Neuropsychopharmacology (2005) 30, 205–211

www.neuropsychopharmacology.org

A Double-Blind, Placebo-Controlled Trial of Modafinil for Cocaine Dependence

Charles A Dackis*[,1], Kyle M Kampman[1], Kevin G Lynch[1], Helen M Pettinati[1] and Charles P O'Brien[1,2]

[1]University of Pennsylvania School of Medicine, Philadelphia, USA; [2]Department of Veterans Affairs Medical Center, Philadelphia, USA

Despite years of active research, there are still no approved medications for the treatment of cocaine dependence. Modafinil is a glutamate-enhancing agent that blunts cocaine euphoria under controlled conditions, and the current study assessed whether modafinil would improve clinical outcome in cocaine-dependent patients receiving standardized psychosocial treatment. This was a randomized, double-blind, placebo-controlled trial conducted at a university outpatient center (from 2002 to 2003) on a consecutive sample of 62 (predominantly African American) cocaine-dependent patients (aged 25–63) free of significant medical and psychiatric conditions. After screening, eligible patients were randomized to a single morning dose of modafinil (400 mg), or matching placebo tablets, for 8 weeks while receiving manual-guided, twice-weekly cognitive behavioral therapy. The primary efficacy measure was cocaine abstinence based on urine benzoylecgonine levels. Secondary measures were craving, cocaine withdrawal, retention, and adverse events. Modafinil-treated patients provided significantly more BE-negative urine samples ($p = 0.03$) over the 8-week trial when compared to placebos, and were more likely to achieve a protracted period ($\geqslant 3$ weeks) of cocaine abstinence ($p = 0.05$). There were no serious adverse events, and none of the patients failed to complete the study as a result of adverse events. This study provides preliminary evidence, which should be confirmed by a larger study, that modafinil improves clinical outcome when combined with psychosocial treatment for cocaine dependence.

Neuropsychopharmacology (2005) **30,** 205–211, advance online publication, 3 November 2004; doi:10.1038/sj.npp.1300600

Keywords: modafinil; cocaine; glutamate; pharmacotherapy; abstinence; addiction

INTRODUCTION

Cocaine dependence is a major public health problem that is characterized by recidivism and a host of medical and psychosocial complications. An effective pharmacotherapy has long been sought to improve treatment outcomes, particularly since this disorder has a significant neurobiological basis (Volkow and Fowler, 2000; Dackis and O'Brien, 2001; Ahmed *et al*, 2002). Although proven pharmacotherapies are available for alcohol and heroin dependence (O'Brien, 2001), none exist for cocaine dependence despite two decades of clinical trials primarily involving antidepressants, anticonvulsants, and dopaminergic medications. Testing glutamate-enhancing agents is a new and promising strategy based on recent findings that cocaine dysregulates reward-related glutamate pathways (Thomas *et al*, 2001; Dackis and O'Brien, 2003; Kalivas *et al*, 2003).

*Correspondence: CA Dackis, University of Pennsylvania Treatment Research Center, 3900 Chestnut Street, Philadelphia, PA 19104, USA, Tel: +1 215 662 8752, Fax: +1 215 243 4665,
E-mail: dackis@mail.med.upenn.edu
Received 8 June 2004; revised 23 September 2004; accepted 24 September 2004
Online publication: 24 September 2004 at http://www.acnp.org/citations/NPP092904040253/default/pdf

Modafinil is a wake-promoting agent that is approved for narcolepsy. Its glutamate-enhancing action (Ferraro *et al*, 1998, 1999) might be clinically advantageous in cocaine dependence because the repeated administration of cocaine depletes extracellular glutamate levels (Keys *et al*, 1998; Bell *et al*, 2000; Hotsenpiller *et al*, 2001; Kalivas *et al*, 2003), and reduces glutamatergic synaptic strength in the nucleus accumbens (Thomas *et al*, 2001). Furthermore, it has recently been demonstrated that normalizing extracellular glutamate levels with *N*-acetylcysteine abolishes cocaine-induced reinstatement, an animal model of relapse (Baker *et al*, 2003). Modafinil has also been proposed as a cocaine detoxification agent (Dackis *et al*, 2003). Cocaine withdrawal symptoms (see Table 1) predict poor outcome (Kampman *et al*, 2001), and modafinil would be expected to reverse these symptoms as it is activating (Dackis *et al*, 2003). In addition, it has recently been reported that patients with baseline cocaine withdrawal (Sofuoglu *et al*, 2003), and abstinence-related depression and irritability (Newton *et al*, 2003), report enhanced euphoria after cocaine administration under controlled conditions, suggesting that the reversal of cocaine withdrawal might be clinically advantageous. Modafinil is a reasonable medication for cocaine-dependent individuals because it has low abuse potential (Jasinski, 2000; Jasinski and Kovacevic-

