Annals of Clinical Psychiatry, 16:101–109, 2004
Copyright © 2004 Taylor & Francis Inc.
ISSN: 1040-1237 print / 1547-3325 online
DOI: 10.1080/10401230490453743

Taylor & Francis
Taylor & Francis Group

Modafinil: Preclinical, Clinical, and Post-Marketing Surveillance—A Review of Abuse Liability Issues

HUGH MYRICK, M.D.

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, and Research and Development Service, Veterans Affairs Medical Center, Charleston, South Carolina, USA

ROBERT MALCOLM, M.D., BRENT TAYLOR, and STEVEN LaROWE, Ph.D.

Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina, USA

Modafinil is an agent that is frequently used in the treatment of narcolepsy. More recently it has been used in the treatment of a variety of psychiatric, neurological, and medical illnesses. Due to its ability to improve wakefulness, modafinil has been viewed as a stimulant. Based on the potential for modafinil to become widely used in a variety of syndromes and settings, evidence from preclinical* in vitro *and* in vivo *studies, human laboratory studies, and post-marketing experiences examining the potential abuse liability of modafinil were reviewed. Initial evidence suggests that modafinil has limited potential for large-scale abuse.

Keywords Modafinil; Substance abuse; Addiction.

INTRODUCTION

Modafinil (diphenylmethyl-sulfonyl-2-acetamide) was first marketed in France in the early 1990s as a new treatment for hypersomnolence that accompanies narcolepsy. In 1998 modafinil was approved by the Food and Drug Administration (FDA) as a Schedule IV agent to improve wakefulness in patients with excessive daytime sleepiness that accompanies narcolepsy. Because of its ability to improve wakefulness, modafinil has been viewed by some as a stimulant. Modafinil significantly increases vigilance, alertness, and wakefulness in several species, including humans, but it appears to have less propensity than stimulants to produce hyperactive motor behavior, elevations of blood pressure, and tachycardia (1–4). Modafinil's effectiveness in treating several other syndromes has been explored in randomized clinical trials. There is evidence that modafinil demonstrates efficacy in attention deficit hyperactivity disorder (5,6), as an augmenting agent for depression (7,8), in improving wakefulness in obstructive sleep apnea (9–11) and Parkinson's disease (12,13), and in the management of fatigue syndromes that accompany deteriorative neurologic illnesses such as multiple sclerosis (14,15). Since the outcomes of these trials have been favorable, the use of modafinil in psychiatry, neurology, and primary care has spread beyond the management of excessive daytime sleepiness due to narcolepsy.

Based on the potential for modafinil to become widely used in a variety of syndromes and patient populations, we felt it was prudent to review the evidence examining the potential abuse liability of modafinil. The body of literature exploring the abuse potential of modafinil spans from preclinical *in vitro* and *in vivo* studies to several human laboratory studies. Most relevant, however, are the post-marketing experiences in France of over a decade and in the United States (US) of approximately five years. Each of these areas will be reviewed in turn.

CHEMISTRY AND PHARMACOLOGY OF MODAFINIL

Modafinil has the molecular formula of $C_{15}H_{15}NO_2S$ and a molecular weight of 273.36. It is only slightly soluble

This manuscript was supported by NIDA N01 DA-9-8102. The authors would like to thank Vicki Brumbelow and Ann Blanton for manuscript preparation.

Address correspondence to Hugh Myrick, M.D., MUSC Institute of Psychiatry 4N, 67 President St, Charleston, SC, 29425. E-mail: myrickh@musc.edu

in methanol and acetone, and it is practically insoluble in water and cyclohexane (16). Modafinil is a racemic compound with the half-life of the l-isomer about three times that of the D-isomer in humans. The isomers do not interconvert to one another. Modafinil is readily absorbed with oral administration with a peak plasma concentrations occurring after about 2–4 hours. Maximum time of absorption is delayed about one hour if taken with food, but overall bioavailability is not reduced by food. Modafinil has a terminal elimination half-life in humans of about fifteen hours. Elimination is mainly via metabolism which occurs through deamination, oxidation of the sulfur group, aromatic ring hydrolyzation, and glucuronide conjugation with primarily renal excretion of the metabolites. Several metabolites of modafinil have been identified in humans, but only modafinil acid and modafinil sulfone are present in appreciable concentrations in the circulation. In preclinical models, neither of these metabolites appeared to have the alerting effects of modafinil (17). In *in vitro* studies using human hepatocyte cultures, modafinil appears to modestly induce CYP1A2, CYP3A4, CYP2B6 and to suppress CYP2C9. In human *in vivo* interaction studies, modafinil does not appear to alter the pharmacokinetics of dextroamphetamine, clomipramine, methylphenidate, or single dose warfarin. After steady state dosing modafinil decreases the C-max and area under the curve of ethinyl estradiol and triazolam. When heated, modafinil is destroyed and therefore cannot be smoked. It can be ground into a powder and therefore may have some potential to be absorbed nasally. Modafinil is classified as pregnancy Category C.

