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Modafinil Decreases Cocaine Choice In Human Cocaine Smokers Only When The Response Requirement And The Alternative Reinforcer Magnitude Are Large

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Abstract

This study examined how response effort (pressing a keyboard button) for cocaine and the value of an alternative reinforcer (opportunity to play a game of chance for money) combined with 'free' cocaine (with no response effort) affected cocaine choice when participants were maintained on modafinil or placebo. Nontreatment-seeking current cocaine smokers were enrolled in a placebo-controlled, double-blind, within-subject study comprising both inpatient and outpatient phases. Participants were maintained on placebo capsules (0 mg/day) during one inpatient phase and modafinil (300 mg/day) capsules during another inpatient phase in counter-balanced order. A minimum of 8 medication-free days separated the two 15-day inpatient phases to allow for medication clearance. Under each medication condition participants had the opportunity to self-administer smoked cocaine (25 mg) when the response effort for cocaine was low (500 responses/dose) and had a low value alternative (2 game plays for money) or when the response effort for cocaine was large (2500 responses/dose) and had a more valuable alternative (4 game plays for money). Under both conditions, participants received one free dose of cocaine (0, 12, 25 or 50 mg) prior to making their first choice of the session. Fifteen individuals began the study and 7 completed it. Participants chose fewer cocaine doses when the response effort for cocaine and the alternative value was high (4.4 ± 0.19) compared to when the response effort for cocaine and the alternative value was low (5.3 ± 0.14). Providing individuals a free "priming" dose of cocaine prior to making their cocaine choice did not alter cocaine taking. Modafinil decreased cocaine choice only when the response effort for cocaine and the alternative value was high. These results suggest that modafinil may be most effective when combined with therapy emphasizing the large personal costs of using cocaine.

Keywords

Cocaine; Self-administration; Modafinil; Drug Choice; Human

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1. Introduction

Behavioral pharmacology studies involving administration of drugs of abuse to naïve and experienced drug users are a powerful tool for providing data both on the abuse liability of novel compounds and on the development of medications to treat substance use disorders (e.g., Comer et al., 2008, Haney & Spealman, 2008). Screening new stimulant medications for abuse liability is readily accomplished by conducting controlled laboratory studies to compare the behavioral effects of a novel compound to a stimulant with known abuse liability: the greater the similarity in effects between the two compounds the greater expected abuse liability of the novel compound. Screening new medications to treat stimulant use disorders has proven more difficult because a parallel approach of comparing a novel medication to an established medication cannot be accomplished due to the absence of an FDA-approved treatment medication for cocaine and other stimulant use disorders (Comer et al., 2008, Haney & Spealman, 2008).

Human laboratory studies from the 2000's suggested that modafinil had potential to be a new pharmacological approach for treating cocaine use disorders. For example, Dackis et al. (2003) reported that in the laboratory modafinil (200 mg/d) attenuated one measure of positive subjective effects [A (amphetamine) score on the Addiction Research Center Inventory (ARCI)] of intravenous cocaine without affecting other more commonly used measures of positive affect including ratings of High and Good Drug Effect. Hart et al. (2008) reported that modafinil (200, 400 mg/d) attenuated ratings of drug quality and estimates of street value, but also did not affect ratings of High and Good Drug Effect. However, both modafinil doses similarly and significantly decreased self-administration of smoked cocaine (Hart et al., 2008). More recently, Verrico et al. (2014) reported that modafinil (200 mg/d) did decrease the positive subjective effects of intravenous cocaine (e.g., ratings of High and Good Drug Effect), but did not affect cocaine self-administration. Although not identical in outcome, these controlled laboratory studies suggested that modafinil might be useful for the treatment of cocaine use disorders.

