during sleep deprivation also were reported. In the above-cited study of modafinil 200 mg [20], modafinil's effects on the multiple sleep latency test (MSLT) and on the amount of micro-sleep obtained during sleep deprivation also were determined. Modafinil significantly lengthened sleep onset latency relative to placebo at 0300, 1700, and 2200 hours on Day 2 (corresponding to 20, 34, and 39 hours of sleep deprivation), and at 0300, 0900, 1400, and 1700 hours on Day 3 (corresponding to 44, 50, 55, and 58 hours of sleep deprivation). The statistically significant modafinil-induced extensions of sleep latency were small (mean sleep latencies of 3-4 minutes following modafinil, versus 1 minute for the placebo group), and it appeared that modafinil failed to restore sleep latencies to baseline levels. It was also found that modafinil reduced cumulated minutes of micro-sleep (defined as a sleep episode of 1-10 sec in duration; typically sleep is scored as at least 50% of a 30-sec epoch) compared to placebo. The overall difference was approximately 90 minutes of cumulated micro-sleep with placebo versus 70 minutes with modafinil, with most of the micro-sleep in the modafinil group accumulating 19 or more hours after drug administration. Under some operational conditions, however, even small improvements in sleep latency and micro-sleep may translate into meaningfully improved performance.

In a report based on data collected in [15], the effect of modafinil on sleep latency during a modified maintenance of wakefulness test (4-minute duration, administered hourly) was determined [46]. Sleep onset latency for modafinil was extended (relative to baseline) following the first drug administration (i.e., at 17.5 hours of sleep deprivation)—an effect that lasted approximately 10 hours relative to placebo.

In another above-cited study [29], effects of modafinil 100, 200, or 400 mg on a modified maintenance of wakefulness test (MWT) were evaluated (in the modified MWT,

volunteers remained undisturbed for 15 minutes rather than being awakened if they fell asleep). Modafinil 200 and 400 mg increased sleep latency compared to placebo; however, differences between the 200 and 400-mg dose of modafinil were not statistically significant. Data from that study [26] suggested that modafinil 400 mg did not restore alertness to baseline levels. In the latter study, volunteers were kept awake an additional 24 hours prior to drug administration compared to an earlier study from the same laboratory [26]; it is worth noting that in [26], neither dextroamphetamine 20 mg nor caffeine 600 mg restored alertness to baseline levels (although all compounds improved alertness compared to placebo).

In the simulated night shift study [25], modafinil 200 mg also improved alertness in a modified maintenance of wakefulness test across the night (0145, 0345, and 0630 hour test sessions). In that study [25], differences between modafinil and placebo were most apparent on the first simulated night shift but less so by the fourth night.

2. Subjective Measures of Alertness

Compared to objective measures of alertness, subjective measures of alertness vary more widely across sleep laboratories. However, the Stanford Sleepiness Scale (SSS [47]), the Karolinska Sleepiness Scale (KSS [48]), and the Epworth Sleepiness Scale (ESS [49]) are most likely to be recognized as "gold standards" since they have been validated in sleep-disordered populations.

In several studies reviewed above, modafinil's effects on ratings obtained using the SSS, KSS, or ESS were reported. Modafinil effects on the SSS were evaluated as part of the Canadian study [15]; modafinil decreased sleepiness ratings (compared to placebo) for approximately 9 hours after each drug administration. During the 9-hour post-drug interval, sleepiness ratings with modafinil approximated those seen during baseline (pre-sleep deprivation) conditions. A 7-point scale similar to the SSS was used to measure subjective alertness in [28]. However, in the latter procedure [28], volunteer rating on the subjective scale was immediately preceded by a 4-minute period in which volunteers sat erect in a comfortable position with their eyes closed but attempting to stay awake. Results indicated that modafinil appeared to dose-dependently decreased subjective ratings of sleepiness following the 4-minute eyes closed period, compared to placebo; effects were significant only for modafinil 100 mg/8 hrs (600 mg total dose) and not until the second night of sleep deprivation [28].

In another study [29], modafinil 200 and 400 mg improved SSS sleepiness ratings compared to placebo, although the effect was not statistically significant. Both the SSS and the KSS were used in the simulated night shift study [25]. For the SSS, they found a trend for greater reported sleepiness in the placebo group compared to modafinil on the first night only. For the KSS, the placebo group reported greater sleepiness than the modafinil group on the first night but only for the first test point (2315 hours); however, on the third night, the modafinil group rated themselves as more sleepy compared to placebo group (but only for the first time point of that night).

