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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 400mg 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

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Contributors:

Peter T. Morgan designed the study and directed its implementation, was responsible for the analysis and interpretation of the data, and wrote the manuscript.

Gustavo A. Angarita, Sofija Canavan, Sarah Hodges, Andrew Bessette, and Erica Forselius participated in recruitment and screening of participants, the collection and organization of research data, and contributed to the drafting of the manuscript.

Brian Pittman contributed to the statistical design of the study and performed statistical analysis of the results.

Robert T. Malison, Lindsay Oberleitner, Caroline Easton, and Sherry McKee contributed to the study design and collection of research data, and contributed to the drafting of the manuscript.

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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.

Keywords

cocaine; sleep; modafinil; slow-wave sleep; treatment

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 (Substance Abuse and Mental Health Services Administration (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, 2014b; 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 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, methaqualone, 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 minutes outside those times; daytime napping was not permitted.

Participants continued in outpatient treatment for 6 weeks following the initial inpatient admission. Outpatient visits occurred 3x/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).

2.3 Medication

Participants were randomized in a double-blind fashion to receive either placebo or modafinil using randomization schedules stratified by age, sex, and quantity of cocaine used in the past 30 days. 100mg tablets of modafinil or similar placebo tablets were placed in capsules along with a riboflavin marker (25mg) by the research pharmacist. All participants took four capsules containing placebo each morning of Study Days 2-4. Participants in the placebo group continued taking 4 placebo capsules thereafter. In the modafinil group, placebo capsules were replaced with modafinil capsules such that modafinil participants received 100mg of modafinil on Day 5, 200mg on Day 6, and 400mg daily thereafter. The 400mg dose was selected because of its demonstrated tolerability in this population and previously demonstrated effects on slow-wave sleep time (Morgan et al., 2010). Following study completion, participants were given 9 additional capsules of either placebo or modafinil and were instructed to take 3 capsules daily the following day, 2 capsules on the next 2 days, and 1 capsule on the subsequent 2 days. On the inpatient unit, participants took the medication at 7:30am; as outpatients, participants were instructed to take the medication 30 minutes after awakening. Outpatient medication adherence was assessed through daily self-report on a diary, checking for the presence or absence of riboflavin in urine with a UV lamp 3x/week (assessed qualitatively by a trained observer through visual inspection for fluorescence), and by the return of medication blister packs weekly during the outpatient portion of the study.

2.4 Psychotherapy

Participants received psycho-education and relapse prevention therapy through daily individual sessions with their unit therapist (5x/week) and daily group therapy (including daily non-substance related groups and 3x/week substance related groups) while on the inpatient unit. Participants received manual-guided cognitive behavioral therapy for cocaine dependence (Kadden, 1992) with an experienced therapist once weekly during the 6 outpatient weeks.

2.5 Contingency Management and participation reimbursement

Contingency management (e.g., Petry et al., 2000) immediately rewarded attendance and adherence to study related duties, but not abstinence. Contingency management was effected through the drawing of prize chits from a large bowl. Increasing numbers of draws were possible at each visit with continued adherence to participation. Half of the prize chits awarded a prize, with most chits awarding the selection of a prize worth approximately \$1, and a small number of chits awarding the selection of larger prizes (up to \$100). The weekly return of medication blister packs was reinforced with small cash payments (\$10 or \$5 if returned late), and study participation was reimbursed 2-4 weeks after participation with a check. Maximum reimbursement was \$560 plus contingency management prizes worth up to an average of \$234 (greater reimbursement was possible if one or more low-probability prizes were obtained).

2.6 Clinical Assessments

Baseline assessments at screening included comprehensive demographics, the Pittsburgh Sleep Quality Index (PSQI; Buysse et al., 1989), Shipley Institute of Living Scale (Shipley IQ; Shipley, 1940), Cocaine Selective Severity Assessment (CSSA; Kampman et al., 1998), Beck Depression Inventory (BDI-II; Beck et al., 1996), and the Addiction Severity Index (ASI; McLellan et al., 1992).

Urine toxicology screens and breathalyzers were administered on Days 1, 4, 8, and 11 of the initial inpatient phase, on all days of inpatient readmissions, and 3 times weekly during outpatient treatment. Participants reported any substance use in the past 30 days or since their last self-report by filling out a timeline follow back calendar at screening, at each admission, and at each of the 3x/week outpatient visits (e.g., Miller and Del Boca, 1994).