The enthusiasm for modafinil as a cocaine treatment was diminished when a large-scale clinical trial (Anderson et al., 2009) failed to show a positive signal for modafinil (200, 400 mg/d) for cocaine abuse. A post hoc analysis of the data suggested, however, that modafinil was effective in a subgroup of cocaine users who did not also abuse alcohol. Dackis et al. (2012) failed to find efficacy for modafinil (400 mg/d) for cocaine use disorders, yet there was the possibility that sex mediated the effect as males receiving modafinil tended ($p < 0.06$) to achieve greater abstinence than females. Schmitz et al. (2014) examined the effect of requiring abstinence to initiate a trial on medication effectiveness for cocaine use disorders and found that modafinil (400 mg/d) was no more effective than placebo in those who had achieved initial abstinence compared to those who had not. In contrast, Kampman et al. (2015) reported that modafinil (300 mg/d) significantly improved the odds of cocaine abstinence during the last 3 weeks of an 8-week clinical trial in cocaine users who did not meet DSM-IV criteria for alcohol dependence. Thus, studies testing the clinical utility of modafinil for cocaine use disorders have been mixed, not unlike the results in human laboratory studies of modafinil and cocaine.

Decreasing the variability in laboratory outcomes by using procedures that better model the clinical situation should increase predictive validity for clinical outcomes. Laboratory studies assessing self-administration of drugs of abuse commonly enroll individuals who are not currently seeking treatment for their drug use (e.g., Haney, 2009), and hence have no intrinsic motivation not to use cocaine, potentially making it difficult to alter cocaine self-administration with medication. In laboratory models testing the effects of possible medications to reduce cocaine self-administration, behavioral factors are often manipulated in nontreatment-seekers to better model the decisions a patient makes in a clinical situation (e.g., Donny et al., 2006; Stoops et al., 2012; Walsh et al., 2001). In the real world, cocaine users make decisions about using cocaine within a complex environment, including potential negative consequences to cocaine use and alternatives to cocaine use. In the laboratory, real world situations are often approximated by 1) having a cocaine user decide to self-administer cocaine or receive an alternative reinforcer; and/or 2) varying the financial cost or response effort needed to take cocaine (e.g., Foltin et al., 2015; Vosburg et al., 2010). In the present study our goal was to increase the sensitivity of the laboratory assay to the effects of modafinil by manipulating these variables.

While potential medications are generally evaluated for the ability to decrease the subjective and reinforcing effects of cocaine, another approach is to evaluate medications that may be helpful in improving decision-making and cognitive skills in order to decrease cocaine taking: modafinil is one such medication (Mereu et al., 2013). For example, modafinil has been hypothesized to improve decision making by improving (or ‘normalizing’) risk-taking behavior (Canavan et al., 2014), and improving attention and memory (Kalechstein et al., 2013) in cocaine users. To model decision-making we examined the effects of modafinil on cocaine choice under two conditions that differed in terms of the personal cost of selecting cocaine. The cost for cocaine was manipulated by having a small or large number of responses required to receive cocaine and by having a small or large monetary value alternative: Low Cost and Alternative – response requirement for cocaine was small and the alternative reinforcer (game plays to earn money) was small vs. High Cost and Alternative - response requirement for cocaine was large and the alternative reinforcer was large. Previous participants have reported that completing the large response requirement, which involved sustained bar pressing at high rates (4/s) for 10 min, was difficult. Thus the High Cost and Alternative condition contained aversive elements related to response effort as well as more opportunities to earn money. We hypothesized that increasing the response effort for cocaine while simultaneously increasing the value of the alternative reinforcer would increase the sensitivity of the procedure such that modafinil would decrease cocaine choice to a greater extent under the High Cost and Alternative condition, indicating an improvement in decision-making.

In addition, modafinil has been reported to attenuate cocaine cue reactivity in cocaine users (Goudriaan et al., 2013). Since individuals in treatment experience cocaine in their natural environment, in the present study we provided participants a dose of cocaine without a response cost at the beginning of each choice session prior to the self-administration period. We hypothesized that receiving a free single dose of cocaine, i.e., a “priming” dose that did not require any responding, would increase cocaine choice and would increase the sensitivity of the procedure such that modafinil would attenuate cocaine-induced drug taking. Because

the goal of the study was to determine if the effects of modafinil on cocaine choice varied as a function of experimental condition the effects of modafinil on choice of placebo cocaine were not examined.