PRECLINICAL MECHANISMS OF MODAFINIL

The precise mechanism of action of modafinil is unknown, and some preclinical information appears contradictory. When examined by c-fos immunocytochemistry in cats (18) and rodents (19), modafinil primarily localized to hypothalamic structures involved in the regulation of daytime alertness. Both studies supported the premise that modafinil differs in sites of action from methylphenidate and amphetamine. Relevant to the present review, modafinil did not demonstrate c-fos activity in areas of the brain that have been implicated in the rewarding aspects of drug abuse such as in the nucleus accumbens or in the ventral tegmental area. Methylphenidate and amphetamine showed significant reactivity in the dopamine neurons of both areas. There were disparate findings between the studies regarding c-fos activity in multiple other areas of the brain, particularly the amygdala, perhaps in part due to species and methodological differences. Scammell and colleagues (20) performed three rodent experiments, again using c-fos immunocytochemistry techniques, evaluating modafinil against vehicle in animals that had modafinil treatment during both sleep and wake cycles. Modafinil increased c-fos immunoreactivity in the tuberomammilary nucleus, in the perifornical orexin neuron area and also in the central nucleus of the amygdala. As in previous studies, neither the nucleus accumbens nor the ventral tegmental area showed any difference between modafinil and vehicle in c-fos immunoreactivity.

Unlike stimulants such as amphetamine, modafinil binds to the dopamine uptake carrier site with low affinity similar to the anti-depressant medication bupropion (21). Subsequent unpublished work (22) has supported this weak binding affinity. Another study using dopamine transporter (DAT) knock-out mice observed no increase in motor behavior following administration of modafinil (23). Other studies have concluded that modafinil, although perhaps not binding directly to alpha-adrenergic receptors, has alpha-adrenergic activity since antagonists to these receptors, such as prazosin, phenoxybenzamine, and reserpine, will prevent modafinil-induced increases in locomotor activity in mice (1,24). Dopamine receptor antagonists such as haloperidol and the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine suppressed hyperactivity induced by amphetamine but not modafinil (2). In the same study, reserpine-induced akinesia was reversed by amphetamine but not modafinil, again supporting the premise for alpha-adrenergic actions of modafinil. Still other studies have found a role for modafinil in increasing brain glutamate in contrast to stimulants (25,26). Another difference between modafinil and traditional stimulants is modafinil's role in protecting against neuronal cell death. Modafinil is neuroprotective against glutamate-induced cytotoxicity in rodent dopamine cell culture models (27). Modafinil also appears to have neuroprotective effects in an *in vivo* marmoset model of MPTP-induced dopamine cell death (28). This is in contrast to amphetamine (29) and to MDMA (30); both can be neurotoxic in preclinical models. Although the above studies have failed to elucidate a single neurobiological mechanism of action for modafinil, they do highlight significant behavioral and pharmacological differences between modafinil and stimulants.

PRECLINICAL STUDIES EVALUATING MODAFINIL ABUSE LIABILITY

Two published papers have evaluated preclinical addiction potential of modafinil. In the first paper, Gold and Balster (31) evaluated cocaine-like discriminative effects of modafinil in rats with previous stimulant experience, and the intravenous reinforcing effects of modafinil in three stimulant-experienced male rhesus monkeys and one stimulant-naive female rhesus monkey. In a second study, Deroche-Gamonet and colleagues (32) studied the addictive potential of modafinil in naive and cocaine-experienced rats in five experimental models of addiction liability.

In the Gold and Balster (31) studies, six male Sprague-Dawley rats with previous intraperitoneal exposure to cocaine, cocoethylene, and unspecified dopamine agonists were trained to discriminate cocaine from saline in a two-lever operant conditioning task requiring 32 bar presses (FR 32) to receive food. After specific accuracy criteria had been obtained for cocaine and saline discriminations, animals were then exposed on separate days to intraperitoneal injections of modafinil, D-amphetamine, and L-ephedrine over a wide dosage range. At five doses between 3 and 100 mg/kg, modafinil was discriminated as saline by all animals. Only at the two highest doses in four of the six animals was modafinil discriminated as cocaine with about 67% correct responding. In contrast, over a wider dosage range D-amphetamine was discriminated 100% as cocaine, and L-ephedrine was discriminated 82% of the time as cocaine. The authors concluded that on a mg/kg basis in this rodent test of addiction potential, modafinil was about 250 times less potent than D-amphetamine and about fifteen times less potent than L-ephedrine.