Two techniques for measuring abstinence from cocaine were used for analysis. Percent of urines negative for cocaine (%negative urines) was the hypothesized main-outcome measure for the study, and was defined as the percent of all outpatient scheduled urine toxicology screens for which a negative result for cocaine was obtained. As %negative urines can underestimate abstinence, a composite of self-report and urine toxicology results was also used to determine the likely number of days abstinent at each study day. Abstinence on each day was determined from self-report, and accepted if it was consistent with urine toxicology screens. However, a single, missed urine was considered negative if the previous and subsequent urines were negative and the self-report from the subsequent session denied use for the intervening period (Angarita et al., 2014a). This technique was used to determine daily abstinence rates, as well as the maximum consecutive number of days abstinent for each participant during the 6-weeks of outpatient treatment.

2.7 Objective Sleep Assessment

Polysomnographic (PSG) sleep recordings were performed on Study Nights 3, 4, 10, and 11. On those nights, participants slept in one of two sleep laboratory rooms connected to the inpatient unit. On Night 3, a full clinical sleep study including electroencephalogram (EEG) leads (C3-A2, C4-A1, F3-A2, F4-A1, O1-A2, and O2-A1), left and right electrooculogram (EOG), a two-lead chin electromyogram (EMG), two-lead electrocardiogram (ECG), right and left leg EMGs, finger pulse oximeter, plethysmographic thoracic and abdominal belts, airflow sensor, and snore microphone was performed using the Siesta PSG system (Compumedics). PSG studies on subsequent nights were recorded using a TEMEC 8 Channel Universal system (TEMEC Instrument B.V., Kerkrade, the Netherlands) and consisted of EEG (C3-A2 and C4-A1), left and right EOG, chin EMG, and ECG.

All PSG records were scored according to American Academy of Sleep Medicine guidelines (Iber, 2007) by an experienced sleep scorer who was blind to treatment group and study night. Times spent in rapid eye movement (REM) sleep and non-REM (NREM) sleep stages N1, N2, and N3 were determined. Sleep onset latency was defined as time from “lights out” until the first epoch of sleep and REM latency was defined as time from sleep onset to the first epoch of REM sleep. Total sleep time (TST) was calculated by taking the time from sleep onset to the final awakening, minus time awake after sleep onset. PSG data from

Nights 4 and 11 were used for analysis, with Nights 3 and 10 serving as accommodation nights. The choice of Night 4 for baseline sleep data for analysis reflects several considerations: first, variability in sleep measurements is high in the first few days following admission or cocaine use (Morgan et al., 2006), so waiting until Night 4 allows for more time for participants to adjust to the inpatient schedule and abstinence prior to measuring sleep; second, based on our previous experience with studies in this population (e.g., Morgan et al., 2008, 2010), participants would be on average one-week abstinent from cocaine on Night 4, and so largely past the strongest rebound effects on sleep from withdrawal from cocaine (e.g., Morgan et al., 2009). The change in N3 sleep time from Night 4 to Night 11 was the main sleep-outcome measure for this study. The change in TST, change in time spent in stages N2 and REM, and change in sleep latency and REM latency were secondary outcomes.

2.8 Statistical Analysis

Mean percent cocaine-free urines and number of consecutive days abstinent were compared between treatments using independent t-tests. Cocaine-free survival distributions were estimated by the Kaplan-Meier product-limit methods and compared using the log-rank test. Daily abstinence rates were analyzed using generalized linear models with binary response with treatment and time (within-subjects) as predictors. Linear mixed models were employed to evaluate PSG sleep outcomes with treatment included as a between-subjects factor and time as a within-subjects variable. The methods outlined by Kraemer (Kraemer et al., 2002) were used to test whether N3 sleep mediated the effect of modafinil on clinical outcome. Ancillary, post-hoc analyses compared outcomes using t-tests (continuous) or chi-square tests (categorical), where appropriate. All data were analyzed using SAS, version 9.4 (Cary, NC).

3. RESULTS

3.1 Demographics, retention, self-report accuracy, and medication adherence

Demographic and baseline data for all randomized participants are given in Table 1. There were no statistically significant differences between the placebo and modafinil groups in any demographic or baseline clinical factor including age, sex, years of education, pre-morbid IQ estimate, and baseline sleep quality. Current and lifetime use of cocaine and other drugs were similar as measured by duration and quantity of use, and other severity indices (Table 1). There were 25 participants in the placebo group (19 men and 6 women) and 22 participants in the modafinil group (18 men and 4 women) on Study Day 5 when active modafinil treatment started. There was no difference in retention between groups, with mean number of days in treatment at 39 ± 4 (placebo) and 41 ± 4 (modafinil; $p=0.78$).