2. Method

2.1. Participants

Fifteen research volunteers (12 Black, 2 White, 1 Hispanic; 13 men and 2 non-pregnant women) began this study. Participants were solicited via word-of-mouth referral and newspaper advertisements in New York City, and signed a consent form approved by the Institutional Review Board of The New York State Psychiatric Institute, which described the study, outlined the possible risks, and indicated that cocaine would be administered. Repeated queries were made to ensure that no potential participant was seeking or had recently been in drug treatment. 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; First et al., 1995). Participants met a minimal cocaine use criterion set in advance based on our prior experience with this non-treatment seeking population: each had smoked ‘crack’ cocaine at least 2 times per week for the past 6 months, and reported spending at least $70 per week on cocaine. From our experience, this quantitative use threshold is more pertinent than the DSM-IV diagnosis of cocaine dependence (or DSM-5 diagnosis of cocaine use disorder), as many of our nontreatment-seeking participants do not endorse the DSM criterion of experiencing “significant impairment or distress” as a result of their use. No participant met current criteria for any other Axis I disorder other than cocaine use disorders.

2.2. Design

Participants were admitted to the Irving Institute for Clinical and Translational Research in the Presbyterian Hospital for each of 2 15-day inpatient phases of the study. The inpatient phases were separated by a 1 to 3 week outpatient phase during which no study medications were administered. Participants came to the laboratory 2-3 times a week during the outpatient phases in order to keep them engaged in the protocol. Admissions occurred on a Thursday and the first laboratory sessions occurred on the following Monday, insuring a minimum of 3 cocaine-free days prior to testing. Placebo or active modafinil was also started on admission day so that there were 4 days of medication administration prior to the first laboratory session. While inpatient, participants were not permitted to leave the unit unless accompanied by a staff member and visitors were prohibited. Urine samples were collected daily for drug monitoring, with no indication of drug consumption aside from study-related dosing. Participants’ private rooms were equipped with a television, stereo, and DVD player to help alleviate boredom. Nicotine replacement was provided to tobacco smokers during their inpatient stays as nicotine polacrilex (Nicorette gum, 2 mg or 4 mg doses, one per hour on request; up to 5 times per day) in order to avert nicotine craving or withdrawal symptoms. No gum use was permitted during cocaine sessions.

The goal of the study was to determine if the effects of modafinil on cocaine choice varied as a function of 1) the response requirement for cocaine and value of the alternative

reinforcer while holding the strength of the cocaine dose constant and 2) the size of the cocaine dose given with no response requirement to the participants before each choice session. During each inpatient phase participants had the opportunity to smoke a 25 mg dose of cocaine or play a game of chance under both the Low Cost and Alternative and High Cost and Alternative conditions. The effects of modafinil on choice of placebo cocaine vs. playing the game of chance were not examined.

During each inpatient phase two Training sessions occurred on the first Monday and one Choice session occurred on the remaining weekdays for a total of 8 Choice sessions; each session lasted approximately 2 hr. One Training session occurred on Monday morning after breakfast and the second Training session occurred on Monday afternoon after lunch. Choice sessions occurred either in the morning or the afternoon with timing held consistent for each participant. Training Sessions: The purpose of the two Training sessions during each inpatient phase was to teach participants to associate the effects of the 25 mg smoked cocaine dose with the label of "Dose A." Separate Training sessions occurred under placebo and modafinil conditions to control for potential differences in response to cocaine as a consequence of modafinil administration. Participants were told that they needed to learn about Dose A because they would later be asked in Choice sessions if they wanted to receive Dose A under a range of experimental conditions. There was no operant requirement for cocaine during Training sessions, and there were no alternatives available. During Training sessions, participants smoked 7 doses of cocaine (25 mg) at 14-min intervals. Choice Sessions: In order to examine the effects of receiving a free dose of cocaine (cocaine plus smoking device) on choice during Choice sessions, the first dose of cocaine (0, 12, 25 or 50 mg) was administered with no response requirement (similar to no response requirement cocaine smoking during Training sessions). The initial free dose of cocaine was followed by 6 choice trials, at 14-min intervals. Each of the 4 free cocaine doses was tested under each of the 2 Cost conditions for a total of 8 choice sessions when participants were maintained on placebo or modafinil. Under the Low Response Cost and Alternative condition, the response cost for Dose A was 500 responses on the space bar and the alternative reinforcer was 2 opportunities to draw a bingo ball in the game of chance. Under the High Response Cost and Alternative condition the response cost for Dose A was 2500 responses on the space bar and the alternative reinforcer was 4 opportunities to draw a bingo ball in the game of chance. Under both alternative conditions there was no response effort associated with choosing to play the game of chance. Twenty balls of varying monetary value were placed in a bingo wheel each choice trial such that each choice provided an independent opportunity to earn money (i.e., balls were replaced). Each ball was assigned a monetary value from $0 (4 balls) to $20 (1 ball): with 2 game plays potential earnings ranged from $0 to $35 and with 4 game plays potential earnings ranged from $0 to $53 (Vosburg et al., 2010). Participants were told that part of their study pay for that day was determined by how often they chose to play the game of chance and how much they earned in that game. After the initial free dose, on each of the 6 choice trials participants were asked to choose either to take cocaine and complete the response requirement (space bar presses) or to draw the number of bingo balls available that session, with a chance to accumulate money.

