

## An evaluation of the abuse potential of modafinil using methylphenidate as a reference

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Modafinil is a unique wake-promoting agent. Preclinical studies indicate a mechanism of action which is distinct from that of amphetamine or methylphenidate. To compare the pharmacodynamic profiles of modafinil, methylphenidate, and placebo in humans, a double-blind Latin square crossover study was conducted in 24 male volunteers with a history of polysubstance abuse that included the stimulant cocaine. Each subject was given single oral doses of methylphenidate (45 mg or 90 mg), modafinil (200 mg, 400 mg or 800 mg) and placebo. Measures of subjective, behavioural, and physiological responses were evaluated at fixed intervals during 72 h after each dosing occasion. Subjects discriminated both modafinil and methylphenidate from placebo. Subjects liked the effects of both drugs. However, modafinil differed from methylphenidate in its lack of a significant response on the Amphetamine Scale of the Addiction Research Center Inventory. The profile of physiological effects for modafinil differed from methylphenidate in that it showed greater inhibition of observed and reported sleep, less facilitation of orthostatic tachycardia and less reduction of caloric intake. These findings are consistent with preclinical pharmacological data suggesting that modafinil is not an amphetamine-like agent.

**Key words:** abuse liability; human subjects; methylphenidate; modafinil; narcolepsy; subjective effects

### Introduction

Modafinil (2-[(diphenylmethyl) sulfinyl] acetamide), is a novel wake-promoting agent that is chemically and pharmacologically distinct from central nervous system (CNS) stimulants. Modafinil differs in several important ways from treatments currently prescribed for narcolepsy-associated excessive daytime sleepiness (EDS), such as amphetamine or methylphenidate (Guilleminault, 1994; Mitler *et al.*, 1994), both of which have recognized abuse potential (Martin *et al.*, 1971; Parran and Jasinski, 1991). Pre-clinical data show that modafinil, which is structurally unrelated to phenylethylamine compounds such as amphetamine and methylphenidate, can be distinguished from these compounds in that it is not a direct or indirect noradrenergic, serotonergic or dopaminergic agonist (Duteil *et al.*, 1990; Akoaka *et al.*, 1991). Modafinil does not bind with high affinity to dopamine uptake carrier sites (Mignot *et al.*, 1994) or stimulate release of dopamine *in vitro* (Simon *et al.*, 1995), increase extracellular catecholamine levels (DeSereville *et al.*, 1994), alter the electrophysiology of dopaminergic (nigrostriatal) or noradrenergic (locus coeruleus) neurons; and is not anxiogenic (Simon *et al.*, 1994). Dopamine antagonists attenuate only the wakefulness and hyperlocomotion promoted by amphetamine, not modafinil (Duteil *et al.*, 1990; Lin *et al.*, 1992). At equivalent wake-promoting doses, amphetamine or methylphenidate, not modafinil, activates basal ganglia, nucleus accumbens and cortical

regions as measured by increases in *c-fos* expression (Lin *et al.*, 1996). Thus, preclinical data are indicative that modafinil is distinct from amphetamine-like agents, and as such, may lack the abuse potential of dextroamphetamine and methylphenidate.

The current study was conducted to test the hypothesis that modafinil, at doses up to four times the minimum proposed therapeutic dose of 200 mg, could be distinguished from the prototypic amphetamine-like drug methylphenidate by a population of polysubstance abusers experienced with drugs of abuse, including stimulants such as cocaine. The experimental procedures and rationale for measuring the effects were those developed and validated in the study of a series of amphetamine-like agents (Jasinski and Henningfield, 1989).

### Materials and methods

#### Subjects

A total of 25 adult male polysubstance abusers, aged 30–46 years (mean 36.5 years), were studied as inpatients at a clinical pharmacology unit at Johns Hopkins Bayview Medical Center (Baltimore, MD, USA). The subjects were abusers of a variety of stimulant agents that included cocaine. The duration of cocaine use among the subjects ranged from 3–21 years. The frequency of cocaine use 1 month prior to the start of the study ranged from one

to two times monthly to up to eight times weekly. The subjects administered cocaine by all routes (intravenous, smoking, and snorting), with some subjects using multiple routes. Subjects were required to have used cocaine within the past 30 days, but could not be actively using the drug at the time of admission [as verified by a urine drug screen (UDS) absent of cocaine]. Subjects reported no use of narcotics, narcotic antagonists, psychotropic drugs or any recreational, prescription, or over-the-counter drugs within 7 days of admission. To rule out the use of non-study drugs, UDS was conducted at screening, admission, discharge, and four times randomly during the study. On the basis of physical examination, medical and psychiatric history, routine laboratory chemistries, and 12-lead electrocardiogram, participants were found to be in good health and without a major psychiatric diagnosis other than their drug abuse. Volunteers were excluded from participation if they had previously demonstrated chest pain, ischemic electrocardiogram changes, clinically significant cardiac dysrhythmia, or clinically significant manifestations of mitral valve prolapse in response to a CNS stimulant. All subjects gave their written informed consent and were paid for their participation. The study was approved by the Johns Hopkins Bayview Medical Center Institutional Review Board for Human Subjects Research.