Mean concordance between urine drug screen results and self-reported cocaine use during the outpatient phase was $79\% \pm 5\%$ [range 19% - 100%] in the placebo group and $88\% \pm 5\%$ [range 27% - 100%] in the modafinil group ($p=0.24$). Thirty-five percent of placebo participants and half of modafinil participants had perfect concordance of urine drug screens with self-reported use. The presence of the riboflavin marker was detected in every

outpatient phase urine sample in all but two placebo participants (detected in 50% and 86% of samples) and all but one modafinil participant (detected in 16% of samples).

3.2 Clinical outcomes

The modafinil treated group had a higher mean rate of %negative urines than the placebo group ($52\% \pm 9\%$ [SEM] vs. $26\% \pm 7\%$, $p=0.02$). In addition, using the composite measure of self-reported use as confirmed by urine toxicology screens, modafinil treatment was found to be associated with a greater maximum number of consecutive days abstinent during the outpatient phase of treatment (20 ± 4 days vs. 10 ± 2 days, $p=0.03$), and was associated with a greater rate of cocaine-free survival (Figure 1, left panel). Modafinil treatment was also associated with higher daily abstinence rates, with separation of the two groups most apparent after the first inpatient readmission (Figure 1, right panel).

3.3 Sleep outcomes

There was a significant group by time interaction ($p=.02$) for N3 (slow-wave) sleep such that modafinil treated subjects showed a significant average increase in N3 sleep time ($+16 \pm 4$ min. [$+50\%$], $p=0.002$) from baseline (pre-medication treatment) to the following week of abstinence (post-treatment initiation), while subjects receiving placebo remained flat (-2.5 ± 4 min. [-6.5%]; $p=0.62$). This difference was also reflected in the frequency of participants showing any increase in N3 sleep time (81% of modafinil-treated vs. 43% of placebo-treated participants ($p=.01$). In addition, there was a statistical trend toward less decrease in TST in the modafinil group compared to the placebo group (-20 ± 13 min. [-5%] vs. -52 ± 13 min. [-14%]). Statistically significant changes from baseline to the following week of abstinence in REM time and REM latency were observed in the placebo group but not in the modafinil group (without significant between group differences); changes in N2 time were observed in both groups (Table 2A).

3.4 N3 sleep and clinical outcome: relationship and test for mediation

The change in N3 sleep time from baseline to the following week of inpatient abstinence was correlated with %negative urines ($r=0.58$, $p=0.0001$) and maximum number of consecutive days abstinent ($r=0.55$, $p=0.0006$; Figure 2) during the outpatient phase. The change in TST and REM latency were correlated with %negative urines, but there were no other associations between change in sleep measures and clinical outcomes (Table 2B).

The positive change in N3 sleep time was influenced by modafinil treatment, and modafinil treatment was associated with better clinical outcome (see above, and Figure 3a). However, the effect of modafinil treatment on clinical outcome was eliminated after controlling for change in N3 sleep time ($p=0.3$; Figure 3b), and the effect of change in N3 sleep time on clinical outcome remained after controlling for modafinil treatment ($p=0.01$; Figure 3c).

3.5 Post-hoc assessments

Neither the Cocaine Selective Severity Assessment ($r=0.03$), Addiction Severity Index (ASI; $r=0.23$), nor ASI-Drug ($r=-0.13$) was correlated with %negative urines. Number of days abstinent at the time of inpatient admission was correlated with %negative urines ($r=0.61$, $p<0.0001$), and was weakly correlated with change in N3 sleep time ($r=0.29$; $p=0.053$).

There was no apparent difference in clinical outcome between groups in the small subset of female participants (%negative urines was $26\% \pm 26\%$ in the modafinil group vs. $24\% \pm 10\%$ in the placebo group; maximum consecutive days abstinent were 7 ± 1 and 8 ± 2 respectively). In male participants the between group differences in clinical outcomes were similar to that in the entire sample (%negative urines: $56\% \pm 9\%$ vs. $26\% \pm 8\%$; maximum consecutive days abstinent: 21 ± 4 vs. 11 ± 3). Although N3 sleep time increased in the four, modafinil-treated female participants by a similar percent (~50%) as in men, baseline N3 sleep time was greater in women (58 ± 11 min.) than in men (27 ± 4 min.; $p=0.007$).

4. DISCUSSION

The results of this study confirm our hypotheses regarding the effectiveness of modafinil in chronic cocaine users and the association between its clinical effectiveness and the slow-wave sleep response to treatment and abstinence. The response of slow-wave sleep time to modafinil treatment was substantial (i.e., ~50% increase) but perhaps somewhat less than observed in a prior study of the same dose of modafinil (Morgan et al., 2010) in which slow-wave sleep time on average doubled. Nevertheless, the present results demonstrate that the improvement in slow-wave sleep time was a statistical mediator of the robust effects modafinil had on clinical outcome.