In the same paper (31) the investigators studied lever-pressing for saline, modafinil, and cocaine. Modafinil was administered intravenously in a low-dose ethanol emulsion because of lack of water solubility. Controls supplied evidence that the low dose of ethanol alone in the vehicle did not serve as a bar-pressing reinforcer. Modafinil was administered in this ethanol emulsion at doses of 0.03 mg/kg, 0.1 mg/kg, and 0.3 mg/kg. Mean self-administered infusions per session was the primary dependent variable. Comparisons were made against baseline saline and cocaine infusions of 0.02 and 0.05 mg/kg/infusion. Modafinil, D-amphetamine, and L-ephedrine were compared to saline and cocaine conditions. All monkeys bar-pressed for a greater number of infusions for at least one of the two higher doses of modafinil when compared to vehicle infusions. However, clear-cut dose response relationships in the four monkeys were not found, and response patterns were variable. For the female monkey that had never been exposed to cocaine or other stimulants before, only the very highest dose of modafinil produced a mean infusion rate per session higher than vehicle conditions, and this rate was higher than the comparison cocaine infusion conditions. For one of the three previously experienced stimulant-using male monkeys, the pattern was similar to the naive female except for the highest doses of modafinil, and although exceeding vehicle, the dose fell within the range of the cocaine infusion comparisons. Comparisons with D-amphetamine or L-ephedrine were only available for two of the male monkeys and the female monkey. Modafinil doses were ten to thirty times mg/kg less than amphetamine doses. The L-ephedrine doses were equal to the middle modafinil 0.1 mg/kg dose. For the previously stimulant-naive female monkey and for one of the male monkeys, the highest dose of modafinil indicated mean infusions per session about the same as for the D-amphetamine and L-ephedrine. For the second monkey, the highest dose of modafinil was about the same for the D-amphetamine and L-ephedrine, but the middle dose was significantly higher in mean infusions per session. Two other points are of interest. Monkeys returned to baseline level of cocaine self-administration on the day after modafinil substitutions. Modafinil did not increase later cocaine use. None of the four animals demonstrated any behavioral toxicity or withdrawal phenomena to modafinil. The 0.03 mg/kg infusion of D-amphetamine in the first male monkey was associated with stimulant-associated repetitive biting behaviors (stereotypies) and hypervigilance. Accordingly, the D-amphetamine dose for the other animals was reduced to 0.01 mg/kg, and the higher dose was not tested.

The investigators concluded the modafinil served as a reinforcer for drug self-administration in cocaine-trained rhesus monkeys and can produce cocaine-like discriminative stimulus effects in rats. They noted that future valuable information could be gained by examining the reinforcing effects of modafinil in naive animals. Considering the mg/kg lower potency of modafinil for both monkeys (10–30 times less potent than D-amphetamine) and in rats (250 times less potent than D-amphetamine), the authors concluded that modafinil should be considered a "relatively impotent" stimulant (Table I).

Deroche-Gamonet and colleagues (32) conducted five experiments in primarily stimulant-naive male Sprague-Dawley adult rats. In experiment 1 stimulant-naive animals were compared as to modafinil and amphetamine's ability to induce place conditioning. In this standard experiment, rodents given a rewarding/addicting drug in a stimulus distinct compartment learn to return to that compartment. Over a wide dosage range from 32 to 256 mg/kg of modafinil injected intraperitoneally (IP), animals did not differ from vehicle-treated control animals in their preference for one or the other two compartments. In contrast, amphetamine animals treated at 2 mg/kg IV showed significant conditioned place preference over vehicle. Both groups of animals had dose-related increased locomotor activity. The highest locomotor response after modafinil was at the 128 mg/kg dose that compared to the amphetamine 2 mg/kg dose. Experiment 2 compared modafinil and cocaine-induced IV self-administration bar pressing. As the bar pressing ratio requirement to obtain intravenous modafinil was increased, animals decreased their behavioral responding for modafinil. In contrast, bar pressing for cocaine administered at 0.8 mg/kg/injection regardless of the ratio of responding necessary maintained steady intake of cocaine. Modafinil responses, even at the lower ratios, were equal to vehicle. In Experiment 3, modafinil, haloperidol, and amphetamine were studied in their ability to alter cocaine IV self-administration using a dose response procedure. Modafinil did not modify behavioral responses or the number of cocaine self-injections. In contrast, amphetamine induced

Table I Modafinil Abuse Potential: Summary of Preclinical Studies

Species	N	Experimental procedure	Treatment	Results	Conclusions
Gold and Balster, 1996					
C-experienced rats	6	C-discrimination (operant conditioning task for food)	· M 3–250 mg/kg IP · A 0.1–3.0 mg/kg IP · E 3–30 mg/kg IP	· M 3–100 mg/kg discriminated as S in 100% · M 150–250 mg/kg discriminated as C in 4/6 · A discriminated as C in 100% · E discriminated as C in 82%	· M produced D-R increased in C selection · C-like discrimination at higher M doses · M 250-times less potent than A, 15-times less potent than E
Rhesus monkeys · C-experienced · C-naïve	3 male 1 female	IV self-administration	· M 0.03, 0.1, 0.3 mg/kg · A 0.01, 0.03 mg/kg · L 0.1 mg/kg · Controls: S, V, C 0.02, 0.05 mg/kg	· Variable response pattern depending on treatment, animal · All animals increased self-administration for at least 1 M dose compared to V · Overall M intake increased depending on dose/infusion · No behavioral toxicity or withdrawal with M	· M served as reinforcer for drug self-administration in C-experienced animals · M 10- to 30-times less potent than A
Deroche-Gamonet et al., 2002					
1. Stimulant-naive rats	7 grps (n = 8/grp)	M- and A-induced place conditioning	· M 32–256 mg/kg IP · A 2 mg/kg IP · V	· M did not induce place preference · D-R increased in motor activity with M, A; highest activity with M 128 mg/kg, A 2 mg/kg	· M did not induce place preference
2. Stimulant-naive rats	6 grps (n = 5 to 9/grp)	IV self-administration	· M 0.28–1.7 mg/kg · C 0.8 mg/kg · V	· M did not induce IV self-administration	· M did not demonstrate reinforcing behavior
3. Stimulant-naive rats	7	Alteration in IV C self-administration using D-R procedure	· M 32–128 mg/kg IP · H 0.1 mg/kg IP · A 1.5 mg/kg IP · V	· M had no effect on C D-R · A left-shifted C D-R · H right-shifted C D-R	· M did not substitute for C
4. Stimulant-naive rats	23	Alteration in IV C self-administration using progressive ratio schedule	· M 32–128 mg/kg IP · V	· M had no effect on C self-administration	· M did not substitute for C
5. C-experienced rats	10	Potential to reinstate IV C self-administration	· M 64 mg/kg IP · V	· M had no effect on C D-R for reinstatement	· M did not have C-like reinstatement behavior