### Study design

Patients were randomized to drug treatments according to a computer-generated 6 × 6 balanced Latin square design (Cochran and Cox, 1957). The purpose of the balanced square is to determine the presence of residual or carryover effects in the crossover study. Drug conditions tested were: placebo, methylphenidate 45 and 90 mg, and modafinil 200, 400 and 800 mg. Doses were administered with 300 ml of water at 09.00 h on day 1, 4, 7, 10, 13 and 16. Subjects fasted from 9 h prior to dosing until 3 h after dosing.

The 45 mg and 90 mg doses of methylphenidate used in this study were selected on the basis of the results of a preliminary dose-ranging evaluation carried out in the clinical pharmacology unit (using different subjects) which showed that these doses produced the expected profile of responses that was both dose-dependent and typically amphetamine-like.

### Experimental session

Each subject participated in six consecutive 3-day sessions, each consisting of drug or placebo administration at 09.00 h on the first day followed by a 2-day washout period. The effects of active drug or placebo on subjective, behavioural, and physiological responses were assessed during each session. Pre-drug physiological measures were recorded at admission, and at 30 and 60 min prior to drug or placebo administration. Baseline subjective effects and behavioural measures were collected at 30 and 60 min before drug or placebo administration.

### Study medication

All drugs were packaged and provided to the principal investigator by Cephalon, Inc. (West Chester, PA, USA). Modafinil (100 mg tablets) and its matching placebo tablets, and methylphenidate (45 mg capsules) and its matching placebo capsules were both packaged. The identical-appearing placebo capsules and tablets were used in a double-blind, double-dummy fashion to ensure that neither the subject, the investigator, nor the clinical staff knew the identity of the study medication being administered.

### Apparatus

The testing room contained four regulation hospital beds, two blood pressure/heart rate apparatus (IVAC Vital check 4200) (Ivac Corporation, San Diego, CA, USA), UK, two tympanic thermometers (IVAC Core Probe), two PupilScan pupillometers (Fairville Medical Optics, Amersham, UK) each attached to a separate monitor and computer, and one electrocardiogram machine (Burdick E350i) (Burdick Inc., Milton, WI, USA). Work stations for data collection were positioned at the foot of each bed.

### Study measures

#### *Physiological measures*

Autonomic and vital sign measures assessed included pupil size, supine and standing mean blood pressure (calculated as diastolic pressure + one-third pulse pressure) and pulse rate, body temperature, and respiratory rate. These measures were recorded on admission, 60 and 30 min before dosing, and 1, 1.5, 2.5, 4, 6, 11, 23, 29, 35, 47, 53 and 59 h after dosing on days 1, 4, 7, 10, 13 and 16 (no differences were seen between any groups on any measures after the 29-h assessment, and these data are not presented in this report). Additional physiologic measures included caloric intake recorded at the noon meal on dosing days, and observed and estimated amount of sleep determined from 18.00 h on each dosing day until 06.00 h on the following day.

