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A double blind, placebo controlled trial of modafinil for the treatment of cocaine dependence without co-morbid alcohol dependence

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Abstract

Background—Modafinil is a medication approved for narcolepsy and shift work sleep disorder. It has both dopaminergic and glutamatergic activity that could be useful for the treatment of cocaine dependence. Modafinil has reduced cocaine subjective effects and cocaine self-administration in human laboratory trials and has reduced cocaine use in cocaine dependent patients in some clinical trials.

Methods—This was an 8-week, double blind, placebo controlled clinical trial involving 94 cocaine dependent subjects. Subjects received 300 mg of modafinil or identical placebo daily along with weekly individual therapy. The primary outcome measure was cocaine use measured by self-report, and confirmed by twice weekly urine benzoylecgonine tests (UBT). Additional outcome measures included cocaine craving measured by the Brief Substance Craving Scale and global improvement measured by the Clinical Global Impression Scale (CGI).

Results—The odds ratio (OR) in favor of abstinence for modafinil vs. placebo was 2.54 ($p = .03$) and modafinil-treated subjects were significantly more likely than placebo-treated subjects to be abstinent from cocaine during the last 3 weeks of the trial, 23% vs. 9%, $\chi^2 = 3.9$, $p < .05$.

Modafinil treated subjects were more likely to report very low levels of cocaine craving intensity

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Conflict of Interest: No conflict declared

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and duration on the Brief Substance Craving Scale (OR = 2.04 $p = .03$ and OR 1.06 $p = .03$ respectively). Modafinil-treated subjects were also more likely than placebo-treated subjects to rate themselves as “very much improved” on the CGI (OR = 2.69, $p = .03$).

Conclusion—Modafinil may be an efficacious treatment for cocaine dependence.

Keywords

modafinil; cocaine; alcohol; clinical trial; placebo

1. Introduction

Cocaine dependence is an important public health problem. In 2013 there were about 1.5 million regular cocaine users in the United States (SAMHSA 2014). Because individual and group psychosocial treatments for cocaine dependence do not provide substantial benefit for many patients (Alterman et al., 1996; Carroll, 2004; Kampman et al., 2001), medications have been tested to augment psychosocial treatment. To date, there are no medications that are FDA-approved for cocaine dependence.

Modafinil is a medication approved to treat narcolepsy and shift work sleep disorder. It may also be effective for the treatment of cocaine dependence. Proposed mechanisms of action for cocaine dependence include: reduction of cocaine withdrawal symptoms, reduction in cocaine craving, and a reduction in cocaine-induced euphoria. As a mild stimulant, modafinil may be able to reduce cocaine withdrawal symptoms (Dackis and O'Brien, 2003). Modafinil has been shown to increase dopaminergic neurotransmission by blocking the dopamine transporter and this may account for its ability to reduce cocaine withdrawal symptoms and reduce the high associated with cocaine use (Volkow et al., 2009). Modafinil also enhances glutamate neurotransmission (Touret et al., 1994). It may therefore be efficacious for cocaine dependence by ameliorating glutamate depletion seen in chronic cocaine users (Dackis and O'Brien, 2003). Improved baseline glutamatergic tone in the nucleus accumbens prevents reinstatement of cocaine self-administration in an animal model of relapse (Baker et al., 2003).

Modafinil reduced cocaine induced euphoria and cocaine self-administration in human laboratory trials. Modafinil was found to block the euphoric effects of cocaine in three independent human laboratory studies (Dackis et al., 2003; Hart et al., 2008; Malcolm et al., 2006). In addition, Hart and colleagues found that modafinil reduced cocaine self-administration in a human laboratory trial (Hart et al., 2008).

Modafinil has reduced cocaine use among cocaine dependent subjects in clinical trials. In a double blind, placebo-controlled pilot trial of modafinil involving 62 cocaine-dependent subjects, modafinil-treated subjects submitted significantly more cocaine metabolite-free urine samples compared to placebo-treated subjects (42% vs. 22%). Modafinil-treated subjects were also rated as more improved compared to placebo-treated subjects (Dackis et al., 2005). The results of the pilot trial were partly replicated in a larger multicenter trial involving 210 cocaine-dependent subjects. In this 16-week trial, cocaine dependent subjects were treated with modafinil 200 mg daily, modafinil 400 mg daily, or placebo. In contrast to

the pilot trial, in which none of the subjects were both cocaine and alcohol dependent, in this trial 41% of the subjects were both alcohol and cocaine dependent. In the group as a whole, modafinil was not superior to placebo in promoting abstinence from cocaine. However, among subjects who were not also alcohol dependent, both doses of modafinil were superior to placebo for promoting abstinence from cocaine (Anderson et al., 2009). Modafinil may be efficacious only in cocaine dependent patients without alcohol dependence.