A = D-amphetamine; C = cocaine; D-R = dose-response; E = L-ephedrine; H = haloperidol; IP = intraperitoneal; IV = intravenous; M = modafinil; S = saline; V = vehicle

a leftward shift in the dose response curve, and haloperidol induced a rightward shift in the dose response curve, findings often interpreted as an increase and a decrease, respectively, in the reinforcing properties of cocaine. In Experiment 4, modafinil did not modify cocaine IV self-administration using a progressive ratio procedure. In Experiment 5, modafinil was studied as to whether it could reinstate cocaine IV self-administration. Ten male animals were trained for cocaine self-administration using a within-session dose-response schedule. Three doses of cocaine were used each session. After response rates were stable, cocaine self-administration was never available for future sessions, and extinction of the bar pressing behavior was achieved. Following this, in random fashion, animals received an injection of modafinil or vehicle ninety minutes into the extinction session. Cocaine injections, as noted in many previous studies, induced a specific and dose-dependent return to lever responding. In animals pretreated with modafinil, non-contingent saline injections produced responding at the behavioral site previously associated with cocaine. However, modafinil did not significantly shift the dose response curve above saline rates for cocaine-induced reinstatement in these cocaine experienced animals.

The investigators concluded that stimulant-naive animals had no addictive potential when studied in a variety of preclinical models. Furthermore, modafinil compared to classic psychostimulants did not appear to alter the reinforcing or incentive properties of cocaine. Modafinil did not modify cocaine-induced dose-response reinstatement above that of saline controls.

In conclusion, two preclinical studies suggest that stimulant-experienced animals perceive modafinil as weakly reinforcing, whereas stimulant-naive animals do not. However, preclinical models have not explored potential gender differences in these findings, since they were almost all exclusively done in male animals.

HUMAN LABORATORY STUDIES IN NON-DRUG DEPENDENT AND DRUG DEPENDENT INDIVIDUALS

Human laboratory studies can predict the abuse potential of numerous psychoactive agents (33). Human laboratory studies generally involve a relatively small number of volunteers, either nondrug using individuals or non-treatment-seeking substance dependent or substance abusers. Methodology varies but generally the paradigms involve double-blind, placebo-controlled studies in which the agent in question is evaluated under acute dosing or steady state. Comparisons are frequently made with multiple drugs of a similar class and against placebo. To date, six studies with varying methodology have been used to examine the abuse potential of modafinil in humans (34–39). Two other studies, while not primarily designed to assess the abuse liability of modafinil, also had measures and subjects that have relevance for the examination of this question (40,41).

Warot and colleagues (34) evaluated eight males and eight females with no current or past history of substance abuse. All subjects were moderate users of caffeine. Using a randomized, double-blind cross-over design, subjects received placebo, modafinil 300 mg, caffeine 300 mg, or amphetamine 15 mg. Subjective drug effects were measured using the Addiction Research Center Inventory (ARCI), Profile of Mood States (POMS), and a variety of visual analog scales at baseline and at one, two, four, and eight hours after a single oral dose. On all of the addiction discrimination scales, subjects reported modafinil and caffeine to be similar, and on some scales and at some time points equivalent to placebo. Subjects taking amphetamine scored significantly higher on all addiction scales. Diastolic and systolic blood pressures and supine pulse rates declined over the course of the day for placebo and caffeine. Peak blood pressure changes for modafinil were only about 4 mm Hg, whereas peak blood pressure changes for amphetamine were about 8 mm Hg. Five subjects on modafinil, five subjects on amphetamine, and one subject on caffeine reported improvement of "intellectual efficiency." Eight subjects on amphetamine and four on modafinil reported a temporary loss of appetite. Eight subjects on modafinil, three on amphetamine, and two on caffeine had moderate transient headaches. No gender differences were reported.