2.3. Experimental Sessions

During the experimental sessions, the participants were seated in a reclining chair in front of a Macintosh computer and video monitor with a mouse manipulandum. A 22-gauge catheter (Quik-Cath, Travenol Laboratories, Deerfield, IL) was inserted in a subcutaneous vein of one arm to permit ready intravenous access if needed in an emergency during the cocaine sessions. Electrocardiograms (ECGs) were monitored continuously (MAC PC, Marquette Electronics, Milwaukee, WI), and heart rate (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 prior to cocaine administration. A Macintosh computer located in an adjacent control room was used for automated data collection. A physician and research nurses located in a control room, with communication via an intercom system, monitored participants via a one-way mirror.

During cocaine administration, participants were blindfolded and presented with cocaine base in a glass pipe ("stem") fitted with mesh smoke screens, and were instructed to take one large inhalation and to hold the vapor as long as they normally would outside of the laboratory. Vaporization of the cocaine base was accomplished by a nurse holding the flame from a pipe lighter beneath the cocaine base in the pipe. Cocaine or opportunities to play the game of chance were not given on any trial in which cardiovascular activity was above the criteria for safe drug administration [systolic pressure (SP) > 160 mmHg; diastolic pressure (DP) > 100 mmHg or a heart rate (HR) ≥ 220–subject age × 0.85, sustained for more than 6 min prior to the next scheduled dose administration]. Each session ended 30 min after the last possible cocaine delivery.

2.4. Subjective Effects Questionnaire

A computerized subjective effects battery displayed on the participant's monitor was completed at baseline 4 min prior to the first cocaine dose (on Training sessions) or "free" cocaine dose (on Choice sessions), 4 min after each cocaine dose or game play was delivered, and twice after the last possible cocaine or game play delivery of the session. The battery consisted of a series of 100 mm visual analog scales (VASs) anchored by "not at all" (0 mm) at one end and "extremely" (100 mm) at the other end. Participants registered their current subjective state by setting a cursor appropriately along the VAS displayed on their monitor. Because the subjective effects of cocaine have been well characterized (e.g., Evans et al., 2002; Foltin & Haney, 2004) we present here only items related to cocaine abuse liability: Ratings of "I want cocaine," "Good Drug Effect," "Cocaine Dose Liking," "Cocaine Dose Quality," and response to the question 'How much would you pay for the cocaine dose you just received?' with a range of $0–25; of these ratings, only ratings of "I want cocaine" were collected at baseline, prior to any cocaine administration.

2.5. Drugs

Cocaine base, derived from cocaine hydrochloride (Mallinckrodt Pharmaceuticals, St. Louis, MO), was prepared in pellets of 12, 25 and 50 mg by the New York State Psychiatric Institute (NYSPI) pharmacy (Foltin et al., 1990). The 0 mg dose consisted of inhaling warm air from the glass stem.

Modafinil (Provigil®) is well absorbed after oral administration and has a terminal elimination half-life of ~12 hrs (Robertson & Hellriegel, 2003). Modafinil was packaged by the NYSPI pharmacy into size #00 opaque capsules with lactose filler; matching placebo capsules were filled only with lactose. Because we had previously shown that both 200 and 400 mg/d of modafinil decreased cocaine self-administration (Hart et al., 2008), 300 mg/d was used in the current study. Under the active medication condition, dosing began with 200 mg on the first day and increased to 300 mg per day for the rest of that phase. Modafinil dose (0, 300 mg/day) order was counter-balanced with 3 of the final 7 participants being tested with modafinil first and 4 being tested with placebo first. Medication (modafinil or placebo) was administered once in the morning (~9:00 AM) and again in the early evening (~5:00 PM). A staff member observed all medication dosing, i.e., a mouth check was performed.

