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# Smoked Cocaine Self-Administration is Decreased by Modafinil

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Modafinil has been reported to reduce cocaine use in a clinical sample of infrequent users (2 days/week), but the effects of modafinil on cocaine self-administration in the laboratory have not been studied. The present study investigated the effects of modafinil maintenance on cocaine self-administration by frequent users (4 days/week) under controlled laboratory conditions. During this 48-day double-blind, crossover design study, the effects of modafinil maintenance (0, 200, and 400 mg/day) on response to smoked cocaine (0, 12, 25, and 50 mg) were examined in nontreatment-seeking cocaine-dependent individuals ($n = 8$). Cocaine significantly increased self-administration, subjective-effect ratings, and cardiovascular measures; modafinil at both doses (200 and 400 mg/day) markedly attenuated these effects. These findings agree with data from previous human laboratory and clinical investigations of modafinil as a potential cocaine abuse treatment medication. Thus, our data support the potential of modafinil as a pharmacotherapy for cocaine dependence.
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## INTRODUCTION

In the United States, each year greater than one quarter of the 2.4 million current cocaine users seek treatment for cocaine-related problems (SAMHSA, 2006). Despite the fact that the number of cocaine treatment seekers is similar to the number of individuals seeking treatment for heroin dependence (for which there are several approved pharmacotherapeutic options), currently there is no approved cocaine abuse pharmacotherapy. For at least two decades, intense research efforts have focused on elucidating the underlying neuronal mechanisms of cocaine-related effects in an effort to identify targets for potential pharmacotherapies. Much of these efforts have concentrated on influencing the activity of midbrain dopaminergic neurons, with disappointing results (for review, see Hart and Lynch, 2005). Because cocaine exerts multiple central nervous system (CNS) effects, including transporter blockade of several monoamine transmitters, some have suggested that the low success rate is not surprising given the relatively narrow and oversimplified previous focus (eg Bardo, 1998; Hart and Lynch, 2005).

Modafinil, approved to promote wakefulness in patients with excessive daytime sleepiness, has received recent research attention as a potential cocaine abuse treatment medication. While the neurochemical mechanisms underlying modafinil's therapeutic actions remain unresolved, the drug has been demonstrated to occupy both the dopamine and norepinephrine transporter at clinically relevant doses (Mignot *et al*, 1994; Madras *et al*, 2006). Its affinity for the norepinephrine transporter, however, is approximately 50% lower than it is for the dopamine transporter (Madras *et al*, 2006). A prominent hypothesis regarding the neurochemical basis of modafinil-associated therapeutic actions proposes that they are due to the drug's ability to increase dopaminergic activity, which stimulates adrenergic receptors in the prefrontal cortex (Wisor and Eriksson, 2005). This perspective is supported by data showing that the wake-promoting effects of the drug are blocked by $\alpha_1$ antagonists (eg Duteil *et al*, 1990; Lin *et al*, 1992) but are unaltered by dopamine antagonists (Lin *et al*, 1992) or lesions of the noradrenergic projections from the locus coeruleus to the forebrain (Wisor and Eriksson, 2005). Alternatively, others have suggested that modafinil-associated therapeutic effects are due to its ability to enhance glutamate release and inhibit $\gamma$-aminobutyric acid (GABA) release (Ferraro *et al*, 1997a, b, 1999). Despite the lack of consensus regarding modafinil's precise mechanism of action, it is clear that many of its neurochemical actions overlap with those of cocaine. This overlap might provide clues about the mechanism(s) mediating the recent report of positive outcome when modafinil was tested as a potential treatment for cocaine abuse (Dackis *et al*, 2005).

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Based on encouraging results from their laboratory investigation of modafinil as a potential cocaine abuse treatment medication, Dackis *et al* (2005) conducted a larger, follow-up clinical trial in which cocaine use, as measured by urine toxicology, was the primary outcome measure. During this 8-week study, cocaine-dependent participants were randomized to receive either placebo or 400 mg/day modafinil. Modafinil significantly reduced the number of cocaine-positive urine samples obtained compared with placebo. While this finding is encouraging, it should be interpreted within the confines of a few important potential limitations. For example, relative to participants in the control group, individuals in the modafinil group reported using cocaine on fewer days (3 *vs* 2) and had more negative cocaine urine samples at baseline ($\sim$20 *vs* $\sim$40%). Together, these factors potentially influenced the study outcome.

