Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study

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Abstract

Modafinil is a novel compound that is approved for the treatment of narcolepsy. It is now being studied as a potential treatment for cocaine dependence. Cocaine withdrawal symptoms are associated with poor clinical outcome and are likely to be reversed by modafinil. In addition, the neurotransmitter actions of modafinil are opposite to cocaine-induced neuroadaptations affecting dopamine and glutamate reward circuits. Since cocaine-dependent subjects might use cocaine during a clinical trial with modafinil, this study tested the safety of intravenous cocaine (30 mg) in combination with modafinil. Each of seven subjects received a baseline (open-label) cocaine infusion. Three subsequent cocaine infusions were administered after subjects received 4 days of low dose modafinil (200 mg/day), high dose modafinil (400 mg/day), or placebo in randomized double-blind sequences. One subject received placebo prior to all infusions. Our results indicate that co-administering modafinil and a single dose of intravenous cocaine is not associated with medical risk in terms of blood pressure, pulse, temperature, or electrocardiogram measures. Furthermore, pretreatment with modafinil did not intensify cocaine euphoria or cocaine-induced craving. In fact, cocaine euphoria was significantly blunted (P = 0.02) in one of our subjective measures.

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1. Introduction

Cocaine dependence remains a disorder for which no pharmacological treatment exists, although considerable advances in the neurobiology of this addiction should guide future medication development. Numerous lines of evidence conclude that cocaine euphoria involves the activation of brain reward circuits that are subsequently dysregulated after repeated cocaine administration (Koob et al., 1998; Dackis and O’Brien, 2002a,b). Pharmacological agents capable of reversing cocaine-induced neuroadaptations are logical choices to ameliorate clinical features of this illness, including withdrawal, craving, and hedonic dysregulation (Dackis and O’Brien, 2002a). Modafinil, a wakefulness-promoting drug approved for narcolepsy, has neurotransmitter actions that are opposite to cocaine-induced neuroadaptations affecting dopamine (DA) and glutamate reward circuits. Repeated cocaine administration depletes glutamate (Keys et al., 1998) while modafinil increases brain glutamate (Perez de la Mora et al., 1999; Pierard et al., 1995; Ferraro et al., 1998). DA depletion by cocaine (Dackis and Gold, 1985; Wu et al., 1997; Volkow et al., 1997) might also be reversed as a result of modafinil’s inhibition of GABA release (Perez de la Mora et al., 1999) because reward-related midbrain DA neurons are under tonic inhibitory regulation by GABA projections (Dackis and O’Brien, 2002a).

Modafinil’s stimulant-like action should also reduce cocaine withdrawal symptoms, including hypersomnia,
anergia, depressed mood, hyperphagia, psychomotor retardation, and poor concentration (Satel et al., 1991; Weddington et al., 1990; Gawin and Kleber, 1986; Cottler et al., 1993; Coffey et al., 2000). Since severe cocaine withdrawal has been linked to poor clinical outcome (Kampman et al., 2001; Mulvaney et al., 1999), its reversal might be clinically advantageous. In addition, since modafinil has some cocaine-like discriminative stimulus effects in animals (Gold and Balster, 1996) and some stimulant-like subjective effects in humans (Jasinski, 2000), it might perform a substitution therapy function in cocaine-dependent patients. Furthermore, modafinil has low abuse potential (Jasinski, 2000; Jasinski and Kovacevic-Ristanovic, 2000), good tolerability (Menza et al., 2000; Lyons and French, 1991), and a neurochemical profile that differs markedly from that of cocaine and amphetamine (Ferraro et al., 1997; Mignot et al., 1994; Akaoka et al., 1991; Lyons and French, 1991; Lin et al., 1996; Simon et al., 1995). These attributes identify modafinil as a potentially efficacious compound for the treatment of cocaine dependence.

Given the high recidivism rates associated with cocaine dependence (Alterman et al., 1994, 1996a; Carroll et al., 1991, 1994; Kang et al., 1991; Higgins et al., 1993), there is significant risk that cocaine will be used by subjects enrolled in clinical trials. Therefore, a drug interaction study with modafinil and cocaine is warranted to maximize subject protection. Although no such study has yet been reported, modafinil has been co-administered with dextroamphetamine (Wong et al., 1998b) and methylphenidate (Wong et al., 1998a), and neither of these studies reported untoward medical complications or pharmacokinetic interactions. Intravenous cocaine infusions in the laboratory have not been found to produce subsequent deleterious changes in cocaine use patterns (Kaufman et al., 2000). The current safety study was conducted to evaluate the effect of modafinil pretreatment on physiological and subjective responses to intravenous cocaine administration.