Previous studies of modafinil in chronic cocaine users have had mixed results. The first clinical study of modafinil (Dackis et al., 2005) showed strongly positive effects, with modafinil treatment associated with %negative urine rates of over 40% compared to 24% in the placebo group (with missed visits regarded as positive). In a large, multi-site clinical trial (Anderson et al., 2009), in which about 40% of participants also met criteria for alcohol dependence, these results were not replicated. However, secondary outcomes including maximum consecutive days abstinent were improved by modafinil treatment. Moreover, the subset of participants without alcohol dependence appeared to benefit more consistently from modafinil treatment, with both a greater frequency of non-use days, and more consecutive days abstinent (15.2 days/13.5 days/6.6 days for 400mg/200mg/placebo during a 12-week trial). Both of these outcomes were based on participant self-report, confirmed by urine toxicology, so did not necessarily impute missed visits as indicative of use.

Another study (Dackis et al., 2012) examined only non-alcohol dependent chronic cocaine users, but failed to replicate earlier results with regard to %negative urine frequency. Despite the lack of a statistically significant overall effect of modafinil on %negative urine rates, there was an interaction between sex and treatment with modafinil 400mg, such that among male participants (about 75% of the sample), modafinil was associated with greater rates of abstinence (approximately 30% compared to 15% at each visit near the end of the 8-week treatment period). More recently, Kampman et al. (2015) demonstrated the clinical effectiveness of modafinil in non-alcohol dependent chronic cocaine users.

The current results are consistent with modafinil reducing cocaine use in chronic users without co-morbid alcohol dependence. Strikingly, the benefit of treatment in the present study appears to be greater than in previous, outpatient-only studies, despite participants in the current study using more cocaine and for longer than participants in other studies. For

example, the observed abstinence rate by urine drug screen was approximately 50% higher than that observed in the male-only sample of Dackis et al. (2012), and the maximum number of consecutive days abstinent (despite only 6 versus 12 weeks in which to achieve that abstinence) was approximately 1/3 greater than in the non-alcohol dependent sample of Anderson et al. (2009).

The most obvious difference between the present study and previous studies of modafinil in the treatment of cocaine dependence is the period of inpatient treatment that begins the study. Although the additional benefit of inpatient treatment of substance use in general has been debated (e.g., Finney et al., 1996), inpatient treatment of cocaine addiction in particular appears to have notable benefits. During the height of the cocaine epidemic in the United States in the 1980s and 1990s, inpatient treatment for cocaine addiction was more available than it is presently, and several retrospective examinations of the role of inpatient versus outpatient treatment were performed (e.g., Simpson et al., 1999). Inpatient treatment in these studies was associated with better treatment retention, better long-term outcomes, and better outcomes associated with longer treatment retention (Simpson et al., 1999), despite inpatient treatment being associated with individuals with more severe addiction and other problems. Additionally, in a randomized trial of residential versus day treatment in a therapeutic community setting in which approximately 2/3 of the clients used cocaine (Greenwood et al., 2001), residential treatment was associated with benefits in substance use outcomes at 6-month follow-up.

Unfortunately, studies examining the effect of treatment setting on clinical outcome in cocaine addiction have had several limitations. These limitations include being retrospective, being focused on outcomes well beyond the end of treatment (rather than “concurrent” outcomes within a period of treatment (McLellan et al., 2005)), and not considering what factors may mediate or moderate the differential effect of setting (Finney et al., 1996), such as maintenance of a regular daily routine, a strict diurnal schedule, a period of abstinence, and adherence to pharmacological and psychotherapeutic interventions. Hence, despite indications that inpatient treatment may improve outcomes, no randomized trial has assessed whether inpatient initiation of treatment improves ongoing outcomes nor has addressed what aspects of inpatient treatment contribute to improved outcomes. The promising clinical outcomes observed in the present study suggest that such a trial may be worthwhile, and point to a possible mediator (or marker thereof) that is amenable to manipulation.

The finding that improvement in slow-wave sleep time is a statistical mediator of clinical response was hypothesized based on the importance of sleep (and slow-wave sleep in particular) to a wide range of functions, the profound deficits in slow-wave sleep time observed previously in chronic cocaine users (Matuskey et al., 2011; Morgan et al., 2006, 2008) and the normalizing effect of modafinil on slow-wave sleep time in chronic cocaine users (Morgan et al., 2010). The present results do not, however, indicate that getting more of the slow, thalamo-cortical oscillations characteristic of slow-wave sleep promotes abstinence itself. Rather, the observed statistical mediation simply suggests that brain processes related to their generation may be relevant to the measured treatment outcomes,

and suggests that whatever causes the impairment in the generation of slow-waves in chronic cocaine users may contribute to ongoing use and relapse.