Nevertheless, findings from two laboratory studies of human cocaine abusers also support the utility of modafinil as a treatment medication for cocaine abuse (Dackis *et al*, 2003; Malcolm *et al*, 2006). The first report was a within-subjects laboratory investigation, during which seven cocaine-dependent individuals were maintained on modafinil (placebo, 200, and 400 mg/day) for 4 days before receiving open-label cocaine (30 mg) i.v. (Dackis *et al*, 2003). Physiological and subjective measures were assessed repeatedly after cocaine administration. Both active modafinil doses markedly reduced cocaine-related ratings on the Addiction Research Center Inventory Amphetamine scale, which was interpreted as a blunting of cocaine-induced euphoria. Malcolm *et al* (2006) replicated this finding and also reported that modafinil attenuated cocaine-induced heart rate (HR) and systolic blood pressure elevations.

It is important to note, however, that previous laboratory investigations of potential cocaine abuse treatment medications have shown reductions in cocaine-related subjective effects without corresponding decreases in cocaine self-administration. For example, data from this laboratory demonstrated that gabapentin, a nonselective GABA agonist, significantly attenuated cocaine-induced euphoria, but did not alter cocaine self-administration (Hart *et al*, 2004). This finding is consistent with results from subsequent laboratory studies and an outpatient, double-blind clinical trial evaluating gabapentin for utility in treating cocaine dependence (Hart *et al*, 2007a, b; Bisaga *et al*, 2006). These observations emphasize the potential utility of assessing a measure of cocaine-taking behavior when evaluating potential pharmacotherapies for cocaine dependence. In this way, the likelihood of obtaining false-positive results is substantially reduced.

Given the above considerations and the increasing interest in modafinil as a potential cocaine abuse pharmacotherapy (Vocci and Ling, 2005; Sofuoglu and Kosten, 2006), we felt further study of this medication for cocaine dependence was warranted. Thus, the present 48-day inpatient/outpatient study examined the effects of oral modafinil maintenance (0, 200, 400 mg/day) on smoked cocaine self-administration in a group of nontreatment-seeking cocaine-dependent volunteers, who reported using cocaine, on average, 4 days weekly. Cocaine-associated cardiovascular and subjective effects were also assessed during modafinil treatment. We hypothesized that cocaine self-administration and subjective effects would be decreased as a function of modafinil maintenance condition. Although we assumed the cocaine–modafinil combination would be well tolerated, no prediction was made regarding the impact of modafinil maintenance on cocaine-induced cardiovascular effects because inconsistent results had been previously reported, that is, Dackis *et al* (2003) reported modafinil produced no significant effects, whereas Malcolm *et al* (2006) reported the drug decreased some cocaine-evoked cardiovascular effects.

## METHODS

### Participants

Eight black research volunteers (seven males, one female) with a mean age of $38.5 \pm 2.8$ ($\pm$SD) completed this study. They were solicited via word-of-mouth referral and newspaper advertisements in New York City, and each signed a consent form that was approved by the Institutional Review Board of The New York State Psychiatric Institute. Before study enrollment, participants passed comprehensive medical and psychiatric evaluations (including a Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders (DSM-IV SCID)) and were within normal weight ranges according to the 1983 Metropolitan Life Insurance Company height/weight table (body mass index, $24.3 \pm 1.5$). All met DSM-IV criteria for current smoked cocaine dependence and stated they were not seeking treatment for cocaine dependence at the time of study participation. No participant met criteria for any other axis I disorder. They reported currently using cocaine $4.1 \pm 1.6$ (mean $\pm$ SD) days per week and spending $\$275 \pm 109$ (mean $\pm$ SD) per week on the drug (the current cost of street cocaine in the New York City area is \$25–40 per gram). On average, participants reported using cocaine for $19.8 \pm 6.6$ (mean $\pm$ SD) years. Five participants reported current alcohol use (0.5–18 drinks per week), five reported current marijuana use (1–5 times per week), and five smoked 5–30 tobacco cigarettes per day. Other reported drug use was infrequent. Urine toxicology analyses during the screening process showed that all participants tested positive for the cocaine metabolite and two tested for the marijuana metabolite. The participants had completed $11.75 \pm 1.9$ (mean $\pm$ SD) years of education.