Cocaine has well-documented effects on blood pressure, pulse, temperature, and cardiac function. Its sympathomimetic action produces tachycardia and hypertension (Casella et al., 1989) that can be sufficiently severe to cause brain hemorrhage (Jacobs et al., 1989; Nolte et al., 1996) and cerebral infarction (Kokkins and Levine, 1993; Daras et al., 1991). Cocaine is also thermogenic and has been reported to cause fatal hyperthermia (Loghmanee and Tobak, 1986; Welli and Fishbain, 1985). Deleterious effects on cardiac function are substantiated by numerous case reports of arrhythmias, myocardial infarction and sudden death (Lange and Hillis, 2001; Combs and Acosta, 1990; Chakko and Myerburg, 1995). Cocaine specifically increases the QTc interval (QT interval corrected for heart rate), which may lead to ventricular tachycardia, ventricular fibrillation, and asystole (Gamouras et al., 2000; Kerns et al., 1997). In recommended doses (200–400 mg/day), modafinil produces a 2% incidence of hypertension, although excessive doses (800 mg/day) can lead to significant hypertension and tachycardia (Wong et al., 1999). In addition, chest pain, palpitations, dyspnea and transient ischemic T-wave changes on electrocardiogram (ECG) have been reported in three patients with pre-existing mitral valve prolapse or left ventricular hypertrophy. Modafinil is thermogenic in animal studies (Lin et al., 1992) but human reports are conflicting (Pigeau et al., 1995; Brun et al., 1998; Bourdon et al., 1994). Given these reports, and the possibility that modafinil might exacerbate the medical risk of cocaine administration, we assessed blood pressure, pulse, temperature, and ECG function in this drug interaction study.

As a secondary objective, we also evaluated the impact of modafinil pretreatment on the subjective responses to cocaine. Aside from producing intense euphoria, cocaine has the ability to stimulate its own craving shortly after administration (Jaffe et al., 1989; O’Brien et al., 1992). Since any amplification of cocaine-induced euphoria or craving by modafinil could be clinically deleterious, these subjective states were specifically evaluated. Side effects and adverse events were also carefully measured to further assess potential interactions and tolerability. The results of our double blind, placebo-controlled, drug interaction study are presented below.

2. Methods

2.1. Subjects

Subjects were recruited from cocaine-dependent individuals (between the ages of 18 and 50) presenting for treatment to the Department of Veterans Affairs Medical Center (DVAMC) in Philadelphia. All participants had full access to treatment and received aftercare referrals at the conclusion of the study. Individuals were excluded if they had a current diagnosis of substance dependence (except cocaine or nicotine), significant medical disease (especially hypertension, seizures, arrhythmia requiring medication, and coronary artery disease) or active psychiatric illness. Subjects requiring medications were also excluded. Other exclusion criteria included abnormal laboratory tests (CBC, blood chemistries, urinalysis, and ECG), abnormal weight (based on parameters published in 1983 by Metropolitan Life Insurance Company), and a history of receiving an investigational drug within the past 60 days. All subjects screened positive for benzoylcegonine, used cocaine via the intrapulmonary roue, and met DSM IV criteria for cocaine dependence, based on a non-structured interview by an experienced psychiatrist.
Ten subjects (all male; 9 African American and 1 Caucasian; mean age 44 years; age range 38–50 years; mean weight 75 kg; weight range 62–103 kg) were enrolled and a total of seven subjects completed the study. Four of the subjects were employed and three were married. None of the three dropouts were married and one was employed. Subjects were compensated for their time and received a total of four cocaine infusions during an inpatient hospitalization lasting 18–24 days. The study was conducted only after subjects signed an informed consent, approved by the subcommittee on human subjects at the Philadelphia DVAMC, which outlined the possible adverse events associated with modafinil, intravenous cocaine, and the combination of these agents. Subjects were specifically advised that their cardiac telemetry and vital signs would be closely monitored during the cocaine infusion. All of the subjects were discharged only after receiving sufficient additional inpatient treatment to counter the destabilizing effects of intravenous cocaine, and none of the subjects reported craving at the time of discharge. Following the study, all ten subjects entered relapse prevention treatment.

