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Modafinil and sleep architecture in an inpatient–outpatient treatment study of cocaine dependence

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ABSTRACT

Objective: To determine whether the increase in slow-wave sleep associated with modafinil treatment in chronic cocaine users mediates improved clinical outcomes.
Method: 57 cocaine dependent participants were randomized to receive modafinil 400 mg or placebo daily during a period of inpatient treatment followed by six weeks of outpatient treatment. Participants underwent polysomnographic sleep recording during inpatient treatment prior to and after starting modafinil. Outpatient treatment consisted of weekly cognitive behavioral therapy. Contingency management was used to promote participation in treatment and research demands, including thrice weekly visits during the outpatient phase for urine toxicology screens and other assessments. The primary clinical outcome was the percent of urine toxicology screens that were negative for cocaine.
Results: Modafinil treatment was associated with a higher mean percentage (52% vs. 26%) of cocaine-free urine screens ($p = 0.02$) and an increase in N3 sleep time ($p = 0.002$). The change in N3 sleep time mediated the higher rate of cocaine-free urine screens. Modafinil treatment was also associated with more consecutive days abstinent during outpatient treatment, greater survival of abstinence, higher daily rates of abstinence, and less sleep degradation typically associated with abstinence from chronic cocaine use.
Conclusions: Morning-dosed modafinil improves slow-wave sleep in abstinent cocaine users in the inpatient setting, and this effect is a statistical mediator of improved clinical outcomes associated with continued modafinil treatment. The high rates of abstinence achieved in this trial suggest that promoting healthy sleep physiology in an inpatient setting may be important in the effective treatment of cocaine dependence.

1. Introduction

Despite reductions in prevalence since the late 1990s, cocaine use continues to be a significant problem in the United States, with approximately three to five times more cocaine users than heroin users (SAMHSA, 2014). However, the number of persons receiving treatment for cocaine use is only comparable to the number of persons receiving treatment for heroin use (SAMHSA, 2014). Likely contributing to this discrepancy is the increasing availability of FDA-approved medications for opiate dependence, and the lack of any approved medication for the treatment of cocaine dependence.

To identify potential treatments, understanding the physiological changes associated with chronic cocaine use is paramount (Morgan et al., 2010). Previous work has identified dramatic alterations in sleep architecture associated with chronic use as examples of targetable neurophysiological abnormalities (Angarita et al., 2014a,b; Morgan and Malison, 2008; Morgan et al., 2010, 2006; Pace-Schott et al., 2005). These alterations include profound and largely stable deficits in slow-wave sleep as well as alterations in REM sleep and total sleep time (Angarita et al., 2014b; Matuskey et al., 2011; Morgan et al., 2010, 2006, 2008). Deficits in slow-wave

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sleep are particularly troubling as slow-wave sleep time is typically preserved despite significant sleep restriction (Van Dongen et al., 2003). Furthermore, such deficits are associated both with clinical disorders and impairments in a wide range of cognitive functions including sensory, motor, and declarative learning, as well as executive function and alertness (e.g., Bellesi et al., 2014; Roth et al., 2010). Unfortunately, most pharmacological interventions that target sleep do not affect slow-wave sleep, or actually diminish slow-wave sleep while increasing the time spent in lighter sleep (e.g., Achermann and Borbely, 1987). Sedating medications that increase slow-wave sleep like gamma hydroxybutyrate (Mamelak et al., 1977) and gaboxadol (Faulhaber et al., 1997) are associated with safety concerns, can have unnatural effects on sleep architecture (e.g., tiagabine; Morgan and Malison, 2008), and/or produce slow-wave activity that differs from physiological slow-waves (Vienne et al., 2012). However, in abstinent cocaine users, daytime use of stimulants increases nocturnal slow-wave production (Morgan et al., 2010, 2006). In particular, we found previously that morning dosing of the stimulant modafinil, which has little effect on sleep architecture in other populations (Roth et al., 2007), normalizes slow-wave sleep time and reduces other sleep deficits in abstinent cocaine users (Morgan et al., 2010).

Modafinil has been regarded as a potential treatment for cocaine dependence for over 15 years, based on its dopaminergic and glutamatergic effects (Dackis et al., 2003). Early studies showed that modafinil could increase the rate of cocaine-free urine screens (Dackis et al., 2005) and reduce laboratory cocaine self-administration (Hart et al., 2008) in persons with cocaine dependence. Since then, outpatient, abstinence initiation treatment studies have cast doubt on its efficacy by not finding statistically significant main effects (e.g., Schmitz et al., 2012). However, secondary and post-hoc analyses in the two larger studies (Anderson et al., 2009; Dackis et al., 2012) showed evidence for positive effects on cocaine use measures like the maximum number of consecutive days of abstinence achieved and rates of cocaine-free urine screens. Recently, an outpatient trial in cocaine users without alcohol dependence confirmed these findings, finding positive effects of modafinil on clinical outcomes (Kampman et al., 2015).