2.6. Data analysis

The primary outcome measure for Choice sessions was the number of cocaine and game of chance choices. Data were analyzed using repeated-measures analyses of variance (ANOVA) with Modafinil dose (placebo, active), cocaine cost (Low, High) and free dose (0, 12, 25, 50 mg) as within group factors. There were two planned comparisons based on the 3-way interaction term (Modafinil × cocaine cost × free dose): choice following the 4 free doses of cocaine during placebo maintenance was compared to choice following the 4 free doses of cocaine during modafinil maintenance under each of the cocaine cost conditions. The cardiovascular and subjective effects of cocaine under placebo and modafinil conditions were based solely on the means of the 2 Training sessions that occurred at the beginning of each inpatient phase because on these sessions all participants received all 7 doses of 25 mg smoked cocaine. Measures included baseline and peak HR, DP, SP, and craving ratings, and peak ratings of dose value and “Good Drug Effect” (estimates of drug effects were not obtained at baseline before cocaine had been given). Baseline cardiovascular measures were the mean of readings obtained (from t = −14 to – 4 min) before the first cocaine dose. Training session data were analyzed using ANOVAs with Modafinil dose (placebo, active) and Session (AM, PM) as within group factors. Results for all analyses were considered statistically significant at $P < 0.05$.

3. Results

Three participants left the study for personal reasons, and 4 were discontinued due to the occurrence of asymptomatic electrocardiogram abnormalities. An additional participant had 1 or 2 choices withheld due to elevated cardiovascular activity each session, and was informed of the reason for the withheld doses. Because withholding cocaine or the alternative reinforcer for safety reasons could affect choice behavior irrespective of other factors, data from this participant was excluded from the analyses. Thus, data from 7 participants was analyzed.

The participants who completed the study (5 Black males, 1 White male and 1 Black female) were 41 to 49 years of age (mean = 45.9 years), had an average of 11.7 ± 2.9 (mean ± S.D.) years of education and reported using cocaine by the smoked route for the past 17.3

± 8.3 years, using cocaine 4.5 ± 1.7 days per week, and spending $200 to $500 per week on cocaine ($250 ± 111.8; the cost of cocaine was about $30/g in the New York City area when these data were collected). All of the participants smoked tobacco cigarettes, smoking an average of 4.9 ± 4.7 tobacco cigarettes per day. Three participants reported no alcohol use, 2 reported drinking 2-4 standardized alcoholic beverages 2 to 3 times a month, and 2 participants reported drinking 2-6 standardized alcoholic beverages 2 to 3 times a week.

3.1. Training Sessions

The 25 mg cocaine doses smoked during the Training sessions produced modest, expected physiological and subjective effects relative to baseline. During placebo maintenance, peak increases in HR were about 4 bpm from a baseline of 76.7 ± 2.2 bpm (Mean ± SEM), peak increases in DP were about 5 mmHg from a baseline of 72.0 ± 2.0 mmHg, and peak increases in SP were about 6 mmHg from a baseline of 118.0 ± 3.2 mmHg. Baseline HR was slightly (though not significantly) greater (4 bpm) during modafinil maintenance, but there were no significant differences between the peak cardiovascular effects of cocaine during placebo and modafinil maintenance.

Modafinil did not alter peak ratings of “I want cocaine” (a measure of cocaine craving) during Training sessions: mean ratings were 54.7 ± 10.2 when participants were maintained on placebo and 60.6 ± 8.7 mm when participants were maintained on modafinil. During Training sessions when participants were maintained on placebo, peak ratings of “Good Drug Effect,” and “Cocaine Dose liking” were each approximately 40 mm ± 6.5 mm, and peak ratings of “Cocaine Dose Quality” were 36.1 ± 6.5 mm when participants were smoking cocaine. During these sessions participants indicated that each 25 mg dose was worth $2.48 ± $0.42. These ratings of cocaine’ effects were not affected by maintenance on modafinil, i.e., modafinil did not alter the subjective effects of smoking 25 mg cocaine doses.