Not every trial of modafinil has been positive. In a clinical trial recently completed by Dackis and colleagues, 210 cocaine-dependent subjects who were actively using cocaine at baseline were randomized to 8 weeks of modafinil (0 mg/day, 200 mg/day or 400 mg/day) combined with once-weekly cognitive-behavioral therapy. The investigators found no effect of modafinil at either dose on cocaine use or cocaine craving (Dackis et al., 2012). In two somewhat smaller trials, Schmitz and colleagues found that modafinil to be ineffective for the treatment of cocaine dependence in cocaine dependent subjects without comorbid alcohol dependence (Schmitz et al., 2014, 2012)

In the current trial, modafinil was evaluated in cocaine dependent subjects without concurrent alcohol dependence. A dose of 300 mg daily was chosen to maximize tolerability. Subjects were not required to be actively using cocaine at the time of randomization but recent cocaine users were evenly distributed between the two medication groups by means of urn randomization.

2. Methods

2.1. Subjects

The subjects were 94 DSM-IV cocaine dependent men and women drawn from treatment-seeking cocaine users between the ages of 18 and 60. Drug dependence diagnoses were obtained using the Structured Interview for DSM-IV (SCID-IV; First, 1996). Other psychiatric diagnoses were obtained using the Mini International Neuropsychiatric Interview (MINI; Sheehan et al., 1998). In the 30 days prior to study entry, subjects used no less than \$200-worth of cocaine.

Medical screening included a complete medical history and physical examination conducted by a certified nurse practitioner. Baseline laboratory testing included a chemistry screen, complete blood count, urinalysis, and a 12 lead EKG. Women received urinary pregnancy testing prior to starting medications, and at monthly intervals throughout the study. Chemistry screening, CBC, urinalysis and EKG were repeated at the end of the trial. Liver function tests, and carbon dioxide levels were obtained monthly during the trial.

Subjects with current dependence (DSM-IV criteria) on any additional drug except nicotine and cannabis were excluded. Psychiatric exclusion criteria included psychosis, dementia, and the use of other psychotropic medications. Medical exclusion criteria included unstable medical illnesses, a history of hypersensitivity to modafinil, use of medication that would adversely interact with modafinil including: propranolol, phenytoin, warfarin, or diazepam.

2.2. Measures

Self-reported alcohol and cocaine use were measured using the timeline followback (Sobell, 1995). Self-reported cocaine use was verified by qualitative urine benzoylecgonine tests (UBT) obtained twice weekly. Urine collection was monitored by temperature checks. Samples less than 90 degrees, or greater than 100 degrees Fahrenheit were considered invalid and were not accepted. Samples were analyzed for benzoylecgonine by fluorescent polarization assay. Samples containing equal to or greater than 300 ng/ml of benzoylecgonine were considered to be positive.

Treatment retention was determined by attendance at research visits. Severity of addiction-related problems was measured by the Addiction Severity Index (ASI; McLellan, 1992) administered at baseline and three more times during the trial. The study nurse practitioner, and the subjects themselves, rated overall improvement weekly using the Clinical Global Impression Scale (CGI; Guy, 1976). Cocaine craving was measured weekly using the Brief Substance Craving Scale (Somoza et al., 1995). Cocaine withdrawal symptoms were measured weekly using the Cocaine Selective Severity Assessment (CSSA; Kampman, 1998). Safety measures included adverse events, which were monitored at each visit.

2.3. Procedures

Subjects were treatment-seeking cocaine users recruited at the University of Pennsylvania Treatment Research Center (TRC). The TRC recruits through advertisement in the local media as well as through professional referrals. All subjects signed informed consent prior to participation in the trial, after an investigator explained to them the study procedures. The study was reviewed and approved by the Institutional Review Board (IRB) of the University of Pennsylvania. Attendance at clinic and completing assessments were reinforced using fishbowl contingency management. For each required treatment visit a participant attended, they received draws from a fishbowl, which contained 500 slips, 250 of which had no monetary compensation, 1 of which had a \$100 value, 219 were worth \$1 and 30 were worth \$25. If a participant attended all visits they were eligible to receive a maximum of 176 voucher draws for attendance for visits 1-16. If needed, two transit tokens were provided at each visit.