Table 1 Clinical Effects of Modafinil are Largely Opposite to Cocaine Withdrawal Symptoms

Cocaine withdrawal	Modafinil effects
Hypersomnia	Increased wakefulness
Depression	Improved mood
Fatigue	Increased energy
Poor concentration	Improved attention and vigilance
Psychomotor retardation	Locomotion (in animals)
Increased appetite	Reduced feeding (in animals)
Enhanced cocaine euphoria	Blunted cocaine euphoria

Ristanovic, 2000; Rush *et al*, 2002a, b), neurochemical effects that differ markedly from those of psychostimulants (Lin *et al*, 1996; Ferraro *et al*, 1997), and good tolerability (Becker *et al*, 2004).

Given these considerations, we began to investigate modafinil in cocaine-dependent patients some time ago by conducting a drug interaction study. This study not only found that modafinil was safely co-administered with intravenous cocaine, but also reported that modafinil significantly blunted cocaine-induced euphoria under controlled conditions (Dackis *et al*, 2003). The consistency of this interesting property was strengthened by another controlled study reporting attenuated cocaine euphoria in modafinil-treated patients (Malcolm *et al*, 2002). We subsequently conducted an open-label modafinil trial and reported high levels of cocaine abstinence in patients experiencing severe cocaine withdrawal at baseline (Dackis and O'Brien, 2003). The current study is a randomized, double-blind, placebo-controlled, 8-week trial of modafinil in 62 cocaine-dependent outpatients.

PATIENTS AND METHODS

Study Participants

We randomized 62 treatment-seeking patients (44 male, 18 female; mean age 44.5, SD 8.7; age range 25–63) from the greater metropolitan Philadelphia area. Patients gave written informed consent to participate in this trial, which was approved by the University of Pennsylvania Human Investigations Committee, and informed consent comprehension was assessed with a quiz that was re-administered until completely correct. Patients were required to meet Diagnostic and Statistical Manual of Mental Disorders (DSM IV) criteria for cocaine dependence, and to have used at least $200 worth of cocaine in the past 30 days. Individuals were excluded if they were dependent on any substance other than cocaine or nicotine, had serious active medical illness (including uncontrolled hypertension, significant cardiac, renal, or hepatic disease, or life-threatening or progressive illness), psychiatric illnesses (history of bipolar disorder, active psychosis, current major depression), required psychotropics or medications that might interact with modafinil, or had significantly abnormal baseline laboratory tests. Pregnant women were excluded and, since modafinil induces the metabolism of steroidal contraceptives, women of childbearing potential were required to use other acceptable birth control methods.

Study Design

This was a randomized, double-blind, placebo-controlled 8-week trial of modafinil for cocaine dependence. Enrollment began in September 2002, ended in October 2003, and the pilot study was completed in December 2003 to determine whether a larger study was justified. The 2-week screening period (3–4 visits) included a comprehensive physical examination and history, blood counts (red and white cells, platelets, hemoglobin, hematocrit), blood chemistries (electrolytes, blood urea nitrogen, creatinine, total protein), liver function tests (bilirubin, alkaline phosphatase, aspartate aminotransferase, alanine amino transferase), urinalysis, urine pregnancy test for women, and a 12-lead ECG. This entire medical evaluation was repeated 4 and 9 weeks after randomization. The diagnosis of current cocaine dependence was confirmed with a Structured Clinical Interview for DSM IV (SCID) (First *et al*, 1996), and other psychiatric disorders were ruled out with the mini-international interview (Sheenan *et al*, 1997). After screening, 62 eligible patients were randomized (with a computer generated code) to receive modafinil 400 mg/day ($n = 30$) or matching placebo ($n = 32$) for 8 weeks. The research pharmacist generated the allocation sequence, assigned participants to their groups, and was the only person aware of the medication assignment code that was kept in a sealed envelope for emergency access. None of the research personnel, who enrolled, treated, and assessed the patients, were aware of the patient assignments until the study was concluded. The study physician dispensed modafinil or matched placebo pills (supplied by Cephalon, Inc.) to patients in weekly blister packs that contained a 9-day supply in case of a missed visit. Treatment was initiated with a single morning dose of 4 pills/day (each containing 100 mg of modafinil or placebo), and discontinued without taper after 8 weeks. The study physician had the option to reduce the dosage in one-pill increments, to a minimum of 2 pills/day, if tolerability problems emerged.