One possible explanation for the slow-wave impairment in cocaine dependence is an inadequate or muted homeostatic response to wakefulness. A normally functioning homeostatic sleep drive responds to additional wakefulness with additional slow-wave sleep. Hence, deficits in slow-wave sleep time despite extended wakefulness could reflect an impaired ability to generate slow-waves. However, findings showing regional specificity of the slow-wave sleep response to regional brain activation during wakefulness (Huber et al., 2004) suggest that the quality of wakefulness may contribute substantially to the generation of slow-waves. Hence, deficits in slow-wave sleep time may reflect abnormalities in the qualities of wakefulness that drive sleep homeostasis, rather than an impairment in the brain's ability to generate slow-waves. Although direct data supporting this hypothesis is limited (Trksak et al., 2013), the increase in nocturnal slow-wave activity caused by daytime administration of cocaine (Morgan et al., 2006) and the normalization of slow-wave sleep time by morning-dosed modafinil (Morgan et al., 2010), suggest that chronic cocaine users do not suffer from an impaired ability to generate slow-waves, but rather suffer from abnormalities in brain activation during wakefulness (but see also Trksak et al., 2013). These abnormalities, similar to the sleep abnormalities observed in chronic users, are presumably related to chronic use (Matuskey et al., 2011), but could also reflect pre-morbid traits. Our present data suggest that correcting these abnormalities with a morning-dosed stimulant may improve clinical outcomes during treatment.

The observed associations between clinical outcomes and increases in slow-wave sleep time were strong, responsible for approximately 30% of the variance in outcomes that are susceptible to many factors beyond experimental control. A similarly strong association was found between number of days abstinent at admission and clinical outcome, indicating that participants who were able to achieve some abstinence prior to admission fared better during treatment. Other potential predictors of treatment outcome like addiction severity or subjective cocaine withdrawal symptoms did not predict clinical outcome in this study. This may be related to the more limited range of these measures in these participants who tended to have moderate to severe illness.

There was no indication of benefit to women from modafinil treatment, but because of the small sample size conclusions about the effectiveness of modafinil in women cannot be drawn from this study. However, previous work with modafinil (Dackis et al., 2012) found significant benefits of treatment only when women were excluded, suggesting the possibility that the benefit of modafinil is less in women than in men. Although speculative with regard to drawing conclusions, it is interesting to note that women in this study had higher baseline slow-wave sleep time than men, but clinical outcomes no better than placebo-treated men. This finding suggests that physiological changes associated with chronic cocaine use and their effect on treatment outcome may be substantially different between men and women.

We have found that morning-dosed modafinil, when initiated in an inpatient setting with a strict and regimented schedule, increases slow-wave sleep time, and that the increase in slow-wave sleep time is a statistical mediator of the positive clinical effects of modafinil.

This finding does not rule out potential contributions from other possible mediators. For example, treatment with modafinil could have interacted with the cognitive behavioral therapy (e.g., by increasing the encoding, relative retention, and/or valuation of the therapy) or affected the response to contingency management rewards given for participation (although retention in the two groups was similar). Lack of data in these areas is a limitation of the study that could be addressed in future work. Another limitation is the relatively small sample size for assessing the clinical effects of modafinil. However, the magnitude of those effects and their association with neurophysiological changes caused by modafinil, provides substantial evidence that this treatment regimen improves clinical outcomes during treatment. Although the generalizability of the findings may be limited by the homogeneity of participants with regard to other substance use (or lack thereof), this study provides evidence that interventions that affect slow-wave sleep, perhaps through modulation of waking brain activity, could improve clinical outcomes in cocaine users with slow-wave sleep deficits. Further study is required to distinguish the relevance of the inpatient setting and related factors like a fixed diurnal schedule to our findings, and to further identify the mechanisms responsible for improved clinical outcomes.