Eligible subjects entered a one-week baseline phase during which all pretreatment measures were obtained and subjects began psychosocial treatment. Eligible subjects were randomized to receive either modafinil or placebo the following week. Subjects remained on modafinil for eight weeks.

Modafinil 100 mg tablets and identical placebo tablets were provided by the manufacturer. Medications were dispensed by a nurse practitioner each week in a blister pack and the previous week's blister pack was collected. Compliance was measured by pill count.

In addition to medication or placebo, subjects received weekly individual cognitive-behavioral relapse prevention therapy utilizing a Cognitive-Behavioral Coping Skills Therapy (CBT) manual. The CBT therapy manual and supporting materials were developed for the National Institute on Alcohol Abuse and Alcoholism Project MATCH (Kadden, 1992). The basic format was accepted, although specific procedures were adapted for

treatment of cocaine dependence by our group. Master's level therapists with additional training in CBT provided therapy.

2.4. Statistical analysis

Subjects were first compared on a variety of baseline characteristics to assess randomization balance across the two treatment groups, using chi-square tests for categorical characteristics and t tests for continuous characteristics. Non-parametric test were used when the data were skewed. The primary analyses did not include additional covariates; characteristics that showed significant imbalance across the groups were examined as covariates in supplementary analyses.

Generalized estimating equation (GEE) models (Diggle et al., 2002) were used to compare the groups on weekly cocaine, as measured by a combination of two UBT measures obtained from qualitative BE assays, together with self-report based on the TLFB. Each study week was coded as abstinent or not abstinent based on the following definition: a study week was coded as an abstinent week if the participant reported no cocaine use during the study week and provided two negative and no positive UBT during the study week. If the participant reported use, or if they provided at least one positive UBT, during the study week then that week was coded as a use week; otherwise the week was coded as missing. To assess the influence of missing UBT measures, GEE analyses of the UBT measures were performed with (1) missing weeks ignored, (2) with pre-dropout missing tests imputed as positive, (3) with all missing tests imputed as positive, and (4) using pattern mixture models (Molenberghs and Verbeke, 2005) based on the number of available weeks as an indicator of missing data.

Our primary models included terms for treatment groups and for polynomial time effects. We also examined whether group-by-time effects improved the fit of the model. In fitting these models to the data, terms significant at the 5% level were included in the GEE models, as were lower order effects contained in a significant interaction. Empirical standard errors (Wald and Score statistics) were used to assess significance.

Similar models were also used to analyze other repeated outcomes (TLFB, CSSA, ASI-Drug, ASI-Alcohol, ASI-Days Cocaine Use, CGI-O, BSCS). Retention in study was compared using Cox proportional hazards models, and the binary response of being abstinent for the final three weeks of the study was compared using a logistic regression model.

3. Results

3.1. Baseline demographic and drug use

Subjects entered into the trial were drawn from an original group of 174 cocaine users who were screened for the trial. From this original group of 174, 25 were lost to follow up prior to randomization, 48 did not meet inclusion/exclusion criteria and 7 withdrew consent (see figure 1). On the whole, the two medication groups, modafinil and placebo, were very similar in demographics and baseline drug use characteristics (see Table 1). The average age of the subjects was about 47. Most were African American men and most smoked crack

cocaine. On average, subjects had used cocaine about 12 days in the month prior to treatment and spent around \$600 on drugs in the month prior to treatment. The mean ASI composite psychiatric score was significantly higher in the modafinil group (.112 vs. .052, Mann Whitney Test $Z=-2.1$, $p=.04$), otherwise there were no significant differences between the two groups in any baseline demographic or drug use variable.

3.2. Treatment retention

Seventy-one of the 94 subjects (76%) of the subjects completed the trial. Survival analysis of time to dropout showed no significant difference between the groups (see figure 2) (Log rank test = .01, $p=.92$). Treatment retention, measured by the number of visits attended was not significantly different between groups. On average, modafinil-treated subjects attended 12 visits and placebo-treated subjects attended 13 visits ($t=1.1$ $p=.28$).