Jasinski (36) studied 24 male, non-treatment seeking volunteers with extensive histories of stimulant abuse including cocaine. Using a double-blind crossover design, subjects were given single oral doses of methylphenidate (45 or 90 mg), modafinil (200, 400, or 800 mg), or placebo. The ARCI was employed as well as pulse and blood pressure measures. Only the highest (800 mg) dose of modafinil was identified as stimulant-like, and no dose of modafinil was different from placebo on the Amphetamine Subscale of the ARCI. Peak mean blood pressure increased about 14 mm Hg for the 90 mg dose of methylphenidate and about 8 mm Hg for the 800 mg dose of modafinil. Modafinil's effect on pulse and caloric intake was comparable to placebo. Adverse events were not reported. In a review article, the same author (42) described an unpublished study of twelve females with polysubstance and stimulant abuse. This study was similar in design to that just described. The female subjects had significant increases above placebo for modafinil 400 mg on the Amphetamine Subscale of the ARCI. In addition, there was a statistically significant response on the Morphine-Benzadrine Subscale for female subjects on modafinil 800 mg relative to placebo. Little additional information was available, and no explanation for these contrasting findings in females was put forward.

Rush and colleagues (37) evaluated modafinil in seven male and two female volunteers with recent histories of

significant cocaine use. Using a randomized double-blind design, subjects received cocaine hydrochloride orally (100, 200, and 300 mg), placebo, and modafinil (200, 400, and 600 mg). Using the Drug Effect Questionnaire, only 600 mg of modafinil increased ratings of "any effect" significantly above placebo. "High," "rush," and "stimulated" were all similar to placebo for modafinil. Generally, all three dose of cocaine were discriminated from placebo. A dose-response effect was seen for all doses of cocaine. Dose response effects were not seen for modafinil. Subjects on cocaine (100, 200, and 300 mg) reported they were willing to pay $3, $6, and $10 respectively for each dose. Regardless of the modafinil dose, subjects were only willing to pay about $2. Modafinil dose-dependently increased heart rate and blood pressure, but these elevations were clinically insignificant. No gender differences were reported, and side effects were not reported. In a second study, Rush and colleagues (38) studied two females and four males with recent history of cocaine use and used a discriminant stimulus design in which all subjects were taught to discriminate 150 mg of oral cocaine hydrochloride from placebo. Once 80% or better correct responding on four consecutive days was achieved, subjects were then administered, in a double-blind fashion, oral doses of cocaine (50, 100, or 150 mg) or modafinil (200, 400, or 600 mg) versus placebo. Methylphenidate 60 mg and triazolam 0.5 mg were included as additional controls. Cocaine and methylphenidate—but not modafinil nor triazolam—produced cocaine-like discriminative responses. No gender differences or side effects were reported.

Dackis and colleagues (39) investigated drug interactions between modafinil and cocaine in a double-blind, placebo controlled study. Seven cocaine-dependent subjects intravenously received 30 mg doses of cocaine in combination with 200 mg of modafinil, 400 mg of modafinil, or placebo. An initial baseline infusion of cocaine preceded four days of modafinil administration prior to three additional infusions of cocaine. Physiologic and subjective effects were recorded. Modafinil, when compared to placebo, did not affect vital sign responses including systolic and diastolic blood pressure, pulse, and temperature. Likewise, modafinil had no effect on ECG measures, cocaine levels in the blood, and prolactin levels. Notably, modafinil's only subjective effect was a slight blunting of cocaine-induced elevations in the amphetamine scale of the ARCI. This effect was significant only for the low, 200 mg dose of modafinil, but the small sample size of the study suggests that further investigation into modafinil's potential to antagonize the subjective effects of cocaine is warranted.

Westensten and colleagues (40) evaluated fifty healthy, non-smoking men ($N = 37$) and women ($N = 13$). Subjects were excluded if their daily caffeine consumption was >400 mg. In double-blind fashion, subjects received either placebo, modafinil (100, 200, or 400 mg) or caffeine 600 mg, followed by hourly testing from midnight through three days. Alertness and performance were the main outcome measures for the study. Both modafinil and caffeine increased alertness and performance during sleep deprivation. Notably, modafinil did not demonstrate significant differences from baseline on subscales of the POMS such as Vigor-Activity or Anger-Hostility. These two subscales are frequently elevated in drugs with abuse potential. Three subjects reported heart-pounding after modafinil, and four subjects reported heart-pounding after caffeine. Three in each group reported heart-pounding after the 600 and 400 mg doses of modafinil. Two subjects vomited in the caffeine 600 mg group, and one reported jitteriness and shaking in the modafinil 400 mg group. No gender differences were reported in this study.

Malcolm and colleagues (41) conducted a safety and pharmacokinetic interaction study between IV cocaine and oral steady-state modafinil (200 mg twice daily and 400 mg twice daily). Subjects had to meet criteria for cocaine dependence and demonstrate one positive urine for cocaine prior to infusion. Visual analog measures of "any drug effect," "cocaine high," and "amount willing to pay" were assessed for both drugs. In a double-blind fashion, cocaine (20 mg or 40 mg) or saline was administered intravenously over one minute. Modafinil was administered open-label. On all subjective visual analog measures of cocaine effects, modafinil reduced these effects by 20–40%. Modafinil 800 mg did not confer any significant benefits over 400 mg of modafinil on any of these measures. Modafinil did not significantly raise systolic-diastolic blood pressure or pulse for either cocaine dose. The six male and six female subjects showed equivalent responses in subjective visual analog scales, hemodynamic measures, and pharmacokinetics. The "amount of money willing to be paid" for cocaine in the presence of modafinil was about $2. Side effects were generally limited to headaches and insomnia. Insomnia was prominent, since to obtain steady-state for modafinil it was administered every twelve hours.