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REFERENCES

- Achermann P, Borbely AA. Dynamics of EEG slow wave activity during physiological sleep and after administration of benzodiazepine hypnotics. *Hum. Neurobiol.* 1987; 6:203–210. [PubMed: 2896653]
- Anderson AL, Reid MS, Li SH, Holmes T, Shemanski L, Slee A, Smith EV, Kahn R, Chiang N, Vocci F, Ciraulo D, Dackis C, Roache JD, Salloum IM, Somoza E, Urschel HC 3rd, Elkashef AM. Modafinil for the treatment of cocaine dependence. *Drug Alcohol Depend.* 2009; 104:133–139. [PubMed: 19560290]
- Angarita GA, Canavan SV, Forselius E, Bessette A, Morgan PT. Correlates of polysomnographic sleep changes in cocaine dependence: self-administration and clinical outcomes. *Drug Alcohol Depend.* 2014a; 143:173–180. [PubMed: 25124303]
- Angarita GA, Canavan SV, Forselius E, Bessette A, Pittman B, Morgan PT. Abstinence-related changes in sleep during treatment for cocaine dependence. *Drug Alcohol Depend.* 2014b; 134:343–347. [PubMed: 24315572]
- Beck AT, Steer RA, Ball R, Ranieri W. Comparison of Beck Depression Inventories-IA and -II in psychiatric outpatients. *J. Pers. Assess.* 1996; 67:588–597. [PubMed: 8991972]
- Bellesi M, Riedner BA, Garcia-Molina GN, Cirelli C, Tononi G. Enhancement of sleep slow waves: underlying mechanisms and practical consequences. *Fron. Syst. Neurosci.* 2014; 8:208.
- Buyse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index - a new instrument for psychiatric practice and research. *Psychiatry Res.* 1989; 28:193–213. [PubMed: 2748771]

- Dackis CA, Kampman KM, Lynch KG, Pettinati HM, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *Neuropsychopharmacology*. 2005; 30:205–211. [PubMed: 15525998]
- Dackis CA, Kampman KM, Lynch KG, Plebani JG, Pettinati HM, Sparkman T, O'Brien CP. A double-blind, placebo-controlled trial of modafinil for cocaine dependence. *J. Subst. Abuse Treat.* 2012; 43:303–312. [PubMed: 22377391]
- Dackis CA, Lynch KG, Yu E, Samaha FF, Kampman KM, Cornish JW, Rowan A, Poole S, White L, O'Brien CP. Modafinil and cocaine: a double-blind, placebo-controlled drug interaction study. *Drug Alcohol Depend.* 2003; 70:29–37. [PubMed: 12681523]
- Faulhaber J, Steiger A, Lancel M. The GABAA agonist THIP produces slow wave sleep and reduces spindling activity in NREM sleep in humans. *Psychopharmacology*. 1997; 130:285–291. [PubMed: 9151364]
- Finney JW, Hahn AC, Moos RH. The effectiveness of inpatient and outpatient treatment for alcohol abuse: the need to focus on mediators and moderators of setting effects. *Addiction*. 1996; 91:1773–1796. discussion 1803-1720. [PubMed: 8997760]
- Greenwood GL, Woods WJ, Guydish J, Bein E. Relapse outcomes in a randomized trial of residential and day drug abuse treatment. *J. Subst. Abuse Treat.* 2001; 20:15–23. [PubMed: 11239724]
- Hart CL, Haney M, Vosburg SK, Rubin E, Foltin RW. Smoked cocaine self-administration is decreased by modafinil. *Neuropsychopharmacology*. 2008; 33:761–768. [PubMed: 17568397]
- Huber R, Ghilardi MF, Massimini M, Tononi G. Local sleep and learning. *Nature*. 2004; 430:78–81. [PubMed: 15184907]
- Iber, C.; Ancoli-Israel, S.; Chesson, AL., Jr.; Quan, SF. *The AASM Manual for the Scoring of Sleep and Associated Events: Rules, Terminology and Technical Specifications*. American Academy of Sleep Medicine; Westchester, IL: 2007.
- Jasinski DR. An evaluation of the abuse potential of modafinil using methylphenidate as a reference. *J. Psychopharm.* 2000; 14:53–60.
- Kadden, R.; Carroll, K.; Donovan, D.; Cooney, N.; Monti, P.; Abrams, D.; Litt, M.; Hester, R. *Cognitive-behavioral coping skills therapy manual: A Clinical Research Guide for Therapists Treating Individuals with Alcohol Abuse and Dependence*. National Institute on Alcohol Abuse and Alcoholism; Bethesda: 1992.
- Kampman KM, Volpicelli JR, McGinnis DE, Alterman AI, Weinrieb RM, D'Angelo L, Epperson LE. Reliability and validity of the Cocaine Selective Severity Assessment. *Addict. Behav.* 1998; 23:449–461. [PubMed: 9698974]
- Kampman KM, Lynch KG, Pettinati HM, Spratt K, Wierzbicki MR, Dackis C, O'Brien CP. A double blind, placebo controlled trial of modafinil for the treatment of cocaine dependence without comorbid alcohol dependence. *Drug Alcohol Depend.* 2015; 155:105–110. [PubMed: 26320827]
- Kate N, Grover S, Ghormode D. Dependence on supratherapeutic doses of modafinil: a case report. *Prim. Care Companion CNS Disord.* 2012;14.
- Kaye S, Darke S. Determining a diagnostic cut-off on the Severity of Dependence Scale (SDS) for cocaine dependence. *Addiction*. 2002; 97:727–731. [PubMed: 12084142]
- Kraemer HC, Wilson GT, Fairburn CG, Agras WS. Mediators and moderators of treatment effects in randomized clinical trials. *Arch. Gen. Psychiatry*. 2002; 59:877–883. [PubMed: 12365874]
- Loland CJ, Mereu M, Okunola OM, Cao J, Prisinzano TE, Mazier S, Kopajtic T, Shi L, Katz JL, Tanda G, Newman AH. R-modafinil (armodafinil): a unique dopamine uptake inhibitor and potential medication for psychostimulant abuse. *Biol. Psychiatry*. 2012; 72:405–413. [PubMed: 22537794]
- Makris AP, Rush CR, Frederich RC, Taylor AC, Kelly H. Behavioral and subjective effects of d-amphetamine and modafinil in healthy adults. *Exp. Clin. Psychopharmacol.* 2007; 15:123–133. [PubMed: 17469936]
- Mamelak M, Escriu JM, Stokan O. The effects of gamma-hydroxybutyrate on sleep. *Biol. Psychiatry*. 1977; 12:273–288. [PubMed: 192353]
- Matuskey D, Pittman B, Forselius E, Malison RT, Morgan PT. A multistudy analysis of the effects of early cocaine abstinence on sleep. *Drug Alcohol Depend.* 2011; 115:62–66. [PubMed: 21144676]