3.2. Effects of Response Cost, Alternative and Free Doses of Cocaine on Cocaine Choice

Fig. 1, which portrays cocaine self-administration as a function of modafinil dose and cost condition, shows that participants chose significantly fewer cocaine doses under the High Cost and Alternative condition compared to the Low Cost and Alternative condition ($F(1,6) = 17.4$, $P = 0.006$). Providing individuals a range of free doses of cocaine (including cocaine-related cues) prior to making their cocaine choice for each session did not alter cocaine taking. Under the Low Cost and Alternative condition, modafinil had no effect on cocaine choice following the 4 free doses of cocaine compared to placebo. However, modafinil significantly decreased cocaine choice following the 4 free doses of cocaine under the High Cost and Alternative condition relative to placebo [planned comparison; $F(1,18) = 6.6$, $P = 0.035$)]. Thus, modafinil was only effective in decreasing cocaine choice when the cost for cocaine was high.

4. Discussion

The results of the present study show that 1) increasing the response requirement and value of the alternative reinforcer for cocaine significantly decreased cocaine choice by about

20%; 2) modafinil further significantly decreased cocaine choice by about 10% but only under the High Cost and Alternative condition; 3) modafinil did not significantly alter the subjective or cardiovascular effects of the 25 mg cocaine dose; and 4) providing a free dose of cocaine before a session did not alter either cocaine choice or the effects of modafinil on cocaine choice.

The “cost” for choosing cocaine was increased by both requiring a larger physical response (keyboard presses) and by raising the potential monetary earnings for playing a game of chance for cash instead of taking cocaine. Modafinil did not affect choice when the response requirement and alternative value were low, but did so when the response requirement and alternative value were high indicating that having a greater cost associated with cocaine choice increased the sensitivity of the procedure to examine the potential efficacy of a medication on cocaine choice. Increasing the response requirement or the value of the alternative reinforcer often (Donny et al., 2004; Nader & Woolverton, 1991; Negus, 2003; Stoops et al., 2010; Thomsen et al., 2013; Vosburg et al., 2010), but not always (Hart et al., 2000; Donny et al., 2003; Walsh et al., 2001) decreases cocaine choice, and most often the effects are small in human and non-human primates. In this study both response effort and value of the alternative were increased in order to maximize the similarities between decisions made in the laboratory and in the real world. The small (20%) decrease in cocaine choice due to this increased cost replicates the earlier studies and confirms that ongoing cocaine self-administration behavior is difficult to disrupt by increasing response cost even in laboratory situations where a wide range of response requirements and alternative reinforcers are evaluated. However, although the decreases in cocaine self-administration are small, in a clinical setting such small decreases may provide a valuable start to reducing drug abuse. As such, laboratory paradigms manipulating the personal cost to take drug may model the clinical utility of contingency management in decreasing cocaine use in humans seeking treatment (e.g., DeFulio et al., 2009; Higgins et al., 1991; Petry et al., 2004). Indeed as the current participants were not seeking treatment for their cocaine use, the results may underestimate the utility of these behavioral procedures in those who desire to decrease their cocaine use.

The goal of the study was to develop a laboratory model for evaluating putative medications for cocaine abuse with the expectation that a medication would be more effective when the response effort for getting cocaine was greater and the value of the alternative reinforcer was greater, i.e., the High Cost and Alternative condition in nontreatment-seekers would better model treatment motivation in treatment-seekers. Although subtle, modafinil was only effective in decreasing cocaine choice under the High Cost and Alternative condition. While the initial promise of modafinil for treating cocaine abuse (Dackis et al., 2005) has not been realized, the balance between the positive (Kampman et al., 2015) and negative clinical trials (Anderson et al., 2009; Schmitz et al., 2014) argues that modafinil has promise. Developing a laboratory model that provides a reliable signal that a medication has clinical promise would be useful for the identification of future medications.