#### *Subject-rated measures*

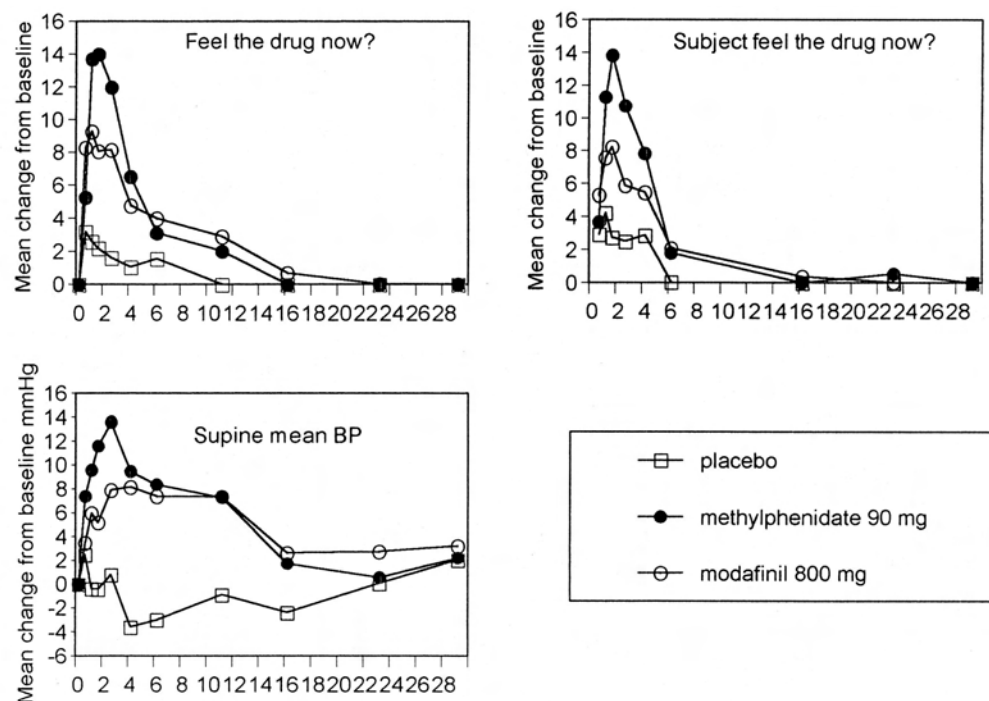
Subjects completed four questionnaires to evaluate their subjective assessment of drug effects: the Subject's Drug Rating Questionnaire, the Subject's Drug Identification Questionnaire, the Subject's Specific Drug Response Questionnaire, each consisting of a visual analog scale with responses ranging from 'not at all' to 'an awful lot'. A short form of the Addiction Research Center Inventory (ARCI) (Martin *et al.*, 1971) was also employed. Previous studies have shown these questionnaires to be valid and sensitive methods of assessing the abuse potential of drugs (Jasinski, 1977; Jasinski and Hanningfield, 1989). All questionnaires were completed 60 and 30 min prior to, and 1, 1.5, 2.5, 4, 6, 11, 23, 29, 35, 47, 53 and 59 h after drug or placebo administration.

The Subject's Drug Rating Questionnaire included the following questions: 'How much do you feel the drug now?'; 'How much do you like the effects you are feeling now?'; 'How much do you dislike the effects you are feeling now?'; 'How high are you?'

On the Subject's Drug Identification Questionnaire, the subject identified the drug effect using the question 'How much is the effect you feel like that of?' for each of the following 10 classes of psychoactive drugs: placebo, opiates, opiate antagonists, phenothiazines, barbiturates and sleeping medications, antidepressants, hallucinogens, benzodiazepines, stimulants and phencyclidine.

The Subject's Specific Drug Effects Questionnaire consisted of the following 22 items: skin itchy; relaxed; nodding; sleepy; drunk; nervous; full of energy; need to talk; sick to stomach; stomach turning; distances, colors, shapes changed; hearing changed; hallucinating (seeing lights and spots); dizzy; hallucinating (hearing sounds and voices); hallucinating (seeing things, animals); confused; afraid; paranoid; depressed or sad; body feels different, changed or unreal; surroundings different or unreal.

The short form of the ARCI consisted of a 49-item questionnaire. The questions were grouped into five scales as



**Figure 1** Mean change from baseline over time for subject- and observer-rated 'feel the drug now' effects and change in supine mean blood pressure

follows: the Amphetamine Scale (a measure of specific dose-related amphetamine-like effects), the morphine-benzedrine group (MBG) (a measure of euphoria); the pentobarbital-chlorpromazine-alcohol Group (PCAG) (a measure of apathetic sedation); the lysergic acid diethylamide (LSD)-specific group (a measure of somatic discomfort and dysphoria); and the benzedrine group (BG) (a measure of stimulant effects relating to intellectual efficacy and energy) (Martin, 1971).

#### Observer's drug rating measures

Observers rated their perception of the subjects' responses at the same times as the subjects using similar questionnaires/visual analogue scales. The Observer's Drug Rating Questionnaire consisted of the following questions: 'How much does the subject feel the drug now?'; 'How much does the subject like the drug?'; 'How much does the subject dislike the drug?'. The Observer's Specific Drug Response Questionnaire consisted of the following 22 items: scratching, withdrawn/detached, relaxed, nodding, sleepy, drunk, nervous, anxious, talking, active, vomiting, hallucinating (auditory), hallucinating (visual), hallucinating (tactile), confused, paranoid, depressed, forgetful, perspiring, tremulous, red eye, restless.