Five additional male participants (four black, one Hispanic) began, but did not complete the protocol; one had an abnormal electrocardiogram before receiving cocaine (this participant was receiving placebo modafinil), one was arrested during the outpatient portion of the study, one developed a rash while being maintained on placebo modafinil, one failed to meet his admissions appointment, and one left the study for personal reasons. Thus, no early dropouts were specifically due to side effects from modafinil.

### Design and Procedures

During this within-subjects, alternating in-patient/outpatient 48-day study, participants were maintained on modafinil (placebo, 200, and 400 mg/day) and four doses of smoked cocaine (0, 12, 25, and 50 mg). They were each

tested twice under each modafinil condition (Table 1). The first participant completed almost the entire study (43 days) on an in-patient basis to evaluate the effects of modafinil in combination with cocaine before providing other participants with modafinil on an outpatient basis. The remaining participants were maintained as in-patients and outpatients alternately over 48 days (for a total of 23 in-patient days per participant). All cocaine self-administration testing occurred during in-patient days. Initially, participants were admitted to the Irving Center for Clinical Research (New York Presbyterian Hospital) for 3 days and modafinil maintenance (placebo, 200, or 400 mg) was initiated. Modafinil was administered in a double-blind fashion throughout the study, but, for safety reasons, the 200-mg condition always preceded the 400-mg condition. Four participants received placebo first, and the other four received modafinil first. Subsequently, the modafinil maintenance dose was continued on an outpatient basis for 4 days. Then, participants were in-patient for 8 days; during 4 of those days, smoked cocaine-related effects (0, 12, 25 and 50 mg) were assessed in the presence of the modafinil maintenance dose. Each cocaine dose was tested twice per maintenance condition (see Table 1). The in-patient days following cocaine testing were used for crossover to another modafinil condition. Subsequently, the modafinil maintenance dose was continued on an outpatient basis for 6 days and then, the 8-day in-patient phase was repeated. After crossing over to a different maintenance condition, participants were maintained on an outpatient basis for 6 days, followed by the final 8-day in-patient phase. The final 5 days of the study were used to taper off modafinil.

During the outpatient phases of this study, participants came to the laboratory every 2–3 days, during which time they (1) were assessed for the emergence of side effects, (2) received study medication, and (3) gave an observed urine sample, which was examined for the presence of the riboflavin marker and drugs of abuse. Modafinil and placebo capsules were filled with powdered riboflavin (fluoresces when urine is exposed to ultraviolet light) to monitor compliance with the dosing regimen. Blood was drawn to measure plasma modafinil levels once during each outpatient period. Participants were given $15 in cash at each outpatient visit, and received $15 in merchandise vouchers for each riboflavin-positive urine sample. Merchandise vouchers were redeemable at local stores.

**Table 1** Experimental Timeline

| Study day | Location | Phase |
|---|---|---|
| 1–3 | In-patient | Initial placebo/modafinil dosing |
| 4–7 | Outpatient | Placebo/modafinil maintenance |
| 8–10 | In-patient | Maintenance |
| 11–12 | In-patient | First cocaine dose–response |
| 14–15 | In-patient | Second cocaine dose–response |
| 15 | In-patient | Medication crossover |
| 16–21 | Outpatient | Placebo/modafinil maintenance |
| 22–24 | In-patient | Maintenance |
| 25–26 | In-patient | First cocaine dose–response |
| 28–29 | In-patient | Second cocaine dose–response |
| 29 | In-patient | Medication crossover |
| 30–35 | Outpatient | Placebo/modafinil maintenance |
| 36–38 | In-patient | Maintenance |
| 39–40 | In-patient | First cocaine dose–response |
| 42–43 | In-patient | Second cocaine dose–response |
| 44–48 | Outpatient | Taper off medication |

## Apparatus

During sessions, each participant sat in a reclining lounge chair facing a computer monitor, which displayed subjective-effects questionnaires. A response manipulandum ('mouse') was used for completion of subjective-effects questionnaires. For blood withdrawal, an 18-gauge catheter (Quik-Cath®, Travenol Laboratories, Deerfield, IL) was inserted in a subcutaneous arm vein. The i.v. line was kept patent by a physiological saline solution drip at a rate of 2 cc/min. The electrocardiogram was continuously monitored via chest electrodes (Tektronix 413 Monitor®, Beaverton, OR; MAC PC®, Marquette Electronics, Milwaukee, WI), while HR and blood pressure (systolic, SP; diastolic, DP) were recorded every 2 min (Sentry II, Model 6100 automated vital signs monitor, NBS Medical, Costa Mesa, CA) beginning 20 min before drug administration. An Apple Macintosh computer located in an adjacent room was used for automated data collection.