2.2. Procedures and measurements

This was a randomized, double blind, placebo-controlled drug interaction study involving the intravenous administration of open-label cocaine (30 mg) in combination with placebo or two oral dosages (200 and 400 mg/day) of modafinil. Four cocaine infusions were assessed during the inpatient hospitalization, starting with an initial baseline infusion and followed by three subsequent cocaine infusions performed after 4 days of treatment with low dose (LD) modafinil (200 mg/day), high dose (HD) modafinil (400 mg/day), or placebo (P) (Table 1). The final 3 infusions comprise a three-session crossover design and one subject was pretreated with placebo prior to each infusion. While these infusions yielded no information on the modafinil effect, the data provided information on carryover and period effects. LD modafinil always preceded HD modafinil for medical safety reasons, with the provision that subjects would not be administered HD modafinil if they experienced significant medical problems with the lower dose. The selection of the 4-day modafinil trial before each infusion was made to achieve steady state levels. Dosages of modafinil (which has an elimination half-life of 13–18 h) were consistent with the manufacturer’s recommended daily dose for the treatment of narcolepsy.

Cocaine infusions were performed 3 h after oral modafinil (or placebo) administration to assess the interaction at peak modafinil levels. At 0 h, a single intravenous injection of cocaine (30 mg) in isotonic saline solution was administered over 60 s. This dose was selected as one likely to produce moderate to strong clinical effects, and is consistent with cocaine infusion doses in other safety studies. The patients remained semi-supine during study procedures and a cardiologist was present for at least 30 min after the infusion, during which time the acute effects of cocaine dissipated. ECG monitoring (using a Physio-Control Lifepack 9) was continuous throughout the sessions and a 12-lead ECG (using a Marquette MAC6) was performed 2 h prior and 2 h after each infusion. Physiological reactions to the cocaine infusion were measured with a battery of safety evaluations, including serial measurements of blood pressure, pulse, temperature, and ECG parameters (Table 2). Vital signs were measured with an Invacare 4200A monitor. An indwelling 20-gauge catheter was inserted 3 h before the cocaine infusion, and remained in place throughout the infusion procedure. Adverse events were recorded on a standardized case report form.

Cocaine and prolactin levels were measured via repeated blood draws through the indwelling catheter. Hyperprolactinemia has been reported in cocaine users (Dackis and Gold, 1985) and prolactin levels were obtained as a measure of DA function. Psychological reactions were measured at varying time points before and after each cocaine infusion with the visual analog scale (VAS), an 11 item Subjective Symptom Checklist, and the Addiction Research Center Inventory (ARCI) Motor, Euphoria, Benzedrine and Amphetamine scales (Haertzen, 1965). The VAS consists of a battery of 21 items (stimulated, high, anxious, sedated, depressed, hungry, friendly, miserable, on-edge, alert, tired, talkative, self-confident, social, irritable, confused, good drug, bad drug, cocaine craving, alcohol craving, and

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<th>Study phase</th>
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<td>Admission and evaluation</td>
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<td>BL cocaine infusion</td>
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<td>Second cocaine infusion</td>
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<td>Discharge</td>
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After a baseline infusion, subjects received three additional cocaine infusions after 4 days of pretreatment with LD modafinil (200 mg/day), HD modafinil (400 mg/day), or placebo (P).
nicotine craving). Subjects were instructed to rate subjective experiences at specified times on a 100 mm scale, ranging from 0 (not at all) to 100 (the most ever). The Subjective Symptom Checklist is an 11-item checklist that assesses the most frequent adverse effects of cocaine (nausea, abdominal pain, shaky, chills, heart racing, restless, headache, hot, weak, irritable, confused), rated as mild, moderate, or severe when present. The ARCI is a self-report measure that was developed nearly 40 years ago to standardize the subjective effects of various mood-altering compounds. It consists of 32 items (rated true, more true than false, more false than true, or false) that are weighted and tabulated to yield a single score.