#### Statistical analysis

Mean changes from baseline were calculated for each measure of drug response. Mean responses for each treatment condition and each time interval were then determined and plotted to assess the time course of modafinil in relation to the time course of methylphenidate and placebo conditions. Using these change scores, the area under the curve (AUC) for the initial 6 h post administration were calculated using the method of trapezoids.

AUC scores were analysed for all 24 subjects who completed the study by analysis of variance (SPSS for Windows version 7.5, SPSS Inc, Chicago, IL, USA). This analysis estimated mean

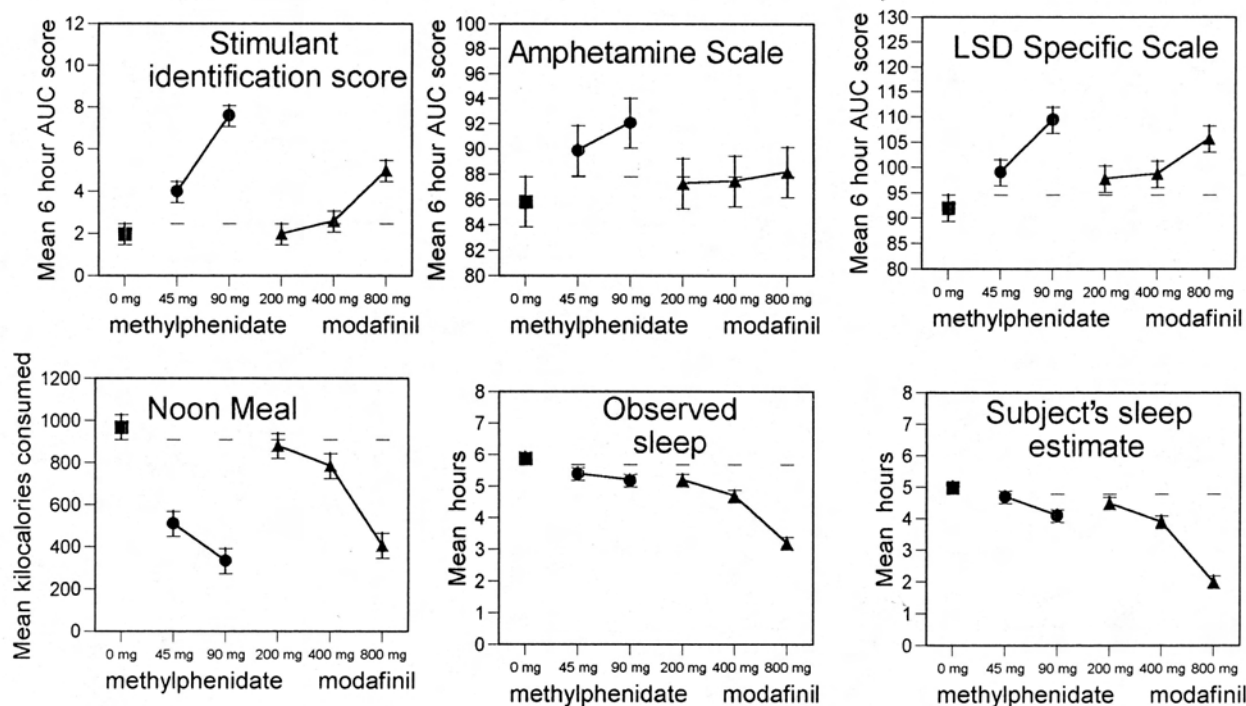
squares for treatments, subjects, and between-test periods, as well as the residual (or error) mean squares. In addition, mean AUC scores for each drug treatment were compared to the corresponding mean AUC for placebo utilizing Dunnett's test for comparison of treatments to controls. To illustrate the comparisons for all treatments graphically, means  $\pm$  (0.5  $\times$  least significant difference) were plotted (Andrews *et al.*, 1980). The between-treatment sum of squares from the analysis of variance was partitioned into orthogonal comparisons of interest. These were: (1) comparison of mean placebo response with the overall mean response to methylphenidate 45 and 90 mg and modafinil 200, 400 and 800 mg; (2) the mean squares for the validity measures of a four-point parallel line bioassay (Finney, 1964) which are regression, preparations, and non-parallelism from a  $2 \times 2$  factorial comparison of methylphenidate 45 and 90 mg and modafinil 400 and 800 mg; and (3) calculation of mg for mg relative potencies. Statistical significance for *F*-ratios was accepted at  $p \leq 0.05$  or less.