The entire study was conducted at the University of Pennsylvania Treatment Research Center, and included thrice-weekly research technician assessments and weekly physician assessments for adverse events, global improvement, and concomitant medications. Patients were asked to attend the clinic three times per week, and provide urine samples during each visit. Two of these sessions included CBT counseling, and at least one session per week included an assessment by the study physician, who dispensed a blister pack (9-day supply of study medications that they took without staff observation) that was to be returned the following week for adherence assessment. Patients were paid $5 for each blister pack returned. Individual, manual-guided CBT (Kadden *et al*, 1992) (adapted for substance abuse) was provided twice weekly for 8 weeks, and CBT sessions were audiotaped and reviewed for clinician manual adherence by the supervising therapist. A follow-up end of medication assessment was scheduled 1 week after the study medications were discontinued.

Outcome Measures, Schedule of Assessments, and Sample Size

The primary efficacy measure for this trial was cocaine abstinence based on thrice-weekly qualitative urinary benzoylecgonine (BE) levels, and we hypothesized that modafinil-treated patients would supply more BE-negative urine samples than placebo-controlled patients over the 8-week trial. Urine temperatures were measured at the time of collection and acceptable samples (temperatures between 94° and 99° Fahrenheit) were analyzed with a fluorescent polarization assay. Urine samples containing BE at concentrations $\geqslant 300$ ng/ml were considered to be positive for cocaine. Secondary efficacy measures included the weekly physician-rated Clinical Global Impression—Objective Scale (CGI-O), (Guy, 1976) self-reported cocaine use on the Timeline Follow-Back Interview (TLFB) (Sobell and Sobell, 1992) and Clinical Global Impression Scale—Subjective (CGI-S) (Guy, 1976), and cocaine withdrawal/craving measured by the Cocaine Selective Severity Assessment (CSSA) (Kampman *et al*, 1998), Brief Substance Craving Scale (BSCS) (Somoza *et al*, 1995), and Cocaine Craving Questionnaire (CCQ) (Tiffany *et al*, 1993). In addition, baseline demographics and clinical characteristics were assessed with the Addiction Severity Index (ASI) (McLellan *et al*, 1992), Hamilton Anxiety Scale (Ham A) (Hamilton, 1969), and Hamilton Depression Scale (Ham D) (Hamilton, 1967), Beck Depression Inventory (BDI) (Beck *et al*, 1974), and the Symptom Checklist 90 Revised (SCL90) (Derogatis, 1977). Safety data were collected weekly, and included vital signs (blood pressure, pulse, temperature), body weight, and adverse events documented by the study physician on a standardized form.

Statistical Analysis

The analysis was by intention-to-treat. The patients were compared on a variety of baseline characteristics, using χ^2 tests for categorical characteristics, and *t*-tests for continuous characteristics, to assess how well the randomization had balanced patient characteristics across the two (moderately sized) treatment groups. The primary analyses did not include additional covariates, but characteristics that showed significant imbalance across the groups were considered for inclusion as covariates in supplementary analyses, together with characteristics known to be of importance such as cocaine positive urine at baseline.