3.3. UBT Results

Of the 1504 possible UBT tests, a total of 333 (22.14%) were missed. In the placebo group, 142/752 (19%) were missed, and 191/752 (25%) were missed in the modafinil group. A poisson regression model (with overdispersion) showed no significant difference between the groups on the rate of missed UBT tests ($\chi^2(1)=1.32$, $p=0.25$). In the placebo group, 52/142 of the missed tests came prior to dropout, and 90/142 post dropout, compared to 69/191 pre-dropout and 122/191 post-dropout in the modafinil group, so missing data was comprised of about 33% intermittent missingness and 67% dropout, in both groups.

Of the 752 person-weeks, all but ten (1.3%) had either zero days or seven days of available TFB reports. Three of the other ten person-weeks had use reported in the partial week, and were regarded as self-reported use weeks, with the other seven regarded as missing for self-reported cocaine use. For the combined UDS/TLFB weekly response, placebo-treated patients had an average of 6.9 (SD=2.1) non-missing treatment weeks, and modafinil-treated patients averaged 6.3 (SD=2.3), with no significant difference between the groups (KW $\chi^2(1)=2.45$, $p=0.12$). For the analysis with all missing weeks ignored, the group by time interaction was not significant (GEE $\chi^2(1)=0.43$, $p=0.51$), and was dropped from the model. The main effects model showed a significant effect for modafinil (GEE Score Test $\chi^2(1)=4.71$, $p=0.03$), with an estimated odds ratio in favor of abstinence for modafinil versus placebo of 2.54 with 95% CI of (1.12, 5.76). When intermittent missing weeks were imputed as non-abstinent weeks, the corresponding estimated odds ratio was 2.45 (95% CI = (1.08, 5.55)), and the effect was again significant (GEE Score Test $\chi^2(1)=4.37$, $p=0.04$). When all missing weeks were imputed as non-abstinent weeks, the corresponding estimated odds ratio was 2.23 (95% CI = (0.97, 5.09)), and the effect was not significant (GEE Score Test Chi-square(1)=3.41, $p=0.06$).

A pattern mixture analysis showed no interaction between treatment group and the number of missed weeks ($\chi^2(1)=0.01$, $p=0.92$), or with completer/noncompleter status ($\chi^2(1)=0.24$, $p=0.63$). Repeating the above GEE analyses using mixed effects models, which have weaker assumptions on missing data but stronger assumptions on repeated measures structure, yielded essentially the same results. The general agreement across the GEE, pattern mixture, and mixed effects models suggest that the missing data do not have much effect on our main

comparisons. The effect of modafinil is weakened as missing weeks are imputed as nonabstinence weeks, because the modafinil group had slightly more missing weeks than the placebo group.

A comparison of the percent of subjects in each group who were abstinent from cocaine for the last three weeks of the trial, based on self-reported cocaine use supported by UBT results showed a significant difference favoring the modafinil treated subjects (figure 3). For missing ignored, we have 4/39=10% abstinent in the placebo group and 11/36=31% abstinent in the modafinil group, ($\chi^2(1)=4.82$, $p=0.03$). The odds of being abstinent for modafinil are 3.85 those of placebo, with 95% ci of (1.10, 13.50). For missing regarded as use, we have 4/47=9% abstinent in the placebo group and 11/47=23% abstinent in the modafinil group ($\chi^2(1)=3.89$, $p=0.05$), and the odds of being abstinent for modafinil are 3.29 those of placebo, with 95% ci of (0.96, 11.21).

3.4 Results from the Addiction Severity Index

We examined the “previous 30 day” measures of days of cocaine use, dollars spent on drugs, and the seven composite scores. There were no significant group by time interactions (all p -values > 0.12). Days of cocaine use ($p<0.001$), dollars spent on cocaine ($p<0.001$), and the alcohol ($p=0.04$) and drug composite scores ($p<0.001$) decreased significantly across the treatment phase, while the dichotomized family social composite ($=0$ vs >0) increased significantly ($p=0.03$) due to a large increase between weeks 4 and 9. The placebo group was more likely to report psychiatric problems ($p=0.03$, $OR=2.75$, 95% $CI = (1.33, 5.68)$) based on a dichotomized version of the psychiatric composite score ($=0$ vs >0). There were no significant group differences on the other nine variables ($p > 0.11$).