## Results

Twenty-five male subjects with a history of polysubstance abuse were enrolled in this study. One subject withdrew his consent after receiving one dose of methylphenidate 90 mg, and was discontinued from the study. This subject was replaced by another subject who was randomized to the same treatment sequence. Therefore, a total of 24 subjects completed the study and were included in the pharmacodynamic analyses.

#### Time course of effects

The time courses of mean effects of high dose methylphenidate (90 mg) and modafinil (800 mg) on the subject- and observer-rated 'feel the drug' visual analog scales and changes in mean blood pressure are presented in Fig. 1. The onset of subjective and



**Figure 2** Dose–response curves for 6 h AUC scores on the Stimulant item of the Subject's Drug Identification Questionnaire (calculated as change from baseline); the Amphetamine LSD-Specific scales of the ARCI (absolute values); kcal consumed at the noon meal and observed and reported sleep from 18.00 h to 06.00 h (calculated as change from baseline). Horizontal bars represent  $0.5 \times$  least significant difference

objective 'feel the drug' effects and increases in mean blood pressure were similar following administration of high-dose methylphenidate (90 mg) and modafinil (800 mg), with peak effects occurring within 2–4 h after dosing.

### Physiological effects

Both methylphenidate and modafinil were associated with significantly greater decreases than placebo in the following physiological measures: kilocalories consumed at the noon meal, the observed sleep from 18.00 h to 06.00 h, and the subject's sleep estimate for the night after dosing when compared to placebo (Fig. 2). When comparing the two active agents, modafinil 200 mg and 400 mg had a significantly lesser effect than methylphenidate 45 mg and 90 mg on reducing caloric intake, while the effect on caloric intake for modafinil 800 mg was similar to that of methylphenidate 90 mg. The durations of observed and reported sleep following administration of modafinil 200 mg and 400 mg were similar to those observed following methylphenidate 45 mg and 90 mg, while that of modafinil 800 mg was significantly reduced relative to modafinil 200 mg, 400 mg and methylphenidate.

Both methylphenidate and modafinil produced dose-related increases in 6 h AUC scores for supine and standing mean blood pressure and pulse rate (Fig. 3). In addition, both agents produced significant orthostatic increases in pulse rate and blood pressure compared to placebo. The effect of modafinil on enhancing orthostatic tachycardia was significantly less than that of methylphenidate.

### Drug Rating Questionnaire

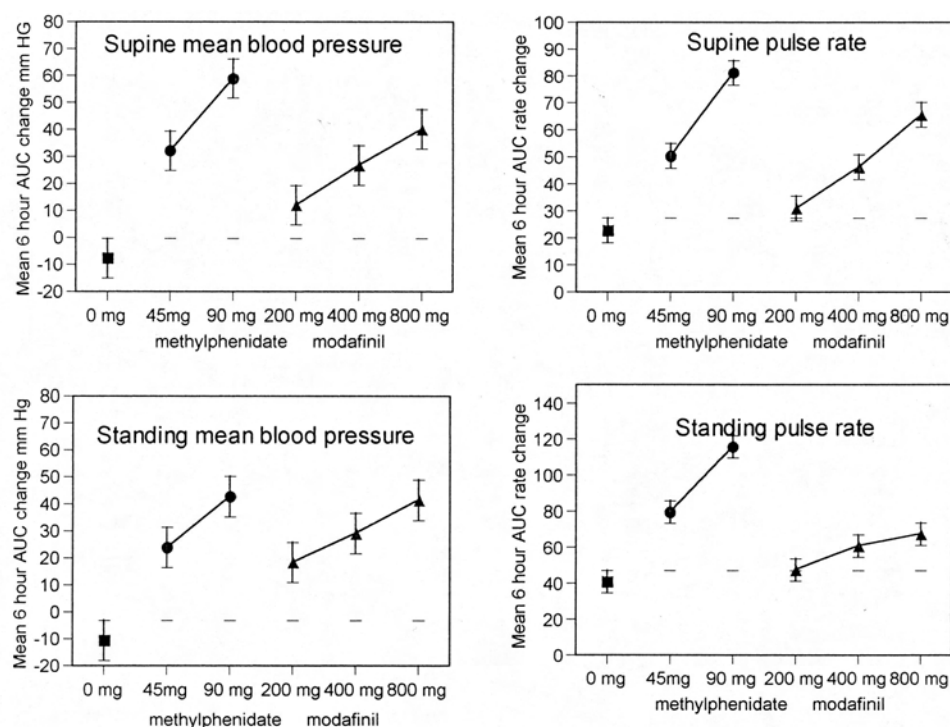
Subjects discriminated both doses of methylphenidate from