A potential concern with modafinil as a treatment for cocaine dependence is abuse liability. However, despite evidence that modafinil shows reinforcing effects when given to humans in a laboratory setting (Stoops et al., 2005), and has alerting effects similar to D-amphetamine (Makris et al., 2007), subjective drug effects from modafinil (e.g., similarity to amphetamine) are not consistently observed (Jasinski, 2000). Furthermore, although modafinil, like cocaine, is a dopamine transporter (DAT) blocker, it binds differently, less potently, less efficaciously, and for longer duration to the DAT than does cocaine (Loland et al., 2012). These factors, along with its slow onset of action and formulation that is resistant to alteration and parenteral use, are likely why modafinil appears to have a low propensity for abuse. Notably, there are only rare case reports of dependence in locations where it is available over the counter and used widely as a "lifestyle" drug (e.g., Kate et al., 2012).

Based on modafinil's apparent clinical effectiveness in treating cocaine dependence, its normalization of slow-wave sleep, and its relatively low propensity toward abuse, we studied modafinil's effects on sleep and clinical outcome in chronic users of cocaine. We hypothesized that modafinil would have a positive effect on clinical outcome in a relapse prevention study, and that this effect would be related to its promotion of slow-wave sleep measured during an initial period of controlled abstinence. Specifically, we hypothesized that modafinil treatment would be associated with an increase in slow-wave sleep and a greater frequency of cocaine-free urine tests, and that the increase in slow-wave sleep time would mediate the clinical effect. To test this hypothesis we performed a combined inpatient-outpatient trial of modafinil in which abstinence and a full dose of medication were achieved in a regimented, inpatient setting prior to discharge to outpatient treatment.

2. Methods

2.1. Participants

1,708 potential participants responded to newspaper, radio, and internet advertisements, flyers, or word of mouth referrals for participation in treatment research related to cocaine use. Phone screening for potential eligibility was performed on 551 respondents, and 114 respondents subsequently completed in-person screening. Of those, 59 were both eligible for the study and presented for inpatient admission, and 57 were randomized to receive placebo or modafinil.

All participants met DSM-IV criteria for current cocaine dependence as determined by a clinical interview with an experienced psychiatrist, were not currently in treatment, and were between the ages of 25 and 50 inclusive. All participants reported current use of cocaine by smoked or intravenous route at least one time each week in the past month and a positive urine test for cocaine metabolite at screening. All participants exhibited dependence on cocaine in the past year as measured by a score ≥ 3 on the Severity of Dependence Scale (Kaye and Darke, 2002) and by self-reported use in at least 9 of the past 12 months.

Potential participants were excluded for history or polysomnographic evidence of sleep apnea, narcolepsy, restless leg syndrome, periodic limb movement disorder, or REM sleep disorder, pharmacological treatment for insomnia of any type within the past 6 months, or seizure disorder. Participants with medical conditions that were not considered stable as evidenced by changes in treatment or exacerbations of their condition in the past 6 months, or that could interfere with the safety of their participation were excluded. Potential participants were also excluded for current dependence on any drugs other than cocaine or nicotine, or for lifetime dependence on alcohol, benzodiazepines, or opiates, or any current, non-substance-related Axis I disorder as determined by structured clinical interview for DSM-IV (SCID). Current use of alcohol in excess of 25 standard drinks/week, or a positive urine test for opiates, methadone, amphetamines, barbiturates, benzodiazepines, PCP, methaquolone, or propoxyphene at any time prior to randomization was exclusionary. History of recent cannabis use was allowed so long as a negative urine test for cannabis use was obtained prior to study start and at the time of inpatient admission.

All participants reviewed and signed a consent form, approved by the local institutional review board, and were assessed in their understanding of the consent form by a short quiz.

2.2. Setting

Participants were admitted to a 12-bed research facility – a full service inpatient psychiatric unit with a structured daily routine – for 12 days and 11 nights. All meals and snacks were provided on the caffeine-free unit and three-times daily, 15-minute outdoor breaks allowed smoking (at 8:45am, 12:45pm, and 5:45pm). Participants maintained an 11pm – 7am time in bed schedule while on the inpatient unit, and were checked by staff every 15 min outside those times; daytime napping was not permitted.

Participants continued in outpatient treatment for 6 weeks following the initial inpatient admission. Outpatient visits occurred 3×/weekly. During the 3rd week, and at the end of the 6th week, participants were readmitted to the inpatient unit for 2 nights for follow-up sleep measurement (published in Angarita et al., 2014b).