POST-MARKETING SURVEILLANCE

Post-marketing surveillance and clinical observations of a pharmacological agent is the most naturalistic and perhaps the most conclusive assessment of a pharmacologic agent's abuse potential. In this setting, clinicians begin using a drug in diverse patient groups, often in dosages and disorders that were not originally studied.

Beginning in January 1999, the Haight-Ashbury Free Clinics Behavioral Research Group has monitored use patterns of modafinil. The program is funded under an independent educational grant from Cephalon, Inc. The program design and dissemination of results are at the discretion of the Haight-Ashbury Free Clinics. This surveillance program is extensive and comprised of information from multiple

standard national and state databases such as DAWN, MEDWATCH, and national drug use surveys. Medical and popular literature are also under surveillance, as well as anecdotal information from clients in the Haight-Ashbury system and multiple focus groups with service providers in addiction, pain management, pediatrics, geriatrics, and primary care. Extensive internet monitoring and sampling also go into this surveillance.

In general, in over four years of surveillance, this group has not detected any generalized or persistent misuse or abuse of modafinil. In internet discussions about abuse/misuse, the drug was discussed as not worthwhile, boring, or a "bust." Isolated case of abuse have been found, but they appear to be limited to particular individuals with idiosyncratic uses and backgrounds. Furthermore, their uses do not appear to have spread to their peer groups. In their report, the Haight-Ashbury group notes that none of the following groups have thus far demonstrated a propensity for abuse of modafinil: stimulant abusers or polydrug abusers; college students; programmers or computer operators; truck drivers; shift workers (43). Health care professionals can represent a bellwether group since they have early knowledge and ready access to medications. The Haight-Ashbury group notes that two physicians have been reported to have abused modafinil and have surrendered their medical licenses. They note that their surrender of licenses was also related to the concomitant abuse of other scheduled and unscheduled drugs of abuse. Both of these health care professionals had extensive substance abuse histories, particularly with stimulants, and one was a former stimulant abuser with a diagnosis of bipolar disorder. "Smart drug" advocates are individuals who believe that various combinations of drugs, vitamins, and herbs can be used to improve mental functioning, vitality, and particularly creativity. Modafinil has been occasionally discussed in chat rooms for "smart drug" forums. The Haight-Ashbury group had found that messages about modafinil represent less than 1% of the total messages per month. Messages about modafinil were found to be brief and frequently negative with respect to any euphoric qualities. Other chat rooms concerned with the treatment of social phobia have mentioned the combination of modafinil with benzodiazepines. One individual was a strong advocate, stating that the combination reduced anxiety and increased social contacts.

The Haight-Ashbury group concluded that in over four years of modafinil surveillance from multiple monitored sources, discussion about interest in and abuse of modafinil has remained sporadic and low. This is despite a growing awareness of modafinil and increased clinical use for both on- and off-label purposes.

Our group (44) reported on a small case series of four individuals who had had extensive stimulant abuse/dependence, and these individuals were later prescribed modafinil for a variety of clinical purposes. We were able to conduct extensive interviews with them. Although some of these individuals reported improvement in mood, energy, and cognitive functions, none took modafinil in a fashion that appeared to mimic the abuse patterns of their previous abuse of methylphenidate, amphetamine, or cocaine. We have since located a fifth case (unpublished) of a 56-year-old white male, former political speech writer who suffered from obsessive-compulsive disorder and attention deficit disorder since adolescence. He had an extensive abuse and dependence on amphetamines and alcohol during his political career. He ultimately developed a paranoid psychosis and was hospitalized. After over a decade of abstinence and high-intensity participation in twelve-step self-help groups, he was placed on modafinil for his attention deficit disorder. He has been maintained on modafinil for over three years at a steady dose of 200 mg/day. There has been no evidence of modafinil abuse nor a return to alcohol or stimulant abuse. While screening subjects for our modafinil/cocaine safety and pharmacokinetic study, we interviewed three individuals (two females, one male) in late adolescence who reported they had ground up and snorted modafinil. All three individuals separately recounted that although they were able to stay up all night (watching TV, going to a party, or house cleaning), they denied euphoric feelings, and one individual stated that modafinil "wrecked [her] high on alcohol and cocaine."

CONCLUSIONS

A variety of evidence suggests that modafinil has limited potential for abuse. First, the chemical and pharmacologic profiles of modafinil are not favorable for abuse. Second, preclinical studies indicate, in general, that modafinil in stimulant-naive animals has little to no addictive potential. In primates and rodents with extensive past stimulant experiences, modafinil appears to have modest addictive potential, but only in doses that milligram per kilogram are far higher than that of amphetamine. Third, eight human studies involving both non–substance abusing volunteers and cocaine-using individuals support the notion of a limited abuse potential for modafinil, in addition to having minimal effects on hemodynamic parameters and appetite. There are some limitations to these studies. In some of these studies the amount of previous cocaine exposure was not defined, and, in most cases, subjects were not DSM-IV defined cocaine-dependent individuals. The study in females reviewed by Jasinski (42) suggests that females with substance abuse histories may be at greater risk than males for abuse of modafinil, but this has not been replicated. Perhaps most importantly, in a report from the Haight-Ashbury Clinics, modafinil did not appear to have created much interest on the internet, had little commercial value in sales, and generated few clinical reports of abuse in over four

years of post-marketing surveillance. Only isolated, idiosyncratic cases of modafinil abuse have occurred. In conclusion, based on the evidence to date, large-scale abuse appears unlikely in the future.