3. Summary - Modafinil's Effects on Objective and Subjective Measures of Alertness

Available results indicate that modafinil improves objective alertness at doses which also improve psychomotor and cognitive performance (i.e., 100 to 400 mg) for similar durations. However, it is unclear from the available evidence what dose of modafinil is required at a given level of sleep deprivation to restore alertness to baseline levels. Modafinil also appears to improve subjective alertness. However, because few studies have used validated measures of subjective alertness, little is known about modafinil's duration of action and dose dependency on subjective alertness.

Subjective alertness also is measured *via* visual analogue scales; however these scales have not been widely validated in sleep-disordered populations. Results from visual analogue scales (which also measure other aspects of mood) are reported in section F (see next).

C. MODAFINIL: OTHER SUBJECTIVE EFFECTS

In this section, modafinil effects on mood and other subjective measures are reported. No clear distinction exists in the literature with regard to what constitutes a "subjective effect" and what constitutes an "adverse effect" or "side effect" – indeed, many subjective effects (e.g., increased headache) can also be considered adverse effects. This section is restricted to subjective effects specifically queried by the investigators *via* scales, questionnaires, or structured interviews. However, if a specific scale or questionnaire included both subjective/mood and subjective/somatic (e.g., jitteriness, palpitations) effects (e.g., [38]), both are reported in this section. With few noted exceptions, only studies already reviewed above (as part of the primary focus of cognitive effects) are included so that the reader can evaluate subjective effects within the context of performance effects. Other effects spontaneously reported by volunteers, elicited *via* open-ended interviews, or specifically marked as symptoms or side effects surveys by the authors (e.g., Symptom Checklist, [29]) are briefly reviewed further below (see Section G).

A variety of different scales have been used to quantify subjective effects; therefore, the specific scale used for each study will be identified and described. One scale used in several studies is the Profile of Mood States (POMS [50]). The POMS consists of 65 adjectives presented sequentially. Volunteers rate how they feel at the moment using a 5-point scale ranging from "not at all" (0) to "extremely" (4). A score for each of six scales is generated, and includes tension-anxiety, depression-dejection, anger-hostility, vigor-activity, fatigue-inertia, and confusion-bewilderment. Studies are reported in chronological order.

1. Modafinil Subjective Effects in Sleep Deprived Volunteers

Modafinil effects on the U.S. Air Force School of Aerospace Medicine Subjective Fatigue Checklist were reported [15], in which sleep-deprived volunteers rated them selves as better than, same as, or worse than, each of 10 statements (e.g., "very lively"; "petered out"). The U.S. Naval Health Research Center Mood Scale (which is similar to the POMS)

also was used in that study [15]. Compared to placebo, modafinil improved positive mood, decreased fatigue, and decreased negative mood. These effects were most apparent from 2 to 8 hours post-drug and dissipated thereafter. Further information regarding which questionnaire these dependent variables were derived from (and/or whether they were based on particular questionnaire sub-scales) was not provided.

In two studies reported above [18, 20], volunteers rated themselves on an 11-item visual analogue scale prior to and again during sleep deprivation. Under placebo, subjects reported having less energy, being less relaxed, in worse condition, sleepier, and more tired during sleep deprivation. Under modafinil, no mood changes were noted. Ratings of drowsiness, confusion, clumsiness, peppiness, depression, anxiousness, sadness, and happiness did not change across sleep deprivation under either placebo or modafinil conditions.

In another study [28], volunteers rated themselves on 4 items (current level of fatigue, motivation, mood, and subjective rating of performance) on 11-point visual analogue scales ranging from "not tired at all" (0) to "very tired" (10). Compared to placebo, modafinil 100 mg/8 hrs (total dose = 600 mg) improved ratings of fatigue, motivation, and subjective ratings of performance during the first night and second day of sleep deprivation. Other (lower) doses of modafinil also appeared to nonsignificantly improve ratings. Similar effects were reported with modafinil 100 mg/8 hrs in the 40-hour sleep deprivation study conducted in a warm environment [17].