## Procedure

While in-patient, participants had access to television, radio, telephone, videotaped movies, and tobacco cigarettes when not participating in a session. They could not leave the unit unescorted by research staff and could not receive visitors.

Each participant completed a total of 24, 2.5-h weekday laboratory sessions; two sessions were conducted per day on study days 11, 12, 14, 15, 25, 26, 28, 29, 39, 40, 42, and 43. During sessions, research nurses located in the adjacent room continuously observed participants through a one-way mirror, and communication was possible via an intercom system. Sessions occurred under all three modafinil conditions (placebo, 200, and 400 mg/day).

Sessions started at approximately 0900 and 1300, and began with a 30-min baseline measurement of cardiovascular activity and mood. At the start of each session, participants were provided with $25 from their study earnings (five $5 bills, one for each choice opportunity). Then, they were allowed to smoke the 'sample' dose of cocaine base (0, 12, 25, and 50 mg) available that session. Cocaine smoking was accomplished by placing a metered dose of cocaine base in an 8 cm glass tubing, or 'stem,' packed with fine metal mesh; participants held the glass stem while the research nurse applied the flame from a lighter until the individual had finished inhaling the volatized cocaine. Participants were blindfolded during inhalation to decrease potential expectancy effects. Following the sample dose, participants were given five opportunities, at 14-min intervals, to purchase the same amount of cocaine as in the sample dose or to keep $5 for that choice opportunity. A cocaine dose was not given on any trial in which cardiovascular activity was above our criteria for safe

drug administration. Cardiovascular criteria for withholding a dose were as follows: (1) SP > 160 mm Hg, sustained for longer than 6 min (ie > 3 consecutive readings); or (2) DP > 100 mm Hg, sustained for longer than 6 min (ie > 3 consecutive readings); or (3) HR > 220, participant's age × 0.85 b.p.m., sustained for 6 min (ie three consecutive readings). Under each modafinil maintenance condition, the four available cocaine doses (0, 12, 25, and 50 mg) were tested in four self-administration sessions (morning and afternoon) over 2 days, and then the procedure was repeated on 2 of the following 3 days. Thus, each cocaine dose was tested twice under each modafinil maintenance condition, with dosing order systematically varied.

### Subjective-Effects Questionnaire

A subjective-effects questionnaire was completed at baseline, 4 min following delivery of the selected option (cocaine or $5) and 30 min following the last selected option of the session. The questionnaire consisted of a series of 10-cm visual analog scales (VAS). To reduce the number of dependent variables, cluster analysis was accomplished as previously described (Evans *et al*, 2002; Foltin and Haney, 2004), and each cluster score was derived by taking the arithmetic average of the items in the cluster. Five clusters were produced from 20 VAS items: (1) Bad Drug Effects consisted of seven items: 'anxious,' 'bad drug effect,' 'confused,' 'depressed,' 'irritable,' 'sedated,' and 'tired'; (2) Self-Esteem consisted of five items: 'alert,' 'friendly,' 'self-confident,' 'social,' and 'talkative'; (3) Calm consisted of two items: 'calm,' and 'able to concentrate'; (4) Good Drug Effect consisted of three items: 'good drug effect,' 'high,' and 'stimulated'; and (5) Drug Quality consisted of three items: 'the choice was of high quality,' 'the choice was potent,' and 'I liked the choice.' Three VAS items were used to operationalize drug craving: 'I want cocaine,' 'I want alcohol,' and 'I want nicotine.' A final question asked individuals 'How much would you pay for the dose you just received?' with a scale range of $0–25.

### Plasma Analysis

Blood samples for the analysis of cocaine levels were drawn three times during each laboratory session: (1) before cocaine administration, (2) 4 min after the first cocaine dose, and (3) 4 min after receipt of the last selected (cocaine or money). All blood samples were analyzed for cocaine and cocaine metabolites (Isenschmid *et al*, 1992). In addition, blood samples were drawn for modafinil levels twice per inpatient week. To monitor compliance with outpatient medication regimens, modafinil levels were also assessed in weekly blood samples drawn during the outpatient phases of the study. Laboratory analyses were carried out by the Analytical Toxicology Laboratory at New York State Psychiatric Institute.