### 2.3. Statistical analysis

Comparisons of pre-cocaine and post-cocaine QTc values were performed using \( t \)-tests on the within-subject differences on these measures. To allow for within-subject correlations in the data, due to each subject providing data on three separate occasions, we used linear mixed effects models to test for differences in the level of pre-treatment (P, LD, or HD). These models were fit using \textsc{proc mixed} (Littell et al., 1996), which uses an iterative estimation procedure to obtain restricted maximum likelihood estimates. We analyzed physiological and subjective responses in the form of repeated measures within the pre-cocaine and post-cocaine periods of the infusion procedure. Although mixed-effects models can accommodate sophisticated models such as repeated observations within each period of a crossover design, we chose to consider summaries of each period, as the small sample size was likely to result in unreliable estimates of the parameters in the more complicated models. The primary derived variable is the area under the curve (AUC, calculated from the Trapezoidal rule), which is a measure of overall ‘level/height’ of the curve given by the repeated measurements on a response across the post-infusion period. For the subjective measures, we were also interested in peak-responsiveness, and measured this using a second derived variable, the increase from pre-infusion level to maximal post-infusion level (\( A_{\text{max}} \)). As the baseline infusion was not preceded by pre-treatment with modafinil, the data from that infusion were not included in the comparisons of the modafinil effect.

In the analyses, the last pre-infusion measurement was used as a covariate to allow for within-subject variation in pre-infusion scores across the three periods. The time at which this pre-infusion value was obtained varied across the measures, being either 10 min pre-infusion (for vital sign data) or 15 min pre-infusion (for prolactin, cocaine, and all subjective measures). The models included main effects of period and treatment, and a term for carryover effect. We also examined the treatment by period interaction, although the small sample size makes estimation of these effects difficult.

### 3. Results

The set of physiology measures is comprised of four vital sign responses (diastolic blood pressure, systolic blood pressure, pulse, and temperature), ECG monitoring, cocaine levels, and prolactin levels. The set of subjective measures is comprised of the ARCI, the Subjective Symptom Checklist, and the VAS. Tests of carryover, period, and period by treatment effects are necessary pre-requisites for the analysis of any crossover design, as the presence of such effects can suggest the need to perform separate comparisons of treatment effects within each period, rather than by pooling across periods. With the exception of one of the secondary measures, these effects were non-significant (at a 5% level) for all of the responses.
3.1. Vital sign analysis

The administration of intravenous cocaine without modafinil (baseline and P conditions) produced expected elevations in systolic and diastolic blood pressure, pulse, and temperature that were not significantly altered by modafinil pretreatment. AUC measures for vital sign responses to cocaine were calculated out to 120 min post-infusion for these scales. Treatment effects were non-significant for diastolic blood pressure \( (F(2, 7) = 0.31, P = 0.74) \), systolic blood pressure \( (F(2, 7) = 1.75, P = 0.24) \), pulse \( (F(2, 7) = 0.05, P = 0.96) \), and temperature \( (F(2, 7) = 0.85, P = 0.47) \). Even the highest vital signs measured when subjects were co-administered modafinil and cocaine were within safe levels for systolic blood pressure (170 mm/Hg), diastolic blood pressure (109 mm/Hg), pulse (101 beats/min) and temperature (99.5 °F). The highest systolic (182 mm/Hg) and diastolic (125 mm/Hg) blood pressures across all infusions (including baseline and placebo conditions) occurred when cocaine was infused without modafinil. Therefore, subjects co-administered cocaine and modafinil did not exhibit medically unsafe vital sign changes and there was no difference in vital sign responses to intravenous cocaine across the three levels (Fig. 1).

3.2. ECG analysis

Neither the subjects pretreated with LD modafinil nor those pretreated with HD modafinil had increased QTc intervals after cocaine when compared to P pretreatment. No rhythm disturbances, ST elevations, or cardiac-related adverse events were observed with direct telemetry or through analysis of ECG tracings performed during any of the 28 infusions. The study cardiologist reviewed a 12-lead ECG obtained approximately 2 h before cocaine administration and none of the infusions required cancellation due to abnormal cardiac findings. Additional 12-lead tracings obtained 30 min before and 120 min after each cocaine infusion were used to calculate ΔQTc (post cocaine QTc minus baseline QTc) values that were analyzed with \( t \)-tests. When compared to P, the ΔQTc scores showed no differences after either LD \( (P = 0.60) \) or HD \( (P = 0.52) \) modafinil, and there were no ΔQTc score differences between baseline and P infusions \( (P = 0.21) \).