3.6 Results from BSCS

Cocaine craving was measured weekly using the BSCS. Changes in craving over the course of the trial were analyzed using GEE. The BSCS measures cocaine craving intensity, frequency and duration. In GEE logistic regression models comparing the lowest level of each scale (no craving) to the set of higher levels, the placebo group was significantly more likely to report higher levels than the modafinil group for intensity ($OR = 2.04$, 95% $Ci = (1.06, 3.92)$, $p=0.03$) and duration ($OR = 1.89$, 95% $Ci = (1.06, 3.38)$, $p=0.03$); there was a similar effect for frequency ($OR = 1.51$, 95% $Ci = (0.84, 2.73)$) which was not significant ($p=0.11$). Ordinal GEE versions of these models showed violations of the proportional odds assumptions, with larger effects for logit comparing lowest level to all higher levels, and smaller effects for other logits; separate GEE logistic models showed no significant effects for modafinil versus placebo for these other logits, suggesting that the effects were confined to the lowest levels versus all *higher levels*.

3.7 Results for the Clinical Global Impression Scale

The modafinil-treated subjects had slightly higher rates of being rated by the nurse-practitioner as “Very Much Improved” rather than other responses, versus the placebo group ($OR=1.93$, 95% $CI = (0.96, 3.85)$) but the difference was not significant ($p=0.06$). The effect was confined to the comparison of the lowest level versus all higher levels, and an ordinal

model showed no significant difference ($p=0.11$). The modafinil-treated subjects were more likely to rate themselves very much improved ($OR=2.69$, 95% $CI=(1.09, 6.65)$, $p=0.03$).

3.8 Results from the CSSA

The CSSA composite measures overall cocaine withdrawal symptoms. GEE models showed a significant decline in the CSSA composite score over the trial for both groups (GEE $\chi^2(1)=20.26$, $p<0.001$), with no group by time interaction (GEE $\chi^2(1)=0.01$, $p=0.91$), and no main effect of group (GEE $\chi^2(1)=0.36$, $p=0.55$).

3.9 Medication adherence

Medication adherence was measured by pill count. The percentage of pills taken was calculated by subtracting the number of pills returned each week from the number of pills dispensed. Both groups showed very good adherence. On average, patients in the placebo group took 92% of prescribed pills, and patients in the modafinil group took 90% of their prescribed pills ($t = .514$, $df = 92$, $p = .608$).

3.10 Safety analyses

Adverse events were assessed at each visit. Modafinil was well tolerated. Adverse events were mainly mild and generally evenly distributed between the modafinil and placebo groups (see Table 2). The most commonly reported adverse events, at least possibly attributable to study medication, included headaches, insomnia, and anxiety. More modafinil-treated subjects reported insomnia and anxiety compared to placebo-treated subjects but the differences were not statistically significant (Fischers exact test $p>.05$). An elevation in blood pressure that was at least possibly attributable to study medication was noted in six modafinil-treated subjects and none of the placebo-treated subjects. Three of the modafinil-treated subjects who experienced elevated blood pressure had preexisting diagnoses of hypertension or had elevated blood pressure noted in their medical history. Blood pressure elevations were relatively mild (140-170 mm Hg. Systolic and 100-108 mm Hg. Diastolic). The elevations were transient and did not require adjustment in the study medications. One subject had metoprolol added to his hypertension medication regimen. In all cases, blood pressure returned to normal at the end of the trial.

4. Discussion

In this trial, modafinil at a dose of 300 mg daily was superior to placebo at promoting cocaine abstinence in cocaine dependent subjects measured by self-report and verified by UBT. Modafinil treated subjects were more likely to rate themselves as very much improved. Modafinil treated subjects were also more likely to report the lowest levels of cocaine craving intensity and duration measured by the BSCS.

This is the second trial of modafinil in which modafinil was superior to placebo in the predefined primary outcome in the complete sample. In the first controlled trial of modafinil, Dackis and colleagues found that modafinil-treated subjects submitted more negative UBT compared to placebo treated subjects (Dackis et al., 2005). In other trials, post-hoc analyses support the efficacy of modafinil for subgroups of cocaine dependent patients. For instance,

in a multicenter trial of modafinil for cocaine dependence Anderson and colleagues showed that cocaine dependent subjects without comorbid alcohol dependence had significantly more cocaine non-use days if they were treated with modafinil compared to placebo (Anderson et al., 2009). In another trial, Dackis and colleagues found that men treated with modafinil submitted significantly fewer cocaine positive UBT (Dackis et al., 2012).