### Cocaine and Study Medication

Cocaine free-base was prepared by the New York State Psychiatric Institute Pharmacy (Foltin *et al*, 1990). Modafinil (100 mg) tablets were packaged into size #00 opaque capsules with riboflavin filler by the New York State Psychiatric Institute Pharmacy. Identical placebo capsules contained only lactose and riboflavin filler. During the inpatient phases, modafinil was administered as two identical capsules at 0700 and 1900 each day on the research unit. During outpatient phases, participants were instructed to follow the same dosing regimen.

### Data Analysis

Repeated measures analyses of variance with cocaine dose (0, 12, 25, and 50 mg), modafinil maintenance condition (placebo, 200, and 400 mg/day) and replication (first and second under each maintenance condition) as within-subjects factors were conducted to examine differences in mean cocaine choice selection and peak values for subjective and cardiovascular effects. Planned contrasts were calculated comparing results from placebo maintenance to the results obtained under active modafinil maintenance for each cocaine dose. The planned contrasts were single-degree-of-freedom comparisons that used the error term for the medication × cocaine dose interaction. Active or placebo cocaine was administered on 440 dosing occasions. When the cocaine dose was withheld, participants still completed the subjective-effects ratings and cardiovascular monitoring continued, and the data obtained, even though cocaine was not administered, were used in the analyses. In addition, because modafinil maintenance order was not entirely random, maintenance order was analyzed as a covariant; no significant effects of order were detected for any of the dependent variables. Data were considered statistically significant at $p < 0.05$, using Huynh–Feldt corrections where appropriate.

## RESULTS

Active or placebo cocaine was purchased 446 times, with only six doses not given because of elevated cardiovascular measures. All six doses were withheld under the placebo modafinil maintenance condition. Doses were more likely to be withheld when the higher cocaine doses were available: one withheld when 12 mg was available, two withheld when 25 mg was available, and three withheld when 50 mg was available.

### Self-Administration

Figure 1 (left panel) shows the number of purchased cocaine doses as a function of cocaine dose and modafinil maintenance condition. Active cocaine was purchased significantly more than placebo cocaine ($F(3,42) = 15.62$, $p < 0.001$), participants purchased about 2, 4, and 4.5 doses when the 12-, 25-, and 50-mg dose was available, respectively. Relative to placebo, both active modafinil maintenance conditions significantly decreased cocaine purchases of the two larger doses (25 and 50 mg, $p < 0.03$ for both maintenance conditions).

### Subjective Effects

Cocaine produced dose-dependent increases in ratings on the Good Drug Effect cluster $F_{(3,42)} = 19.85$, $p < 0.001$; the Drug Quality cluster (Figure 2, left panel), $F_{(3,42)} = 16.43$, $p < 0.001$; and how much participants were willing to pay for

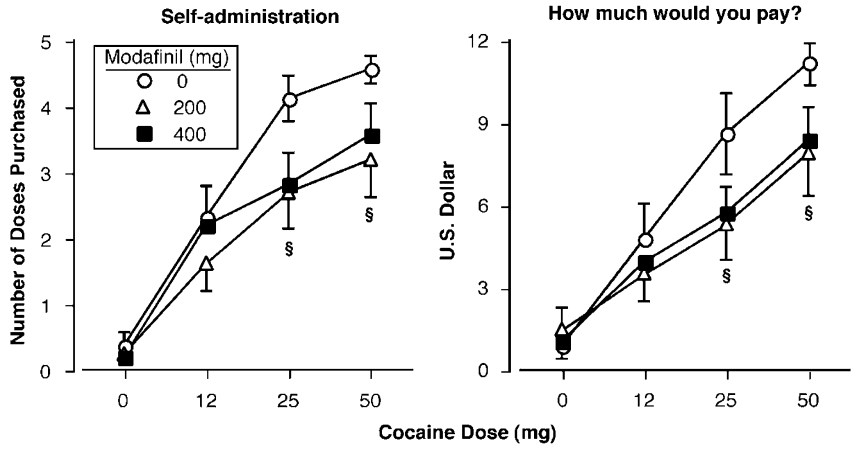


**Figure 1** Left panel: mean number of cocaine doses purchased as a function of cocaine dose and modafinil maintenance condition. Right panel: peak values for VAS ratings for estimates of monetary value of the cocaine dose as a function of cocaine dose and modafinil maintenance condition. A § indicates a significant difference between both active maintenance conditions and the placebo maintenance condition ($p<0.05$). Error bars represent one SEM. Overlapping error bars were omitted for clarity.