3.3. Cocaine level analysis

Cocaine levels were obtained to confirm cocaine administration and compare treatment conditions.
There were no significant differences in the cocaine levels across periods or across modafinil pretreatment levels. Our study did not assess pharmacokinetic parameters such as the effect of modafinil on cocaine clearance or elimination half-life. It is possible that modafinil could produce an effect on cocaine elimination that might be important in the setting of repeated cocaine dosing.

3.4. Prolactin analysis

AUC measures were calculated out to 120 min post-infusion for prolactin. The treatment effect was non-significant.

3.5. Subjective measures

The subjective measures comprised four ARCI scales (Motor, Euphoria, Amphetamine, and Benzedrine), the Subjective Symptom Checklist, and the VAS. Five of the 21 items in the VAS were selected as most likely to assess euphoria (stimulated, high, alert, good drug) or craving (cocaine craving) and are reported below.

3.5.1. Visual analogue scale

For the VAS items, we report results where the integration for the AUC was cut-off at 45 min post-infusion. The conclusions for cut-offs at 90 or 120 min were entirely consistent with these results. For the alert scale, there was a significant period by treatment interaction ($F(2, 5) = 14.7, P = 0.008$). On inspection, this appeared to be due to the subject who received placebo across all active sessions, and had a lower score in his second session than in the others. Within each period, there was not a significant treatment effect. There were non-significant treatment effects for the stimulated, high, good drug and cocaine craving scales. As described above, we also examined peak-responsiveness for the subjective scales. The results for the $\Delta_{\text{max}}$ statistic were essentially the same as for the AUC statistic.

3.5.2. ARCI responses

AUC measures were calculated out to 120 min post-infusion for the ARCI scales. Treatment effects were non-significant for the Motor, Euphoria, and Benzedrine scales. For the Amphetamine scale, there was a significant treatment effect ($F(2, 7) = 6.72, P = 0.02$). Comparison of least-squares means showed that both modafinil doses had lower Amphetamine scores than placebo, but they were not significantly different from each other (Fig. 1). The least-squares means for P, LD, and HD were 581.29, 403.82, and 461.98, respectively. The $P$-values for comparisons between the P/LD, P/HD, and LD/HD levels were 0.008, 0.09, and 0.36, respectively.

3.5.3. Tolerability and subjective symptom checklist

Adverse events were recorded throughout all infusions and did not differ qualitatively across P, LD and HD conditions. There were no significant effects for the Subjective Symptom Checklist scale. Three subjects dropped out of the study. One completed the baseline infusion (without modafinil) and opted out of the study due to anxiety during the infusion. The other two subjects dropped out because of their reluctance to remain in the hospital for the required number of days.

4. Discussion

The primary goal of this safety study was to determine whether medically significant complications would result from the co-administration of modafinil and cocaine. We found no evidence of modafinil exacerbating cocaine-induced increases in blood pressure, pulse, or temperature, or that adverse ECG effects resulted from this combination. Analysis of cocaine levels confirmed that our results were not confounded by significant differences in levels across periods. The results are limited by the fact that we tested only one dose of intravenous cocaine in a single administration. Malcolm tested five cocaine-dependent individuals with two doses (20 or 40 mg) of intravenous cocaine under controlled conditions after modafinil (400 or 800 mg/day) was given for 1 week, and found that modafinil did not exacerbate blood pressure, pulse, or temperature effects of cocaine (Malcolm et al., 2002). However, multiple doses of cocaine administered to patients maintained on modafinil have not been tested, and this combination might produce medical risk. Modafinil can produce significant hypertension and tachycardia at 800 mg/day, suggesting it may have a rather narrow therapeutic index. This is important because a mistake in modafinil dose by a cocaine user could have serious consequences, especially in combination with cocaine.

A secondary goal of our study was to evaluate whether modafinil pretreatment would alter the subjective effects of cocaine. After infused cocaine, ratings on the ARCI Amphetamine scale were significantly lower ($P = 0.02$) in modafinil compared to placebo treated subjects. We qualify this finding by pointing out the small subject sample of our study. Also, our finding must be qualified by the fact that the blunting effect on cocaine-induced euphoria was significant for the LD ($P = 0.008$) but not the HD ($P = 0.09$) of modafinil in the comparison of least square means. Nonetheless, a cocaine euphoria-blunting effect of modafinil would be clinically advantageous and we believe our finding justifies further investigation with larger sample size. Importantly, these results give no indication that modafinil pretreatment heightened cocaine-induced craving or cocaine-induced euphoria,
which represent potentially destabilizing states in the clinical management of cocaine-dependent patients.