Previous studies have suggested that modafinil might improve treatment outcome by improving cognitive function related to decision-making (Canavan et al., 2014; Mereu et al., 2013) and/or attenuating cue-elicited behavior (Goudriaan et al., 2013). We were unable to

test the effects of modafinil on cocaine and cue-elicited behavior as providing a free dose of cocaine accompanied by cocaine-related cues prior to making cocaine choices did not significantly alter the choice to self-administer cocaine under either medication condition. Modafinil also did not alter the cardiovascular, subjective or craving effects of the 25 mg cocaine dose. As observed with the clinical trial data, modafinil attenuated different measures of cocaine-induced positive mood across laboratory studies (Dackis et al., 2003; Hart et al., 2008; Verrico et al., 2014). In the present study, modafinil reduced choice behavior without modifying any other cocaine effects.

The small sample size is a significant limitation to the study: 7 out of 15 participants provided complete data sets. Approximately half of the dropouts were discontinued due to medical events and half left for personal reasons. It is difficult to assess whether the completers or perhaps the dropouts were a better sample of the cocaine-using population. Furthermore, to what extent do study dropouts affect the generalizability of the study outcome? This issue is a significant one when conducting laboratory studies administering drugs that produce significant physiological effects. Medical requirements may result in a study sample that is healthier than the general population of drug users; yet similar medical issues most often would not be exclusionary for a clinical trial. In this study, participants were also not seeking treatment for their cocaine use and this may have also affected study generalizability. However, we endeavored to model the treatment situation by studying cocaine choice when the personal “cost” to use cocaine was high, similar to situations that individuals in treatment encounter on a regular basis.

The efficacy of modafinil for cocaine abuse varies widely across clinical trials (Mariani & Levin, 2012). Similar variability was observed here as modafinil decreased cocaine taking only when the response requirement for cocaine and the alternative reinforcer were large. This suggests that drug self-administration procedures appear to be more sensitive to medication-induced changes in choice when the behavioral and/or financial costs for choosing drug are large. These results also suggest that modafinil may be most effective when combined with therapy emphasizing the large personal costs of using cocaine.

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Highlights

- Increasing the response requirement for cocaine and value of an alternative reinforcer decreased cocaine choice
- Providing a dose of cocaine without a response requirement did not alter cocaine choice
- Modafinil significantly decreased cocaine choice only when the response requirement for cocaine and value of an alternative reinforcer was high
- Modafinil should be combined with therapy emphasizing the large personal costs of using cocaine

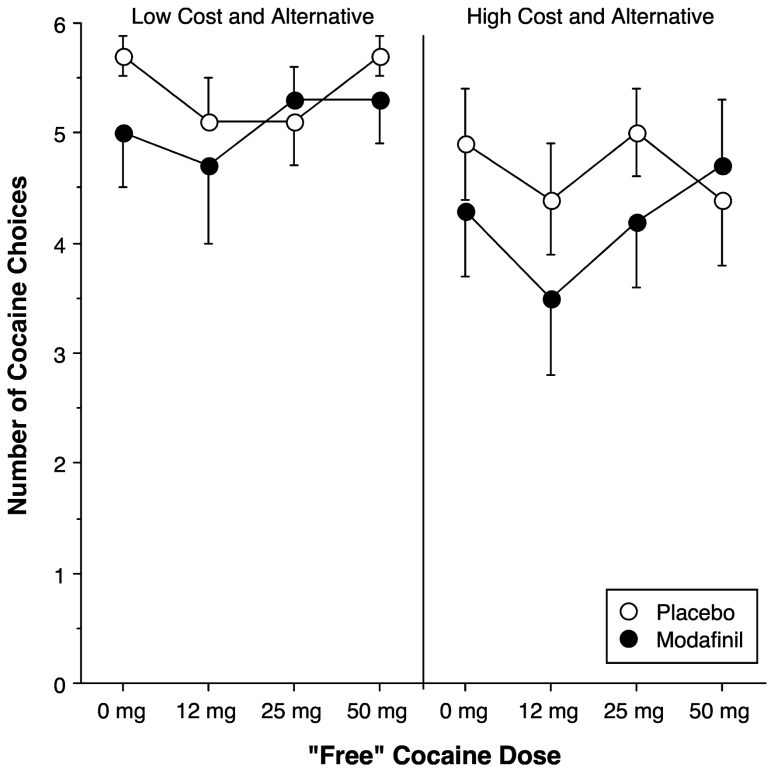

Figure 1. Mean number of cocaine choices as a function of "cost" condition and the dose of cocaine smoked with no response requirement before the choice session in 7 human cocaine smokers

Error bars represent 1 SEM.