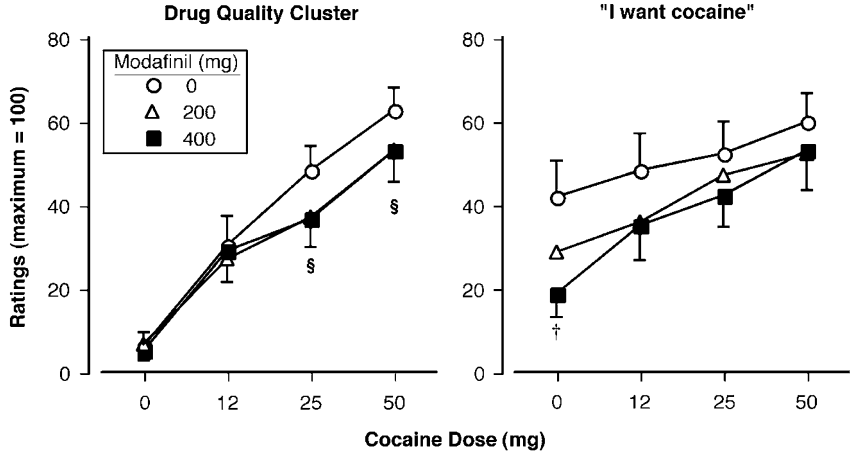


**Figure 2** Peak values for VAS ratings on the 'Drug Quality' cluster and 'I want cocaine,' as a function of cocaine dose and modafinil maintenance condition. A § indicates a significant difference between both active maintenance conditions and the placebo maintenance condition ($p<0.05$). A † indicates a significant difference between the 400 mg/day maintenance condition and the placebo maintenance condition ($p<0.05$). Error bars represent one SEM. Overlapping error bars were omitted for clarity.

the dose (Figure 1, right panel), $F_{(3,42)}=8.64$, $p<0.002$. Some subjective effects of cocaine were significantly altered by modafinil maintenance. Similar to the self-administration data, modafinil (200 and 400 mg) decreased the amount participants were willing to pay and ratings on the Drug Quality cluster following the 25- and 50-mg doses ($p<0.05$). On average, modafinil decreased the amount participants were willing to pay for the larger cocaine doses by approximately $3 (US). In addition, cocaine craving (operationalized using an 'I want cocaine' VAS item) was significantly decreased by 400 mg modafinil following the 0-mg cocaine dose ($p<0.006$, Figure 2, right panel).

## Cardiovascular Effects

Figure 3 shows cardiovascular measures as a function of cocaine dose and modafinil maintenance condition. Cocaine dose dependently increased peak HR ($F_{(3,42)}=42.16$, $p<0.001$), SP ($F_{(3,42)}=37.16$, $p<0.001$), and DP ($F_{(3,42)}=12.71$, $p<0.001$). In general, modafinil significantly attenuated these cardiovascular elevations. Both active maintenance doses significantly decreased HR, SP, and DP following both larger cocaine doses (25 and 50 mg, $p<0.01$), with one exception. Modafinil did not significantly attenuate DP produced by the 50-mg cocaine dose.

## Plasma Cocaine Levels

Out of the 576 total possible blood samples during the in-patient portions of the study, 45 (8%) were not completed due difficulties in accessing the participants' veins. Plasma cocaine levels were dose dependent and not affected by modafinil maintenance condition (data not shown).

## Plasma Modafinil Levels and Urine Fluorescence

Blood samples for the measurement of plasma modafinil levels were drawn twice weekly during in-patient phases and