Modafinil (200 mg at 16, 20, and 24 hours of sleep deprivation) effects on POMS ratings also have been reported [23]. Compared to placebo, modafinil significantly increased vigor-activity at 0750 and 1135 hours test times and decreased fatigue-inertia from 0335 to 1535 hours test times. The authors also noted a significant increase in confusion-bewilderment in the placebo group but not in the modafinil group. Modafinil did not reverse sleep deprivation-induced increases in tension-anxiety and depression-dejection; and anger-hostility was unaffected by sleep loss or drug [23]. In a similarly designed study using modafinil 100 mg [24], it was reported that compared to placebo, modafinil marginally improved depression-dejection at 0830 test time; modafinil significantly improved anger-hostility and vigor-activity across all test times. Sleep deprivation-induced increases in fatigue-inertia and confusion-bewilderment were not improved by modafinil. A visual analogue scale of alertness, anxiety, energy, confusion, irritability, jitteriness, sleepiness and talkativeness also was included in the latter study [24]. Compared to placebo, modafinil improved self-perceived alertness and energy. Sleep-deprivation induced increases in jitteriness and sleepiness, and decreases in talkativeness, were not affected by modafinil. Anxiety and irritability were not affected by sleep deprivation or drug. Self-ratings of confidence (not otherwise described) were less degraded with modafinil than with placebo [24].

Modafinil effects on POMS ratings were reported in another study [29], and a marginal mood-improving effect of modafinil 400 mg on tension-anxiety was found. Modafinil 100 mg increased ratings of fatigue-inertia and confusion-

bewilderment, but only compared to caffeine 600 mg. Modafinil did not reverse sleep deprivation-induced increases in fatigue-inertia, confusion-bewilderment, vigor-activity, or anger-hostility; and depression-dejection was unaffected by sleep loss or drug [29].

2. Modafinil Subjective Effects in Non-Sleep Deprived Volunteers

Modafinil's subjective effects also were evaluated in most of the above-reported studies of cognitive effects in non-sleep deprived volunteers. In one study, mood was evaluated using the von Zerssen scale (not described) and affectivity was evaluated using a semantic differential polarity profile (also not described) in non-sleep-deprived volunteers [13]. Scores were reported as a change from baseline (pre-drug). Statistical analyses revealed no changes in mood (otherwise unspecified) over 8 hours post-drug. However, an inspection of data plots suggested that compared to placebo, some deterioration in mood was found with modafinil 400 mg at 2 and 4 hours post-dose and with modafinil 600 mg at 8 hours post dose. Significant mood and affectivity enhancement was found with modafinil 200 mg at 6 hours compared to placebo (however, the placebo group demonstrated decreased mood at this time point, which appeared to be the locus of the statistically significant effect) [13].

In a study specifically designed to evaluate subjective effects (and not reported above), the effects of a single administration of modafinil 300 mg on the POMS and on visual analogue scales (VAS-anxious, tired, happy, relaxed, drowsy, dizzy, clumsy, alert, energetic, sad, and depressed) was assessed [50]. In a double-blind, placebo-controlled, crossover design (1-week washout), volunteers (N = 16) received drug or placebo after an initial test session at 0900 hours. They were tested again at 1, 2, 4, and 8 hours post-dose. Compared to placebo, modafinil 300 mg did not increase or decrease ratings on any POMS or VAS scales. It is unlikely that nonsignificance was due to a lack of scale sensitivity since, in the same study, dextroamphetamine 15 mg significantly affected ratings on most of the scales compared to both placebo and modafinil [50].

In another study not involving sleep deprivation [38], volunteers completed visual analogue scales evaluating mood, aggression, and bodily symptoms; they also completed an 11-item fatigue questionnaire. Items from the bodily symptoms scale were combined into a factor which the authors called "somatic anxiety." Scales were completed both before and after cognitive testing (i.e., approximately 3 and 4.25 hours post-drug, respectively). Compared to placebo, modafinil 100 mg increased the somatic anxiety factor as well as individual items including shaking, palpitations, dizziness, restlessness, muscular tension, physical tiredness and irritability. Compared to modafinil 200 mg, modafinil 100 mg increased shaking, palpitations, and dizziness. These effects were significant both before and after cognitive testing. In addition, from pre- to post-cognitive testing, modafinil 100 mg marginally increased anxiety and appeared to increase aggressive mood ratings including aggressiveness, furiousness, and spitefulness (significant Drug x Pre/post testing interaction but no significant post-hoc comparisons). Measures of alertness and well-being were not affected by

drug or testing. Although the reasons for negative mood effects at modafinil 100 mg versus 200 mg were not clear, the authors hypothesized that neurochemical effects at higher modafinil doses may counteract anxiogenic effects of lower doses [38]. Similar scales were used in another study from the same authors in which middle-aged volunteers were evaluated [36]. No significant drug effects were found for any ratings of bodily symptoms; however, several symptoms significantly increased over time for both modafinil and placebo groups (including muscular tension, anxiety, resentfulness, furiousness, quarrelsomeness, aggressiveness).