placebo with significant increases on the 'feel the drug', 'like the drug', and 'high now' responses of the Drug Rating Questionnaire (Table 1). Modafinil was discriminated on all three responses at the 400 mg and 800 mg dose levels. Modafinil 200 mg was discriminated on the 'like the drug' response only. For both drugs, responses were dose-related. The responses to modafinil 800 mg were intermediate to those of the two methylphenidate doses, with the exception of the 'like the drug' response which was similar to methylphenidate 90 mg.

The observer-rated responses on the Drug Rating Questionnaire generally paralleled those of the subject's questionnaire. The observers reported that subjects 'felt' and 'liked' methylphenidate 45 mg and 90 mg significantly more than placebo and all doses of modafinil (Table 1). They reported that subjects discriminated modafinil 800 mg from placebo on both the 'feel the drug' and 'like the drug' responses, while modafinil 400 mg was discriminated only on the 'feel the drug' scale. Observers did not believe subjects discriminated modafinil 200 mg from placebo on these scales.

### Drug Identification Questionnaire

On the Drug Identification Questionnaire, both methylphenidate and modafinil produced significant decreases in the 'no drug at all' item, indicating that subjects were able to discriminate these drugs from placebo (Table 1). Both methylphenidate doses produced significant stimulant ratings compared to placebo while only high dose modafinil (800 mg) produced such a rating (Fig. 2). Furthermore, the stimulant ratings for methylphenidate were significantly greater than those produced by modafinil. These stimulant identifications are considered non-specific and cannot be generalized to amphetamine. In addition to its stimulant rating,



**Figure 3** Dose-response curves for 6 h AUC scores (calculated as change from baseline) in supine and standing mean blood pressure and pulse rate. Horizontal bars represent  $0.5 \times$  least significant difference

methylphenidate 90 mg produced a slight but significant opiate rating (Table 1).

#### Addiction Research Centre Inventory (ARCI)

On the ARCI (Fig. 2), both methylphenidate doses produced significant increases in the Amphetamine score, while no dose of modafinil produced such an increase. Both methylphenidate and modafinil produced significant increases on the LSD-Specific scale that measures the somatic changes usually regarded as discomforting. Neither drug produced significant changes on the remaining scales (MBG, BG, PCAG).

#### Drug Response Questionnaire

On the Subject's Specific Drug Response Questionnaire (Table 1), both methylphenidate and modafinil produced significantly larger responses than placebo on the following items: 'nervous'; 'stomach turning'; 'hearing changed'; 'body feels different, changed or unreal'; and 'need to talk'. When compared to methylphenidate, modafinil produced a significantly lesser response on the following items: 'nervous'; 'need to talk'; 'dizzy'; 'hearing changed'; and 'body feels different, changed, or unreal'. Scores on the 'sleepy' item were significantly lower for all three modafinil doses relative to those for methylphenidate 45 mg and placebo.

On the Observer's Specific Drug Response Questionnaire, both methylphenidate and modafinil produced significantly lower responses than placebo on the parameters of 'sleepy' and 'nodding' (Table 1). Overall, the profile of responses for modafinil and methylphenidate were similar, with indications of quantitative differences on certain items. Notable differences between the two active agents were lower responses for modafinil on the parameters of 'sleepy', 'relaxed', and 'tremulous'.

#### Bioassay

The responses to modafinil 400 mg and 800 mg and methylphenidate 45 mg and 90 mg were compared using the statistical procedure for a 4-point bioassay. When the between-treatment sums of squares with 3 d.f. were partitioned into regression, preparations, and parallelism, a significant *F*-ratio for the preparations mean square indicated that the criteria for a valid 4-point bioassay were not met. This indicates that the mean responses observed for modafinil 400 mg and 800 mg are significantly less than the mean response for methylphenidate 45 mg and 90 mg.