- McLellan AT, Kushner H, Metzger D, Peters R, Smith I, Grissom G, Pettinati H, Argeriou M. The Fifth Edition of the Addiction Severity Index. *J. Subst. Abuse Treat.* 1992; 9:199–213. [PubMed: 1334156]
- McLellan AT, McKay JR, Forman R, Cacciola J, Kemp J. Reconsidering the evaluation of addiction treatment: from retrospective follow-up to concurrent recovery monitoring. *Addiction.* 2005; 100:447–458. [PubMed: 15784059]
- Miller WR, Del Boca FK. Measurement of drinking behavior using the Form 90 family of instruments. *J. Stud. Alcohol Suppl.* 1994; 12:112–118. [PubMed: 7722987]
- Morgan PT, Malison RT. Pilot study of lorazepam and tiagabine effects on sleep, motor learning, and impulsivity in cocaine abstinence. *Am. J. Drug Alcohol Abuse.* 2008; 34:692–702. [PubMed: 18850496]
- Morgan PT, Paliwal P, Malison RT, Sinha R. Sex differences in sleep and sleep-dependent learning in abstinent cocaine users. *Pharmacol. Biochem. Behav.* 2009; 93:54–58. [PubMed: 19379771]
- Morgan PT, Pace-Schott E, Pittman B, Stickgold R, Malison RT. Normalizing effects of modafinil on sleep in chronic cocaine users. *Am. J. Psychiatry.* 2010; 167:331–340. [PubMed: 20080983]
- Morgan PT, Pace-Schott EF, Sahul ZH, Coric V, Stickgold R, Malison RT. Sleep, sleep-dependent procedural learning and vigilance in chronic cocaine users: evidence for occult insomnia. *Drug Alcohol Depend.* 2006; 82:238–249. [PubMed: 16260094]
- Morgan PT, Pace-Schott EF, Sahul ZH, Coric V, Stickgold R, Malison RT. Sleep architecture, cocaine and visual learning. *Addiction.* 2008; 103:1344–1352. [PubMed: 18855824]
- Pace-Schott EF, Stickgold R, Muzur A, Wigren PE, Ward AS, Hart CL, Clarke D, Morgan A, Hobson JA. Sleep quality deteriorates over a binge--abstinence cycle in chronic smoked cocaine users. *Psychopharmacology.* 2005; 179:873–883. [PubMed: 15672273]
- Petry NM, Martin B, Cooney JL, Kranzler HR. Give them prizes, and they will come: contingency management for treatment of alcohol dependence. *J. Consult. Clin. Psychol.* 2000; 68:250–257. [PubMed: 10780125]
- Roth T, Benca RM, Erman M. An introduction to the clinical correlates of disrupted slow-wave sleep. *J. Clin. Psychiatry.* 2010; 71:e09. [PubMed: 20409443]
- Roth T, Schwartz JR, Hirshkowitz M, Erman MK, Dayno JM, Arora S. Evaluation of the safety of modafinil for treatment of excessive sleepiness. *J. Clin. Sleep Med.* 2007; 3:595–602. [PubMed: 17993041]
- Schmitz JM, Rathnayaka N, Green CE, Moeller FG, Dougherty AE, Grabowski J. Combination of modafinil and d-amphetamine for the treatment of cocaine dependence: a preliminary investigation. *Front. Psychiatry.* 2012; 3:77. [PubMed: 22969732]
- Shipley WC. A self-administering scale for measuring intellectual impairment and deterioration. *J. Psychol.* 1940; 9:371–377.
- Simpson DD, Joe GW, Fletcher BW, Hubbard RL, Anglin MD. A national evaluation of treatment outcomes for cocaine dependence. *Arch. Gen. Psychiatry.* 1999; 56:507–514. [PubMed: 10359464]
- Stoops WW, Lile JA, Fillmore MT, Glaser PE, Rush CR. Reinforcing effects of modafinil: influence of dose and behavioral demands following drug administration. *Psychopharmacology.* 2005; 182:186–193. [PubMed: 15986191]
- Substance Abuse and Mental Health Services Administration. Results from the 2013 National Survey on Drug Use and Health: Summary of National Findings. Rockville, MD: 2014. NSDUH Series H-48. HHS Publication No. (SMA) 14-4863
- Trksak GH, Bracken BK, Jensen JE, Plante DT, Penetar DM, Tartarini WL, Maywalt MA, Dorsey CM, Renshaw PF, Lukas SE. Effects of sleep deprivation on brain bioenergetics, sleep, and cognitive performance in cocaine-dependent individuals. *Scientific World Journal.* 2013:947879. 2013. [PubMed: 24250276]
- Van Dongen HP, Maislin G, Mullington JM, Dinges DF. The cumulative cost of additional wakefulness: dose-response effects on neurobehavioral functions and sleep physiology from chronic sleep restriction and total sleep deprivation. *Sleep.* 2003; 26:117–126. [PubMed: 12683469]