In another study of non-sleep deprived volunteers, subjective effects of modafinil 100 or 200 mg were evaluated prior to drug administration, then again immediately prior to cognitive testing (which commenced 2 hours post-dose), 1 hour into testing, and again upon completion of testing [35]. A 16-item visual analogue scale was used. Both modafinil doses increased ratings of alertness and attentiveness (effects which increased over time) and decreased lethargy compared to placebo. Ratings on the other 13 dimensions were unaffected by modafinil.

The Canadian group used a 4-item scale assessing current level of fatigue, motivation, mood, and subjective rating of performance (identical to that used in previous studies from the same laboratory) along with a global vigor affect scale (not described) in their recently published study [27]. Volunteers rated themselves 90 min prior to, 90 min after, and 3 hours after drug ingestion. Compared to placebo, modafinil decreased ratings of mental fatigue and increased ratings of vigor. No other effects were significant.

Modafinil effects on the state-trait anxiety inventory part 1 (in which volunteers indicate how they feel right now) and subjective well being (*via* the Befindlichkeitsskala, not described) have also been evaluated [37]. Modafinil had no effects on either test.

3. Summary – Modafinil Other Subjective Effects

Different subjective scales have been utilized across the relatively few studies in which modafinil's subjective effects have been evaluated. However, a general picture emerges when considering effects on volunteers who were sleep deprived versus those who were not: in studies of sleep deprivation, modafinil appears to possess mood enhancing-effects, if any. In contrast, in non-sleep deprived volunteers modafinil causes more negative subjective effects. Thus, sleep debt status plays some role in determining the volunteer's subjective response to modafinil. This is perhaps not surprising, since sleep deprivation generally increases negative affect whereas under well-rested conditions volunteer affect is likely near optimal (and in some studies, potential volunteers who scored out of range on depression and anxiety inventories were excluded from participating). Exceptions to this are results of [35] and [27], in which it was reported that modafinil improved mood in non-sleep deprived volunteers. The latter findings suggest that modafinil possesses some direct mood-elevating effects. Nonetheless, floor and ceiling effects (under conditions of sleep deprivation and under well-rested conditions, respectively) appear to play some role in modafinil's mood-altering profile.

D. MODAFINIL SIDE EFFECTS

In addition to subjective effects, in some of the above studies other side effects were noted. These include items solicited *via* questionnaire (e.g., [24, 26, 29]) or items reported by volunteers spontaneously or during open-ended interviews. These items are reported in summary form in Table **1**. Unless otherwise indicated, only those studies already reported in one or more sections above are summarized in Table **1**. The frequency and/or severity of most effects listed in Table **1** were not subjected to statistical analyses (exceptions are the symptom questionnaire administered in [26] and [29]; also, in study [24] frequencies of side effects queried were tabulated and reported).

An inspection of Table **1** would suggest that modafinil causes few side effects. However, in many of the studies cited, it was unclear whether volunteers were queried (either formally or informally) for potential side effects. When noted, the types of side effects appeared to be similar whether volunteers were sleep deprived or non-sleep deprived. In addition, in one study vertigo was reported by sleep-deprived helicopter pilots flying a helicopter simulator [23]. Although the authors hypothesized that vertigo was caused by some interaction between modafinil and the motion-based simulator used in that study [23], in a more recent publication it was reported that some volunteers who received placebo also reported vertigo [24]. The latter suggests that vertigo was caused by an interaction between sleep deprivation and the simulator used in those studies rather than an effect of – or interaction with—modafinil. In another study, volunteers specifically queried about vertigo-like symptoms did not report an increased incidence of this side effect (no simulator was used in that study) [29].

E. MODAFINIL EFFECTS ON RECOVERY SLEEP AND SUBSEQUENT PERFORMANCE

When pharmacological agents are used to sustain or restore cognitive performance during sleep deprivation, another issue to be considered is whether these agents affect subsequent recovery sleep. Drug-related impairments in sleep may translate into post-recovery sleep performance decrements, thus potentially limiting the rate at which the operator can cycle back on duty.