#### Discussion

One method of assessing the abuse potential of a new drug is to determine if the drug is pharmacologically equivalent to a prototypic drug of abuse. In a series of prior studies, it was shown that methamphetamine, ephedrine, phenmetrazine, methylphenidate, diethylpropion and phentermine produced a grossly similar profile of subjective and physiologic effects to amphetamine (Martin *et al.*, 1971; Chait *et al.*, 1987). For the most part, the relative potencies of these agents, calculated from parallel line bioassays, were similar across pressor response, decreases in caloric intake, and subjective measures, indicating a lack of pharmacological selectivity among these agents. For these reasons, it was judged that all of these phenylethylamines possessed the same potential for producing reinforcing effects and adverse effects as amphetamine. Consequently, all were judged to have similar potential for abuse.

Using these same methods, this study compared the subjective, behavioural, and physiologic responses of modafinil to those of

**Table 1** Least significant differences (LSD) and mean AUC scores for selected effects

	LSD	Placebo	Methylphenidate		Modafinil		
			45 mg	90 mg	200 mg	400 mg	800 mg
Subject-rated measures							
Drug Rating Questionnaire							
Feel the Drug?	7.6	10.1	32.3*	49.6*	15.4	19.6*	37.4*
Like the Drug?	8.5	5.0	25.4*	37.5*	15.0*	21.6*	38.5*
High Now?	6.9	8.6	26.1*	41.6*	9.8	16.0*	30.0*
Drug Identification Questionnaire							
None	1.6	-2.8	-9.2*	-10.6*	-4.6*	-6.0*	-10.0*
Opiates	0.5	0.6	0.8	1.3*	0.1	0.1	0.8
Drug Response Questionnaire							
Nervous	0.8	-0.4	1.0*	3.5*	0.1	0.7*	2.3*
Stomach turning	0.6	0.2	1.4*	1.8*	0.7	0.6	2.2*
Hearing changed	0.4	0.1	0.5	1.4*	0.6*	0.4	0.7*
Body feels different, changed, or unreal	0.2	0.2	3.4*	5.4*	1.9*	1.7*	3.8*
Need to talk	0.4	0.2	0.5	1.4*	0.0	0.3	0.7*
Dizzy	0.4	0.7	0.4	1.0	0.1	0.0	0.2
Sleepy	1.2	2.7	1.7	0.0*	-0.1*	-0.3*	-0.5*
Observer-rated measures							
Drug Rating Questionnaire							
Feel the Drug?	8.0	16.9	56.0*	62.9*	18.3	25.3*	38.6*
Like the Drug?	9.4	9.3	47.3*	53.6*	11.6	17.1	31.9*
Drug Response Questionnaire							
Sleepy	1.3	3.8	3.3	0.7*	-0.3*	0.5*	0.3*
Nodding	0.4	0.8	0.5	0.1*	0.0*	0.1*	-0.1*
Relaxed	1.4	1.6	2.4	1.7	2.6	1.5	0.4
Tremulous	0.6	0.4	0.8	2.7*	0.4	0.6	0.6

\*Statistically significantly different from placebo at the  $p = 0.05$  level.

methylphenidate and placebo in adult males with a history of polysubstance abuse that included cocaine. Single doses of methylphenidate (45 mg and 90 mg), modafinil (200 mg, 400 mg and 800 mg) and placebo were administered to each subject under double-blind conditions according to four balanced  $6 \times 6$  Latin squares. The chosen doses of modafinil represent one to four times the daily unit dose of 200 mg recommended for the treatment of excessive daytime sleepiness in patients with narcolepsy. The doses of methylphenidate represent 2.5 to 4.5 times the unit dose of 20 mg used in the treatment of narcolepsy. The doses of methylphenidate were chosen on the basis of initial dose-ranging studies conducted to identify oral doses that produced clear dose-related amphetamine-like effects, yet were safe and tolerated by subjects. Based on the results of safety assessments from another Phase 1 study (Wong *et al.*, 1999), the doses of modafinil used in this study were limited to a maximum of 800 mg.

In this study, methylphenidate (the positive control) was reliably distinguished from placebo (the negative control) and produced the expected dose-related profile for amphetamine-like effects (Martin *et al.*, 1971). Therefore, this group of stimulant-abusers would be expected to be valid identifiers of the psychoactivity of amphetamine-like drugs.

In this study, valid 4-point bioassays between modafinil 400 mg and 800 mg and methylphenidate 45 mg and 90 mg were not obtained, indicating the mean responses for the methylphenidate doses were significantly higher than those of modafinil 400 mg and 800 mg.

