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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 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.

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

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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 et al. (2008) found that modafinil reduced cocaine self-administration in a human laboratory trial.

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 et al. (2012) 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 et al. (2014, 2012) found that modafinil to be ineffective for the treatment of cocaine dependence in cocaine dependent subjects without comorbid alcohol dependence.

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 et al., 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 follow-back (Sobell and 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°, or greater than 100° F 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 et al., 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 et al., 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 et al., 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