Available results suggest that modafinil impairs objectively measured recovery sleep following sleep deprivation [52]. In the latter study, modafinil reduced total sleep time (sum of stages 2, slow-wave sleep, and REM; 9.78 hours) relative to placebo (11.43 hrs) on the first night of recovery sleep but not on the second night [52]. Results from other studies suggest some impairment with modafinil 200 mg on nocturnal sleep in non-sleep deprived volunteers [14], particularly in older individuals [53]. Modafinil also impairs recovery sleep as recorded subjectively *via* sleep logs and delays rebound recovery sleep: results from one study indicated that sleep duration increased on the first recovery sleep night for the placebo group but not for the modafinil group (10.0 vs. 8.5 hrs, respectively), compared to baseline sleep [20]. On the second night, the reverse was found -- placebo subjects reported 8.1 hrs of sleep whereas modafinil subjects reported sleeping 10 hours. These results suggest that mo-

dafinil delays recovery sleep (perhaps due to an active drug metabolite that is still present in the body) but does not reduce sleep need. In a more recent study, results suggested no effects of modafinil 400 mg compared to placebo on recovery sleep time during a 12-hour recovery sleep period [20]. In that study, the recovery sleep period commenced 20 hours after drug administration, which corresponds to approximately two half-lives for modafinil. Therefore, it is likely that modafinil had been substantially cleared from the body.

Whether modafinil's sleep-impairing effects translate into effects on post-recovery-sleep performance has received little attention. In several studies in which post-recovery sleep performance was measured, statistical results were not provided [15, 18-20]. Post-sleep performance data were statistically analyzed in one study, and results indicated no differences between modafinil 400 mg and placebo (as would be expected given modafinil's lack of effect on recovery sleep time)– and it appeared that performance was restored to baseline levels following recovery sleep [26]. In two studies, recovery sleep periods were relatively long (greater than eight hours), and therefore may have been sufficient for full recuperation even if sleep had been impaired by drug [26, 52]. Sleep periods of shorter duration – or post-recovery sleep testing periods extending beyond one day – might reveal more subtle effects of drug-induced recovery sleep impairments on performance.

F. MODAFINIL SAFETY DATA

An in-depth review of modafinil's safety profile will not be attempted here. Safety data specific to the use of modafinil during sleep deprivation in otherwise normal, healthy adults is lacking. In the above-reviewed studies, however, no life-threatening adverse events were reported. More information on modafinil's safety profile is provided in the product package insert. The interested reader also is referred to the modafinil product website which contains information on obtaining the pending updated product monograph (see www.provigil.com/physician/resources/reprints.aspx).

G. MODAFINIL PERFORMANCE AND ALERTNESS EFFECTS -- COMPARISON TO OTHER STIMULANTS

An additional issue to be considered when selecting a pharmacological agent to sustain or restore cognitive performance during sleep deprivation is its relative efficacy compared to other available stimulants. In several of the above studies, modafinil's performance- and alertness-enhancing effects were directly compared with one or more stimulants (see Table **1**). This section is not intended as a thorough review of all available stimulants, nor are other relevant issues (safety, side effects) reviewed in detail. The intent is to provide the interested reader with a brief overview of modafinil's relative cognitive performance efficacy compared to other stimulants against which it has been compared to date. Because few head-to-head comparisons among modafinil and other stimulants have been conducted, this section is necessarily brief.

In one study, amphetamine 20 mg was evaluated in addition to modafinil 300 mg; performance- and alertness-restoring effects were similar between the two drugs [15]. In

the same study, it was later reported that dextroamphetamine 20 mg did not impair the ability to self-monitor to the same extent as modafinil 300 mg [34]. Also in the same study, it was also later reported that both modafinil and d-amphetamine reduced the "number of turns taken" and "word tokens used to describe a map" compared to placebo [33]; however, the extent to which modafinil and dextroamphetamine groups differed from the placebo group on these tasks was not clear. Differential effects of modafinil 300 mg versus dextroamphetamine 20 mg were reported for the human waking electroencephalogram [46] from the original study [15]. However, the relevance of those findings to performance (and whether such effects reflect an advantage of one drug over the other) is probably minimal since results from the first publication from that study indicated that modafinil 300 mg and dextroamphetamine 20 mg exerted comparable performance and alertness-restoring effects [15].