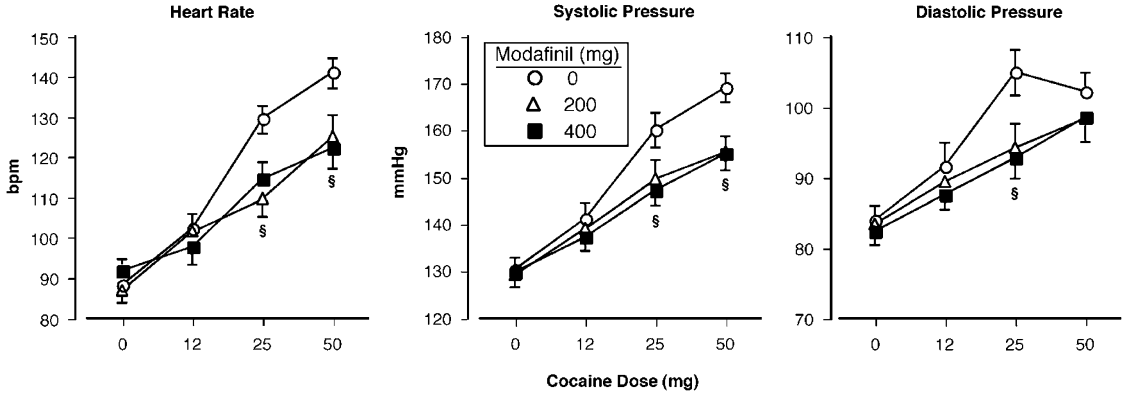


**Figure 3** Peak values for heart rate, systolic pressure, and diastolic pressure as a function of cocaine dose and modafinil maintenance condition. A § indicates a significant difference between both active maintenance conditions and the placebo maintenance condition ($p < 0.05$). Error bars represent one SEM. Overlapping error bars were omitted for clarity.

once per each outpatient week. Mean ± SD modafinil levels were as follows: 2.17 ± 0.76 μg/ml (200 mg outpatient), 3.83 ± 1.59 μg/ml (200 mg in-patient), 6.20 ± 2.25 μg/ml (400 mg outpatient), and 7.53 ± 2.44 μg/ml (400 mg in-patient). As expected, modafinil plasma levels were greater during the in-patient phases because the outpatient phases were used to crossover to another maintenance dose condition. All urine samples collected during outpatient phases were positive for riboflavin, as verified by ultraviolet fluorescence, suggesting good medication compliance.

### Cocaine-Positive Urines During Outpatient Phase

Attendance at the outpatient visits was excellent: 41 of 42 scheduled visits were attended. There was no effect of modafinil on the number of urines that tested positive for cocaine in this group of nontreatment seekers, as 37 of 41 urines were positive for cocaine. Also, 6 of 41 urine samples tested positive for the marijuana metabolite $\Delta^9$-tetrahydrocannabinol.

## DISCUSSION

The major finding from the present investigation was that modafinil (200 and 400 mg/day) decreased cocaine self-administration in a sample of nontreatment-seeking cocaine-dependent individuals. These are the first human laboratory data demonstrating that cocaine self-administration is markedly reduced during modafinil maintenance. The significance of this result is underscored by data from previous studies demonstrating that cocaine-taking behavior in this population is robust and extremely difficult to alter, even when 'positive' subjective responses to cocaine are decreased by a potential treatment medication (Haney *et al*, 1999; Foltin *et al*, 2003; Hart *et al*, 2004). The current data also show that cocaine-associated subjective-effect ratings and cardiovascular responses were significantly reduced when participants were maintained on modafinil. Modafinil doses produced equipotent effects on all measures. These results replicate and extend findings from human laboratory studies (Dackis *et al*, 2003; Malcolm *et al*, 2006) and are consistent with results from a clinical trial (Dackis *et al*, 2005) investigating cocaine use during modafinil treatment.

While the mechanism(s) mediating modafinil-related effects on cocaine self-administration is unknown, pharmacokinetic interactions between modafinil and cocaine can be excluded because plasma cocaine levels in the current study were unaffected by modafinil maintenance condition. Modafinil modulates the activity of CNS catecholamine transporters, which are established sites through which many of cocaine-related effects are mediated, so it is possible that this feature played a role in altering cocaine self-administration. Consistent with such a mechanism, modafinil is well absorbed after oral administration and has a terminal elimination half-life of approximately 12–15 h (Wong *et al*, 1999), whereas the half-life for cocaine is only about 1 h. In addition, modafinil inhibits the firing of midbrain dopamine neurons, possibly through $D_2$ autoreceptors (Korotkova *et al*, 2007). Thus, in the current study, it is conceivable that modafinil dampened the ability of the sampled dose of cocaine to acutely increase catecholamine transmission, and thereby reduced the perceived potency and subsequent choice to self-administer the drug. Other agonist mechanisms are also plausible as modafinil, like cocaine, increases glutamatergic activity and diminishes GABAergic transmission (Ferraro *et al*, 1997a, b, 1999; Cameron and Williams, 1994; Reid *et al*, 1997), and a combination of these neurochemical actions may have contributed to our findings. Such explanations are speculative, of course, and suggest avenues for future studies.