The repeated binary outcomes obtained from the quantitative BE assays were analyzed using generalized estimating equation (GEE) models (Diggle *et al*, 2002). In these analyses, missing urine screens were imputed as positive, which is a standard practice in clinical trials for which cocaine abstinence is a primary outcome (Shoptaw *et al*, 2002), although it does create a bias against treatment dropouts. Other repeated outcomes (CGI-O, CGI-S, TLFB, CSSA, BSCS, CCQ) were also analyzed using GEE models for continuous or count responses. In all the repeated measures analyses, the models included terms for treatment group (placebo *versus* modafinil), together with linear and quadratic time effects, and some group by time interactions. Quadratic time effects were included in the models to allow for the possibility that rates of cocaine use might decrease (or increase) early in treatment, and remain at a lower (or higher) level through the rest of the trial. Group by quadratic time interactions allow these patterns to be different for the different groups. In fitting these models to the data, terms were included in the GEE models if they were significant at the 5% level, and lower order effects contained in a significant interaction effect were also included. Model-based standard errors (Wald statistics) were used to assess significance.

RESULTS

Baseline Measures

There were no significant (5% level) differences between the modafinil and placebo groups on a battery of measures drawn from the baseline ASI, TLFB, Ham A, Ham D, BDI, SCL-90, and CSSA. A selection of important baseline demographic, clinical, and psychosocial characteristics of enrolled patients are listed in Table 2. As race, mean weekly cocaine cost, mean days of weekly use, and years of lifetime cocaine use were significant at the 10% level, they were included as covariates in supplementary GEE analyses.

Pill Compliance

There were no significant differences between the modafinil and placebo group on pill compliance or pill overuse. A total of 41 patients (21 placebo, 20 modafinil) had at least 1 week where they did not return all of the expected unused

Table 2 Baseline Characteristics as Percentages or Means (Standard Deviations) with *p*-Values Based on χ^2 Tests for Categorical Variables, or *t*-Tests for Continuous Characteristics

Characteristics	Modafinil ($n=30$)	Placebo ($n=32$)	*p*-value
Demographic			
Age	46 (8.4)	43 (8.4)	0.28
% Males	67%	75%	0.47
% Married	23%	31%	0.49
Race (% African American)	90%	72%	0.07
Total years of education	12 (2.1)	13 (1.9)	0.27
Days in last 30 employed	11 (9.9)	15 (9.9)	0.11
Clinical			
% crack (smoking) use	87%	88%	0.92
% BE-positive baseline urines	63%	78%	0.20
CSSA scores at baseline	16 (12.1)	21 (13.2)	0.15
Days of cocaine use/week	2.0 (1.8)	2.9 (2.1)	0.07
Weekly cocaine cost	115 (113.8)	180 (203.3)	0.10[a]
Years of cocaine use	14 (7.2)	11 (7.0)	0.10
Hamilton Anxiety Scale	7.4 (5.4)	8.7 (5.9)	0.36
Hamilton Depression Scale	12 (8.9)	14 (9.9)	0.31
Beck Depression Inventory	9.9 (7.5)	12.6 (9.7)	0.26
SCL-90 total score	30 (30.1)	53 (63.1)	0.30[a]

[a]Log-transformation performed prior to comparison of means.

pills in their blister packs (9-day supply given weekly). A χ^2 test showed no difference in the group proportions with at least one such week (χ^2 (1) = 0.01, $p = 0.93$). In each group, the median number of weeks in which unprescribed modafinil pills were retained 2 (third quartile of 3), and a Mann–Whitney test of the number of weeks of unprescribed pill retention among these patients showed no differences between the two groups ($Z = -0.14$, $p = 0.99$). Across weeks in which an excess of pills were used, the total numbers of excess pills were also very similar: the mean 8-week-total overused was 11.82 (SD = 8.25) in the placebo patients, and 12.80 (8.52) in the modafinil patients (Mann–Whitney Z-score = −0.33, $p = 0.77$). When queried, patients typically stated they could not recall, or were reluctant to disclose, why they did not return the extra blister packaged pills. Three modafinil-treated and four placebo-treated patients retained more than 16 of the extra 64 pills supplied over 8 weeks.

Treatment Retention

In the modafinil group, 19/30 (63.3%) of patients were still present at the end of the eight weeks, compared to 21/32 (65.6%) in the placebo group. Also, for each group, the median time to drop out was 24 visits. When defined as failing to complete the first 2 weeks of treatment, there were two dropouts in the modafinil group, and three in the placebo group. A log-rank test showed no significant difference in the distribution of time to drop out (χ^2 (1) = 0.79, $p = 0.37$). There was no significant difference with regard to CBT attendance for the modafinil (50.0%) compared to the placebo (54.6%) groups ($t(60) = 0.64$, $p = 0.53$).