The inconsistent results of modafinil in cocaine dependent subjects without comorbid alcohol dependence are puzzling. The main difference between this trial and the previous negative trial (Dackis et al. 2012) was medication adherence. In the Dackis et al. 2012 trial, the retention rate was 57% and the 34% urines were missing. In the current trial the retention rate was 76% and only 22% of urines were missing. The more aggressive contingency management practices used to encourage adherence to study procedures in the current trial could account for the difference. It is also possible that the 300 mg dose of modafinil was better tolerated than highest dose in the Dackis et al. 2012 trial (400 mg) but more efficacious than the lower dose (200 mg). In the Dackis et al. 2012 trial, 64% of subjects assigned to modafinil completed the trial compared to 83% in the current trial.

This trial has several limitations. It was a relatively small single site trial. The patients included in this trial were mainly African American residents of a large city who smoked crack cocaine and who did not have comorbid alcohol dependence. Therefore, the results of this trial may not generalize to other populations of cocaine dependent patients, especially cocaine dependent patients with comorbid alcohol dependence. Medication adherence was measured only by pill count and thus may not be accurate.

The strengths of this trial include the outstanding medication adherence, high rate of treatment retention, and consistency among the various outcomes. Slightly more than ninety percent of prescribed study medication was consumed, based on pill counts. Seventy six percent of subjects completed the trial. The secondary efficacy outcomes were consistent with the primary outcome of greater cocaine abstinence in the modafinil treated subjects. Modafinil treated subjects were more likely to rate themselves very much improved compared to placebo treated subjects. Modafinil treated subjects were more likely to report very low levels of cocaine craving intensity and duration compared to placebo-treated subjects.

Cocaine dependent patients are a heterogeneous group and it is unlikely that any one medication will be efficacious for all cocaine dependent individuals. Modafinil has demonstrated efficacy in the subgroup of cocaine dependent patients without comorbid alcohol dependence in three separate trials, including the current trial (Anderson et al., 2009; Dackis et al., 2005). Although concurrent use of cocaine and alcohol is common (Grant and Harford, 1990) current alcohol dependence is estimated to be present in only 30% of cocaine dependent patients and lifetime alcohol dependence in about 60% (McCance-Katz et al., 1998). In the Anderson trial, the subgroup of cocaine dependent subjects without a current or lifetime history of alcohol dependence represented 59% of the overall sample (Anderson et al., 2009). Thus, modafinil could be effective for a large number of cocaine dependent patients. The results of this trial support the continued study of modafinil and related compounds for the treatment of cocaine dependence.

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Highlights

- This was a double blind placebo controlled trial of modafinil for cocaine dependence
- It involved 94 subjects treated with 300 mg of modafinil or placebo daily for 8 weeks
- Modafinil treated subjects were more likely to achieve cocaine abstinence
- Modafinil treated subjects were more likely to report very low levels of cocaine craving
- Modafinil treated subjects were more likely to rate themselves very much improved

Figure 1. Patient flow

Figure 2. Treatment retention

Figure 3. Percent of subjects abstinent from cocaine during weeks 6-8

Table 1

Subject characteristics, expressed as percents or means (standard deviation).

Variable	Modafinil N=47	Placebo N=47
Age	47 (8.1)	46 (9.4)
% Male	81%	81%
Race		
African American	81%	68%
Caucasian	19%	32%
Years of education	12.9 (2.0)	12.9 (2.4)
Days of cocaine use in past 30 days	12 (8)	12 (8)
Years of cocaine use, lifetime	13 (8)	12 (8)
Days of alcohol use in past 30 days	5 (7)	5 (8)
\$ spent for drugs	\$588 (549)	\$616 (737)
\$ spent for alcohol	\$13 (20)	\$23 (36)
Route of cocaine use		
Intranasal	11%	17%
Smoked	89%	79%
Injected	0%	4%
ASI Composite Drug Score	.230 (.055)	.240 (.075)
ASI Composite Alcohol Score	.066 (.099)	.086 (.117)
ASI Composite Employment Score	.657 (.274)	.671 (.250)
ASI Composite Legal Score	.046 (.135)	.065 (.162)
ASI Composite Family/Social Score	.143 (.181)	.096 (.160)
ASI Composite Psychiatric Score *	.112 (.156)	.052 (.110)
ASI Composite Medical Score	.256 (.326)	.251 (.330)

* significantly different (Mann Whitney Z= -2.1 P= .04)

Table 2

Adverse events at least possibly medication associated reported by 10% or more of subjects.

Adverse event	Modafinil n =47	Placebo n= 47
Headache	12.8%	14.9%
Insomnia	21.3%	6.4%
Anxiety	14.9%	4.3%

Fisher's exact test $P > .05$ in all cases.