Modafinil attenuated several subjective effects of cocaine (eg cocaine craving and the amount participants were willing to pay for the dose sampled) and this is in line with results from previous laboratory studies that have assessed subjective response to cocaine in the presence of modafinil (Dackis *et al*, 2003; Malcolm *et al*, 2006). Note, however, that a decrease in the subjective effects of cocaine alone appears insufficient to account for the reduction in the number of cocaine doses purchased during modafinil maintenance. Data from a number of studies evaluating medications for the treatment of cocaine abuse show that cocaine-related positive subjective and reinforcing effects (self-administration) are dissociable (eg Foltin *et al*, 2003; Hart *et al*, 2004). Haney *et al* (1999), for example, reported

that ABT-431, a selective agonist at the dopamine $D_1$ receptor, produced significant dose-dependent decreases in the subjective effects of cocaine, including ratings of 'high,' 'stimulated,' dose liking, estimates of dose value, 'quality,' and 'potency,' but it did not reduce cocaine self-administration. Fischman *et al* (1990) found a similar pattern of effects when they investigated the impact of desipramine maintenance on i.v. cocaine self-administration; these results were congruent with negative findings from follow-up clinical trials testing desipramine for efficacy as a pharmacotherapy for cocaine abuse. Several researchers reported that the medication did not decrease cocaine use, as measured by urine toxicology (Arndt *et al*, 1994; Campbell *et al*, 2003; McDowell *et al*, 2005). Indeed, this is consistent with the broader literature evaluating medications for utility in treating cocaine abuse. A number of medications examined have been shown to decrease the subjective effects of cocaine when tested under controlled laboratory conditions, but the decrease in subjective effects has failed to predict clinical utility (eg gabapentin; Hart *et al*, 2004; Bisaga *et al*, 2006). In contrast, the present results argue that clinical efficacy might be best predicted by a decrease in subjective effects *and* cocaine self-administration in the laboratory.

Modafinil has a relatively benign side-effect profile and no clinically significant drug interactions (Wong *et al*, 1998; Hellriegel *et al*, 2001). Data from the current investigation are consistent with previous findings. The modafinil–cocaine combination was well tolerated and did not produce additive cardiovascular effects. In fact, modafinil markedly attenuated cocaine-associated blood pressure and HR increases with the most pronounced effects being observed on HR and SP. Increases in HR and SP produced by the larger cocaine doses (25 and 50 mg) were significantly lessened by both maintenance modafinil doses. The pattern of effects obtained in this study is in agreement with findings from a recent investigation of cardiovascular and subjective responses to i.v. cocaine during modafinil maintenance. Malcolm *et al* (2006) reported that not only did modafinil decrease subjective effects of cocaine, but the drug also reduced cocaine-evoked increases in SP and HRs. Together, these data indicate that the drug combination does not increase cardiovascular toxicity and may offer protection to some of the cardiovascular effects of cocaine.

The present results should be interpreted within the context of at least two potential study limitations. All study participants were black and the overwhelming majority were males. While black cocaine abusers comprise about 50% of the individuals seeking treatment for smoked cocaine-related problems, a substantial proportion ($\sim$50%) of smoked cocaine treatment-seekers are nonblack (SAMHSA, 2006). Similarly, female cocaine abusers represent about 40% of persons enrolled in treatment for smoked cocaine abuse. While it is possible that the characteristics of our sample may limit the generality of our findings, this seems unlikely because there is a dearth of data indicating that there are racial or sex differences in response to potential pharmacotherapies for cocaine abuse (but see, Evans and Foltin, 2006).

In conclusion, the current findings indicate that modafinil maintenance reduced cocaine-associated reinforcing, subjective, and cardiovascular effects without producing noticeable adverse consequences. The current overall pattern of effects is consistent with a developing body of research obtained in human cocaine abusers under both laboratory and clinical conditions. The data suggest that modafinil may have clinical utility as a treatment for cocaine dependence, although further study of the drug is needed to better understand the mechanism(s) underlying its therapeutic effects.

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## DISCLOSURE/CONFLICT OF INTERESTS

The authors declare that except for income received from my primary employer no financial support or compensation has been received from any individual or corporate entity over the past 3 years for research or professional service and there are no personal financial holdings that could be perceived as constituting a potential conflict of interests.

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