Cocaine Abstinence

The trial was designed to obtain 24 urines from each patient during medication treatment. The percent obtained of expected urines for the modafinil group was 74.5%, and for the placebo group was 63.0%: a t-test showed that the average number of urines provided was not significantly different across the two groups ($t(60) = 1.58$, $p = 0.12$). Figure 1 shows the within-group percentages of BE-negative urines provided across the study. The mean proportion of BE-free urines supplied (calculated for each patient as a percentage of the 24 requested) was 42.3% for the modafinil group, and 24.0% for the placebo group. A full GEE model of the log-odds of a clean urine *vs* a missing or dirty urine screen showed significant group by quadratic time ($Z = -2.25$, $p = 0.02$) and group by linear time ($Z = 2.49$, $p = 0.01$) effects. Examination of predicted probabilities of BE-negative urine ('abstinent visit') suggested that the groups had similar initial probabilities of a BE-negative urine (0.29 for modafinil, 0.25 for placebo), that these probabilities decreased steadily in the placebo group (0.23 at week 5 and 0.18 at week 8), and initially increased and later decreased in the modafinil group (0.46 at week 5 and 0.32 at week 8). (Note: If significance was assessed using the more conservative (Stokes *et al*, 2000) empirical standard errors, then the group by quadratic effect was not significant ($p = 0.09$), and dropping further nonsignificant terms from the model yielded a final model with a significant main effect for cocaine abstinence in the modafinil group (odds ratio = 2.41, 95% CI = (1.09, 5.31), $p = 0.03$), compared to placebos, together with a significant quadratic time effect.) Analyses adjusting for race, and for baseline measures of mean weekly cocaine cost, mean days of weekly use, and years of lifetime cocaine use, yielded virtually identical estimates to those given by unadjusted analyses.

The baseline level of cocaine use has been reported to be an important predictor of treatment outcome (Kampman *et al*, 2001). In this study, there was a trend towards a higher proportion of BE-positive urines at baseline in the placebo group compared to the modafinil group. A complex model was formulated that included terms representing baseline urine BE status and its interactions with treatment group and time. There was a significant group by baseline status by quadratic time effect ($p = 0.01$), indicating significantly different quadratic trends across the four groups (baseline BE status by treatment condition). Table 3 shows the estimated probabilities of an abstinent visit at the beginning, middle, and end of the 8 weeks, for each of the four groups.

As expected, based on previous work, the dominant effect is that people with a BE-negative baseline status are more likely to attain abstinent visits during the study. Within each level of baseline status, the modafinil effect is similar to that observed in the analyses described above: the groups are similar at the beginning, the modafinil group appears to improve more than the placebo group through the first 5 weeks, and the groups are similar at the end of the 8 weeks.

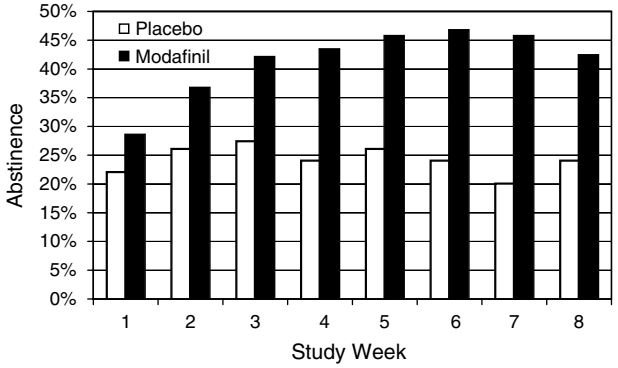

Figure 1 Weekly cocaine abstinence in modafinil and placebo groups, defined as the percentage of urine samples that were (1) submitted (requiring attendance), and (2) found to be BE-negative. Missing urines are therefore imputed as positive.

Table 3 Estimated Probabilities of an Abstinent Visit at the Beginning, Middle, and End of the 8-Week Trial for the Placebo and Modafinil Groups, According to Baseline BE Status

Tx group; baseline BE status	Week 1	Week 5	Week 8
Placebo; BE-negative	0.68	0.46	0.56
Modafinil; BE-negative	0.64	0.61	0.45
Placebo; BE-positive	0.13	0.19	0.14
Modafinil; BE-positive	0.11	0.30	0.10

In addition to this effect, a greater percent of the modafinil (33%) than placebo (13%) were able to attain prolonged abstinence, as defined by the achievement of 3 consecutive weeks of BE-negative urines (none missing) during any time period ($\chi^2 = 3.84$, df = 1, $p = 0.05$).