REFERENCES

1. Duteil J, Rambert FA, Pesssonnier J, Hermant JF, Gombert R, Assous E. Central alpha 1-adrenergic stimulation in relation to the behaviour stimulating effect of modafinil: studies with experimental animals. *Eur J. Pharmacol* 1990; 180:49–58.
2. Simon P, Hemet C, Ramassamy C, Costentin J. Non-amphetaminic mechanism of stimulant locomotor effect of modafinil in mice. *Eur Neuropsychopharmacol* 1995; 4:509–514.
3. Edgar DM, Seidel WF. Modafinil induces wakefulness without intensifying motor activity or subsequent rebound hypersomnolence in the rat. J Pharmacol Exp Ther 1997; 283(2), 757–769.
4. US Modafinil in Narcolepsy Multicenter Study Group. Randomized trial of modafinil as a treatment for the excessive daytime somnolence of narcolepsy. *Neurology* 1998; 54(5):1166–1175.
5. Taylor FB, Russo J. Efficacy of modafinil compared to dextroamphetamine for the treatment of attention-deficit-hyperactivity disorder in adults. *J Child Adolesc Psychopharmacol* 2000; 10(4):311–320.
6. Rugino TA, Copley TC. Effect of modafinil in children with attention-deficit/hyperactivity disorder: An open-label study. *J Am Acad Child Adolesc Psychiatry* 2001; 40(2):230–235.
7. Menza MA, Kaufman KR, Castellanos A. Modafinil augmentation of antidepressant treatment in depression. *J Clin Psychiatry* 2000; 61(5):378–381.
8. Kaufman KR, Menza MA, Fitzsimmons A. Modafinil monotherapy in depression. *Eur Psychiatry* 2002; 17(3):167–169.
9. Kingshott RN, Vennelle M, Coleman EL, Engleman HM, Mackay TW, Douglas NJ. Randomized, double-blind, placebo-controlled crossover trial of modafinil in the treatment of residual excessive daytime sleepiness in the sleep apnea/hyopnea syndrome. *Am J Respir Crit Care Med* 2001; 163:918–923.
10. Pack AI, Black JE, Schwartz JR, Matheson JK. Modafinil as adjunct therapy for daytime sleepiness in obstructive sleep apnea. *Am J Respir Crit Care Med* 2001; 163:918–923.
11. Black JE, Douglas NJ, Earl CQ, Modafinil OSA Study Group. Efficacy and safety of modafinil as adjunctive therapy for excessive sleepiness associated with obstructive sleep apnea (abstract). *Sleep* 2002: 25(Suppl 1): A22.
12. Hogl B, Saleto M, Brandauer E, Glatzl S, Frauscher B, Seppi K, Ulmer H, Wenning G, Poewe W. Modafinil for the treatment of daytime sleepiness in Parkinson's disease: a double-blind, randomized, crossover, placebo-controlled polygraphic trial. *Sleep* 2002: 25(8):905–909.
13. Adler CH, Caviness JN, Hentz JG, Lind M, Tiede J. Randomized trial of modafinil for treating subjective daytime sleepiness in patients with Parkinson's disease. *Mov Disord* 2003; 13(3):287–293.
14. Rammohan KW, Rosenberg JH, Lynn DJ, Blumenfeld AM, Pollak CP, Nagaraja HN. Efficacy and safety of modafinil (Provigil) for the treatment of fatigue in multiple sclerosis: a two center phase 2 study. *J Neurol Neurosurg Psychiatry* 2002; (2):179–183.
15. Zifko UA, Rupp M, Schwarz S, Zipko HT, Maida EM. Modafinil in treatment of fatigue in multiple sclerosis. Results of an open-label study. *J Neurol* 2002; 249(8): 983–987.
16. Provigil® (modafinil) Package Insert: Cephalon, Inc., West Chester, PA, 2002. Available at: http://www.provigil.com
17. Robertson P Jr., Hellriegel ET. Clinical pharmacokinetic profile of modafinil. *Clin Pharmacokinet* 2003; 42(2):123–137.
18. Lin JS, Hou Y, Jouvet M. Potential brain neuronal targets for amphetamine-, methylphenidate-, and modafinil-induced wakefulness, evidenced by c-fos immunocytochemistry in the cat. *Proc Natl Acad Sci USA* 1996; 98(24):14128–14133.
19. Engber TM, Koury EJ, Dennis SA, Miller MS, Contreras PC, Bhat RV. Differential patterns of regional c-Fos induction in the rat brain by amphetamine and the novel wakefulness-promoting agent modafinil. *Neurosci Lett* 1998; 241(2–3):95–98.
20. Scammel TE, Estabrooke IV, McCarthy MT, et al. Hypothalamic arousal regions are activated during Modafinil-induced wakefulness. *Journal of Neuroscience* 2000; 20(22):8620–8628.
21. Mignot E, Nishino S, Guilleminault C, Dement WC. Modafinil binds to the dopamine uptake carrier site with low affinity. *Sleep* 1994; 17(5):436–437.
22. Roth BL. Personal Communication. July 10, 2003.
23. Wisor JP, Nishino S, Sora I, Uhl GH, Mignot E, Edgar DM. Dopaminergic role in stimulant-induced wakefulness. *J Neurosci* 2001; 21(5):1787–1794.
24. Stone EA, Cotecchia S, Lin Y, Quartermain D. Role of brain alpha1B adrenoreceptors in modafinil-induced behavioral activity. *Synapse* 2002; 42:269–270.
25. Ferraro L, Antonelli T, O'Connor WT, et al. Modafinil: an antinarcoleptic drug with a different neurochemical profile to d-amphetamine and dopamine uptake blockers. *Biol Psychiatry* 1997; 42:1181–1183.
26. Perez de la Mora M, Aguilar-Garcia A, Ramon-Frias T, et al. Effects of the vigilant-promoting drug modafinil