Modafinil also has been compared to caffeine [29]. In that study (reviewed above), modafinil 100, 200, and 400 mg were compared with caffeine 600 mg (a dose previously shown to restore performance during sleep deprivation) and placebo. Drugs were administered at 41 hours of sleep deprivation. Similar performance- and alertness-restoring effects of modafinil 400 mg and caffeine 600 mg were found [29]. In the other study from that laboratory reported above [26], modafinil 400 mg was compared to caffeine 600 mg and dextroamphetamine 20 mg during 85 hours of sleep deprivation. Doses of each drug were chosen based on results from previous studies indicating roughly comparable performance-enhancing efficacy [29, 54, 55]. As previously noted, drug or placebo was administered at 64 hours of sleep deprivation. All three drugs improved psychomotor vigilance (PVT) speed and increased sleep latency for several hours post-dose (most notably during the hours of 0700 and 1100), with modafinil and dextroamphetamine effects lasting longer than those of caffeine. Probe tasks of executive function also were administered post-drug (Tower of Hanoi; Iowa Gambling Task; Stroop; Biber Cognitive Estimation), and results suggested that impairments on these tasks were most effectively countered by caffeine 600 mg, followed by modafinil 400 mg and less so by dextroamphetamine 20 mg [26]. However, differential effects on executive functions may have been due to drug dose.

In sum, results from the few studies available to date indicate that modafinil's cognitive performance-sustaining/restoring effects during sleep deprivation are comparable to those of caffeine and dextroamphetamine (however, the duration of modafinil's effects appear to be longer than those of caffeine, which is likely a function of drug half-life). Whether mood effects, side effects, etc. are comparable among drugs at doses which are equipotent for sustaining/restoring cognitive performance remains to be determined.

H. MODAFINIL – GENERAL SUMMARY

Evidence suggests that modafinil, in repeated doses ranging from 100 to 300 mg per dose, and in single doses ranging from 100 to 400 mg, restores cognitive performance, objective and subjective alertness, and mood during sleep loss periods of up to 85 hours in otherwise normal, healthy adults. Although in some studies it was clear that modafinil

improved performance and alertness beyond levels seen in the placebo group, in other studies the findings were less clear due to lack of appropriate (or missing) statistical analyses. A notable exception to modafinil's general performance-enhancing effect were modafinil's negative effects on a verbal map reconstruction task [34] as well as modafinil's negative effects on self-monitoring of performance [35] (an effect that may be dose-related and/or an interaction with sleep deprivation; results from a later publication [27] failed to replicate those results in non-sleep deprived individuals using a lower dose of modafinil). These exceptions require further investigation within the context of modafinil's general performance enhancing properties.

Modafinil also impairs recovery sleep initiated within 14 hours of administration; however, with sufficient recovery sleep periods (e.g., at least 10 hours), the minimal loss in total sleep time does not appear to affect post-recovery sleep performance. Other subjective and side effects associated with use of modafinil appear to be benign in nature; however, modafinil use under specific operational conditions may be contraindicated by specific side effects. Other potentially operationally relevant physiologic effects of modafinil were not reviewed here but include cardiovascular and thermoregulatory effects (e.g., [56, 57]).

Although it appears that modafinil may have advantages over other controlled stimulants (e.g., dextroamphetamine, methylphenidate) in terms of abuse potential, it has yet to be determined whether modafinil would provide advantages over non-controlled stimulants (e.g., caffeine). For modafinil to replace any stimulant as the drug of choice for restoration and maintenance of performance and alertness during sleep deprivation in normal, healthy adults, it would be necessary to show that modafinil is at least as efficacious as, and display a comparable (or more favorable) side effect profile than, the drug it will replace.

Finally, and specifically with regard to cognitive performance enhancement, of particular interest is modafinil's (and other stimulants') effects on executive functions during sleep deprivation. The currently available body of literature pertaining to stimulant effects on executive functions during sleep deprivation is extremely limited. It may be that each stimulant restores only some aspects of executive functioning, or that complete restoration of executive function comes at a price of increased side effects. Until such information becomes available, modafinil's known effects on other aspects of cognitive performance could serve as a basis for decisions regarding stimulant selection (along with other criteria such as safety, side effects, and availability).

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