Patient-Reported Use (TLFB, CGO-S)

There were no significant modafinil effects on self-reported (TLFB) rates of cocaine use (GEE model Z-score = 0.35, $p = 0.73$), or on dollars spent on cocaine (GEE model Z-score = −1.08, $p = 0.28$). CGI-S showed no differences between modafinil and placebo groups in reported cocaine severity (GEE model Z-score = −0.37, $p = 0.72$) or functional impairment.

Physician-Rated Assessments

The CGI-O summary scales were rated weekly by the study physician. The modafinil group showed consistently lower overall severity scores, and consistently greater improvement scores, although these differences did not reach significance: for the Global Severity of Cocaine Dependence Scale (GEE model Z-score = −1.47, $p = 0.14$); for the Global Improvement of Cocaine Dependence of the CGI-O (GEE model Z-score = −1.88, $p = 0.06$).

Cocaine Craving and Withdrawal (CSSA, BCSC, CCQ)

There were no treatment group differences in the total CSSA scores (mixed effects model $F(1, 57) = 0.75$, $p = 0.34$) over the 8 weeks. For the intensity of craving item, there were significant group by linear (GEE model Z-score = −3.16, $p = 0.002$) and group by quadratic (Z-score = 3.10, $p = 0.002$) time effects. Each group showed a decrease in scores, and the modafinil group showing a greater initial decline in scores. However, while modafinil group means were consistently lower than those of the placebo group, within-time-point contrasts showed no significant group differences at any point. Similar results were found for the frequency of craving item: there were significant group by linear (Z-score = −2.91, $p = 0.004$) and group by quadratic (Z-score = 3.10, $p = 0.002$) time effects, but no significant group differences at any point. There were no significant treatment group differences in the BCSC intensity (Z-score = 0.47, $p = 0.64$), frequency (Z-score = −0.35, $p = 0.73$), length of time (Z-score = −0.08, $p = 0.94$), and number of times (Z-score = −1.52, $p = 0.13$) scales or in the CCQ total score (Z-score = −0.76, $p = 0.45$).

Tolerability

There were no medication-related serious adverse events, and none of the patients discontinued modafinil due to adverse events. There were no clinically significant differences between the two groups with regard to laboratory, vital sign, electrocardiogram, body weight, or physical examination findings. Adverse events occurring in at least 5% of modafinil patients, and with at least twice the incidence of occurrence in placebo patients, included: nausea (23%), upper respiratory symptoms (17%), anxiety (13%), tachycardia (13%), urinary tract infection (10%), dizziness (7%), reduced appetite (7%), racing thoughts (7%), and dry mouth (7%). None of the patients ascribed euphoria or cocaine-like effects to the study medications. Dose reductions due to adverse events were made in six of 30 modafinil-treated patients, from the initial dose of 400 to 300 mg/day ($n = 2$) or 200 mg/day ($n = 4$), and adverse events subsequently resolved in each case (see Table 4). Dose reductions were not made for any of the placebo-treated patients.

DISCUSSION

The current study found that modafinil-treated patients provided a significantly greater proportion of BE-negative urine samples than placebo-treated patients over the 8-week clinical trial. Also, a significantly greater number of modafinil-treated patients attained the important clinical goal of protracted cocaine abstinence. It is important to note that missing urines were imputed as positive in our analysis. This approach is widely used in cocaine treatment research, based on the assumption that missing urine samples are not ignorable (and more likely to be positive), but it makes clinic attendance an essential factor in the definition of abstinence and may represent a limitation in our study. Both groups received an equivalent number of CBT sessions, further attributing improved outcome to modafinil administration. Although enrolled patients were predominantly African Americans living in an urban setting, other demographic and clinical characteristics are reasonably consistent with the general cocaine-dependent population. Modafinil was well tolerated with a dose

Table 4 Clinical Information Regarding Six (20% of Total) Modafinil-Treated Patients Requiring Dose Reductions from the Initial 400 mg/day

Modafinil patients	Week dose reduced	End dose of modafinil (mg/day)	Retention after modafinil reduction	Reason for modafinil dose reduction
#17	3	200	Completed study	Insomnia
#19	4	200	Completed week 7	Headache, dizziness
#30	2	300	Completed study	Nausea
#43	2	200	Completed week 6	Nausea, Lightheaded
#53	6	200	Completed study	Tachycardia
#57	2	300	Completed week 5	Anxiety

titration option, there were no serious adverse events, and there were no medication-associated dropouts.