on the synthesis of GABA and glutamate in slices of rat hypothalamus. *Neuroscience Letter* 1999; 259:181–185.
27. Antonelli T, Ferraro L, Hillion J, Tomasini MC, Rambert FA, Fuxe K. Modafinil prevents glutamate cytotoxicity in cultured cortical neurons. *Neuroreport* 1998; 9(18):4209–4213.
28. Jenner P, Zeng BY, Smith LA, et al. Antiparkinsonian and neuroprotective effects of modafinil in the MPTP-treated common marmoset. *Exp Brain Res*. 2000; 133(2):178–188.
29. Davidson C, Gow AJ, Lee TH, Ellinwood EH. Methamphetamine neurotoxicity: necrotic and apoptotic mechanisms and relevance to human abuse and treatment. *Brain Res Brain Res Rev* 2001; 36(1):1–22.
30. McCann UD, Eligulashvili V, Ricaurte, GA: (+/−) 3,4-Methylenedioxymethamphetamine ('Ecstasy')-induced serotonin neurotoxicity: clinical studies. *Neuropsychobiology* 2000; 42(1):11–16.
31. Gold LH, Balster RL. Evaluation of the cocaine like discriminative stimulus effects and reinforcing effects of modafinil. *Psychopharmacol* 1996; 126:286–292.
32. Deroche-Gamonet V, Darnaudery M, Bruins-Slot L, Piat F, Le Moal M, Piazza PV. Study of the addictive potential of modafinil in naïve and cocaine-experienced rats. *Psychopharmacology* (Berl) 2002; 161(4):387–395.
33. Vocci FJ Jr. *The necessity and utility of abuse liability evaluations in human subjects: the FDA perspective. Testing for abuse liability of drugs in humans.* Bethesda, Md: National Institute on Drug Abuse; 1989 NIDA Research Monograph 92:7–20. Available at: http://www.drugabuse.gov/pdf/monographs/download92.html
34. Warot D, Corruble E, Payan C, Weil JS, Puech AJ. Subjective effects of modafinil, a new centeral adrenergic stimulant in healthy volunteers: a comparison with amphetamine, caffeine, and placebo. *Eur Psychiatry* 1993; 8:201–208.
35. Jasinski DR. *Distinguishing modafinil from methylphenidate in a study of abuse potential: gender comparison.* Presented at the Annual Meeting of the College on Problems of Drug Dependence, June 14–19, 1997, Nashville, TN.
36. Jasinski DR, Kovacevic-Ristanovi ĆR. Evaluation of the abuse liability of modafinil and other drugs for excessive daytime sleepiness associated with narcolepsy. *Clinical Neuropharmacology* 2000; 23(3): 149–156.
37. Rush CR, Kelly TH, Hays LR, Baker RW, Wooten AF. Acute behavioral and physiological effects of modafinil in drug abusers. *Behavioural Pharmacology* 2002; 13(2): 105–115.
38. Rush CR, Kelly TH, Hays LR, Wooten AF. Discriminative-stimulus effects of modafinil in cocaine-trained humans. *Drug and Alcohol Dependence* 2002; 67: 311–322.
39. Dackis CA, Lynch KG, Yu E, et al. Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. *Drug Alcohol Depend* 2003; 70(1):29–37.
40. Westensten NJ, Belenky G, Kautz MA, Thorne DR, Reichardt RM, Balkin TJ. Maintaining alertness and performance during sleep deprivation: modafinil versus caffeine. *Psychopharmacology* 2002; 159:238–247.
41. Malcolm R, Devane L, Donovan J, et al. Modafinil dampens multiple aspects of intravenous cocaine high. Unpublished. Presented June 15, 2003; College of Problems of Drug Dependence, Bal Harbour, FL.
42. Jasinski DR. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. *Journal of Psychopharmacology* 2000; 14(1):53–60.
43. Galloway G. Personal Communication. June 15, 2003.
44. Malcolm R, Book S, Moak D, DeVane L, Czepowicz V. Clinical applications of modafinil in stimulant abusers: low abuse potential. *Am J Addictions* 2002; 11:247–249.