All doses of modafinil were discriminated from placebo as noted by a significantly lower 'no drug at all' score on the Drug

Identification Questionnaire. Although some activity was observed at the 200-mg and 400-mg dose levels, clear effects were only observed at the 800-mg dose level. The supine blood pressure data, as well as the results of the Drug Rating Questionnaire, suggest that 800 mg of modafinil is most similar to 45 mg of methylphenidate. However, there were differences in the profiles of subjective and physiological effects between the two agents including, most notably a lack of a significant response on the Amphetamine Scale of the ARCI. Administration of modafinil also resulted in a greater inhibition of observed and reported sleep, a lesser facilitation of orthostatic pulse increases and a lesser reduction of caloric intake relative to methylphenidate. These differences in subjective and physiological responses are suggestive of pharmacological selectivity for modafinil.

The subjective findings from our study are consistent with those from a study by Warot and colleagues (1993) in which they compared the effects of amphetamine 15 mg, modafinil 300 mg, and caffeine 300 mg in healthy volunteers. Their results showed that modafinil was clearly differentiated from amphetamine on the Amphetamine Scale of the ARCI. Furthermore, subjects indicated that if they had to take the drug on another occasion, they would chose amphetamine rather than modafinil or caffeine.

Overall, the results from these human studies are consistent with preclinical studies that show modafinil promotes wakefulness through mechanisms that are distinct from those of central nervous system stimulants such as amphetamine and methylphenidate (Duteil *et al.*, 1990; Lin *et al.*, 1992; DeSereville *et al.*, 1994; Mignot *et al.*, 1994; Simon *et al.*, 1994; Lin *et al.*, 1996). This selective wake-promoting activity of modafinil indicates that modafinil does

not show pharmacological equivalence to methylphenidate and other amphetamine-like agents.

If pharmacological equivalence to a drug with known abuse potential is not shown, a second method of assessing the abuse potential of a new drug is to determine if the drug produces reinforcing or toxic effects that could lead to abuse. At the doses tested in our study, modafinil was 'liked' by the subjects and raised mean blood pressure; however, it is our opinion that these qualities alone do not indicate that the drug will be abused. Other drugs with adrenergic 'stimulant' activity, such as phenylpropranolamine and caffeine, raise blood pressure and promote wakefulness, but do not represent significant public health or safety concerns as drugs of abuse (Chait *et al.*, 1988; Warot, 1993). In a prior study, Warot *et al.* (1993) determined that the subjective effects of modafinil 300 mg were very similar to those produced by caffeine 300 mg; however, further study may be required to compare the effects of higher doses of modafinil to those produced by these agents.

Several other characteristics of modafinil suggest that it does not possess the abuse potential of amphetamine and methylphenidate. First, modafinil is virtually insoluble in water and therefore cannot be injected. The necessity for oral administration reduces the likelihood of direct or indirect toxicities that are associated with intravenous drug use. In addition, modafinil degrades when heated and cannot be smoked like methamphetamine. Furthermore, the long duration of activity for modafinil allows for once-daily dosing rather than the 2–3 daily doses required for methylphenidate. This translates into fewer tablets dispensed with each prescription.

We have shown that, at the doses tested in our study, modafinil is not pharmacologically equivalent to methylphenidate, and does not appear to have toxic or reinforcing effects that may lead to abuse. However, it should be noted that non-pharmacological factors that are part of the social response to its availability will also determine whether this drug will be abused or misused. Because of the unique pharmacologic profile and low toxicity, there is likelihood for off-label use in which physicians prescribe modafinil to promote wakefulness in situations other than patients with narcolepsy. Physicians should be encouraged to prescribe modafinil cautiously and judiciously in such situations.

In conclusion, at the doses tested in this study, modafinil did not show pharmacological equivalence to methylphenidate. The findings in our study further differentiate modafinil from amphetamine-like drugs such as methamphetamine, phenmetrazine, diethylpropion, phentermine and ephedrine, that clearly produce significant dose-related increases on the Amphetamine Scale of the ARCI (Martin *et al.*, 1971; Chait *et al.*, 1987). The data suggest that the subjective effects of modafinil may be more similar to agents such as phenylpropranolamine or caffeine, although direct comparison to these agents would be required to draw adequate conclusions. The lack of pharmacological equivalence to amphetamine-like agents, coupled with modafinil's inability to be injected intravenously or smoked, and its once-daily dosing in the management of excessive daytime sleepiness in patients with narcolepsy, suggest that it does not possess the same public health or safety concerns for abuse compared with the amphetamine-like agents. The potential for its misuse exists if physicians prescribe modafinil to promote wakefulness in situations other than narcolepsy. The exact influence of the social response to the availability of modafinil can only be determined by post-marketing surveillance.

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