Even though modafinil is pharmacologically distinct from classic psychostimulants (Lin *et al*, 1996; Ferraro *et al*, 1997), it is listed on Schedule IV as having mild abuse potential. Consequently, we carefully monitored the possibility of modafinil overuse and our data showed no discernible evidence of this phenomenon. None of the patients enrolled in this study ascribed cocaine-like effects to their study medication, and blister pack compliance data showed no evidence of modafinil compared to placebo overuse. Both groups had a small and equivalent tendency to retain extra pills that were supplied in their blister packs, but it is unclear whether the pills were ingested, hoarded, lost, or otherwise disposed. Still, since pertinent animal (Gold and Balster, 1996; Deroche-Gamonet *et al*, 2002) and human (Jasinski, 2000; Rush *et al*, 2002a, b) studies suggest that modafinil might be weakly reinforcing, overuse should be further assessed in future trials with this population.

None of the secondary efficacy measures attained significance, although physician-rated improvement showed a trend ($p = 0.06$) for the modafinil group. There was no evidence that modafinil reduced cocaine craving, which is notoriously difficult to quantify. There was also no evidence that modafinil reversed cocaine withdrawal, but our study was not designed to assess this possibility and the majority of enrolled patients had insignificant cocaine withdrawal at baseline. Detoxification remains an important research question because patients with cocaine withdrawal symptoms have poor clinical outcome (Kampman *et al*, 2001), and enhanced euphoric responses to cocaine (Newton *et al*, 2003; Sofuoglu *et al*, 2003). Modafinil promotes feelings of well-being (Beusterien *et al*, 1999) has clinical effects that are largely opposite to cocaine withdrawal symptoms, and blunts cocaine-induced euphoria. It is possible that the steady improvement seen in modafinil-treated patients (see Figure 1) reflects the effect of diminished reward on their cocaine use.

Although we report significant objective improvement (clean urines) with modafinil, our results are limited by the sample size, the subjective nature of craving and withdrawal questionnaires, and the fact that a substantial proportion of our patients had a cocaine-negative sample at baseline. While our assessment of baseline cocaine use might have been different had we collected multiple urine samples during screening, it is also possible that our patients had only moderate addiction severity, and a greater likelihood of responding to placebo treatment. On the other hand, although not statistically significant, the modafinil group had fewer days of cocaine use, fewer cocaine-positive urines, and lower cocaine withdrawal scores (although more years of cocaine use), so baseline differences may have created a disadvantage for the placebo group. Another study weakness is that medication adherence was only confirmed by pill counts. Finally, our subjects received manual-guided CBT, which might not generalize to the clinical setting where this treatment is seldom available. Nevertheless, we did find that modafinil significantly improved cocaine abstinence in this randomized, controlled pilot study, suggesting that further research should be conducted to determine whether modafinil might become a first-line treatment for cocaine dependence.

ACKNOWLEDGEMENTS

Financial disclosures: Dr Dackis has participated in the Cephalon speakers' bureau. Dr O'Brien was a consultant to Cephalon approximately 10 years ago.

Author contributions: Dr Dackis, as principal author of this article, and Dr Lynch, as principal statistician for the analysis, had full access to all study data and take responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Dackis, Kampman, Pettinati, O'Brien, Lynch

Statistical expertise: Lynch

Obtained funding: O'Brien, Pettinati

Administrative, technical, or material support: O'Brien, Pettinati, Kampman

Study supervision: Dackis, O'Brien

Funding/support: Funding for this trial was provided by the National Institute of Drug Abuse (NIDA) with NIDA Grants DA P60-05186 and DA P50-12756. Cephalon provided modafinil and matched placebo tablets.

Investigators: Dackis, Kampman, Pettinati, O'Brien

Role of sponsor: Dr Dackis was the sponsor and was the principal investigator.

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