Modafinil might attenuate some aspects of cocaine withdrawal because, in patients not addicted to cocaine, it has effects (Saletu et al., 1989; Berset et al., 1996; Mitchell, 1995; Menza et al., 2000; Beusterien et al., 1999; Rugino and Copley, 2001; Duteil et al., 1990; Nicolaidis and De Saint Hilaire, 1993) that are qualitatively opposite to the cocaine withdrawal syndrome. The rationale for detoxification is based largely on the finding that patients with severe cocaine withdrawal show poor treatment retention and are less likely to abstain from cocaine (Kampman et al., 1998, 2001). This finding, in and by itself, does not necessarily imply that the pharmacological reversal of cocaine withdrawal would improve clinical outcome. Cocaine withdrawal might serve more as a marker for patients with persistent neuroadaptations and impaired hedonic function, a consequence of chronic cocaine exposure that has been demonstrated in animal studies (Markou and Koob, 1991). In fact, cocaine withdrawal is generally viewed as a mild syndrome (Weddington et al., 1990) that may not require pharmacological treatment (Satel et al., 1991). If cocaine withdrawal represents a marker for hedonic dysregulation, agents that reverse this syndrome might also improve hedonic function in cocaine-dependent patients.

Another rationale for investigating modafinil in cocaine dependence relates to its interesting neurotransmitter effects. Several lines of evidence demonstrate that the administration of cocaine can produce DA depletion (Dackis and Gold, 1985; Wu et al., 1997; Volkow et al., 1997; Little et al., 1999; Dackis and O’Brien, 2002a; Robertson et al., 1991; Parsons et al., 1991; Imperato et al., 1992; Wise, 1996), which has been theorized to underlie cocaine craving (Dackis and Gold, 1985) and hedonic dysregulation in cocaine-addicted patients (Wise, 1996). The DA-rich ventral tegmentum, a mid-brain region intrinsic to natural reward and drug euphoria (Schultz, 2001), is under tonic excitatory regulation by prefrontal glutamate projections (Karreman and Moghaddam, 1996) and tonic inhibitory regulation by GABA projections (Ikemoto et al., 1997). Modafinil increases brain glutamate (Perez de la Mora et al., 1999; Pierard et al., 1995; Ferraro et al., 1998) and inhibits GABA release (Perez de la Mora et al., 1999; Ferraro et al., 1996; Tanganelli et al., 1995), producing an expected net excitation of DA neurons in the ventral tegmentum. We attempted to assess DA function by measuring prolactin levels, since hyperprolactinemia has been reported in a subset of cocaine-dependent patients. However, none of our subjects had elevated prolactin at baseline, and we found no effect of cocaine or modafinil on this marker. In addition, glutamate depletion has been reported with repeated cocaine administration (Keys et al., 1998) and might be reversed with modafinil. Glutamate is acutely released by cocaine (Kalivas and Duffy, 1998; Reid et al., 1997) and its importance in cocaine reward and cocaine addiction has become increasingly evident (Kalivas and Duffy, 1998; Dackis and O’Brien, 2002a, 2001). Reversing chronic cocaine-induced dysregulation of DA and glutamate systems might improve hedonic function in cocaine-addicted patients and thereby reduce their compulsion to seek transient reward from cocaine.

In conclusion, we found no evidence of increased medical risks associated with a single dose of intravenous cocaine given to individuals maintained for 4 days on oral modafinil. It is important to note that our results are limited since we did not assess the medical safety of repeated cocaine use by patients taking modafinil, and we report a small sample size. We found no significant drug-drug interaction with regard to blood pressure, pulse, temperature, or ECG function. We also found no evidence that modafinil pretreatment increases cocaine euphoria or cocaine-induced craving. In fact, our ARCI data indicate that modafinil pretreatment might actually blunt cocaine-induced euphoria, an effect that could have significant clinical value. Given our preliminary findings of safety and tolerability when administered in combination with cocaine, and the theoretical ability of modafinil to reverse cocaine withdrawal and cocaine-induced neuroadaptations, this compound may be a promising agent to test in cocaine-dependent individuals.

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