Vienne J, Lecciso G, Constantinescu I, Schwartz S, Franken P, Heinzer R, Tafti M. Differential effects of sodium oxybate and baclofen on EEG, sleep, neurobehavioral performance, and memory. *Sleep*. 2012; 35:1071–1083. [PubMed: 22851803]

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Highlights

A translational trial of modafinil's effects on sleep and treatment outcome was conducted in persons with cocaine use disorders

A relapse prevention design incorporated initiation of treatment in an inpatient setting with regulated diurnal schedule followed by continued outpatient treatment.

Modafinil was found to increase slow-wave sleep time and improve treatment outcomes

The effect of modafinil on slow wave sleep was a statistical mediator of improved clinical outcomes

Figure 1.

Abstinence survival curve (left); *, $p < 0.05$ for difference in survival between groups. Day to day abstinence rates (right). Shaded boxes indicate the window in which the first 2-night inpatient readmission was scheduled. The second 2-night inpatient readmission occurred immediately after completion of outpatient treatment.

Figure 2.

The relationship between clinical outcome and response of N3 sleep to abstinence. Greater increases in N3 sleep time from inpatient week 1 to week 2 correlate with consecutive days abstinent during the outpatient phase in the modafinil group (red squares), placebo group (blue diamonds) and the entire sample (trend line shown for entire sample).

Figure 3.

Test for mediation of clinical effects of modafinil by N3 sleep time; a) modafinil increases N3 sleep time and cocaine free urines; increased N3 sleep time is associated with greater number of cocaine free urines; b) the effect of modafinil on cocaine free urines is not significant when controlled for change in N3 sleep time; c) the relationship between increases in N3 sleep time and cocaine free urines persists when controlled for modafinil treatment. Black arrows represent statistically significant relationships; grey arrow represents non-significant relationship.

Table 1

Baseline characteristics of randomized participants

Baseline Information	Placebo	SD	Modafinil	SD	p
n	27		30		
Sex (% female)*	22%		23%		
Age (yrs)*	44	7	42	7	0.3
Education (yrs)	12	1	12	2	0.5
ShipleyIQ	85	13	87	15	0.7
PSQI	9	5	8	4	0.5
CSSA	18	13	20	17	0.6
BECKDI	7	5	11	8	0.1
ASI-Comp	0.23	0.1	0.25	0.13	0.7
ASI-Drug	0.22	0.08	0.17	0.1	0.1
Total Use (years)	24	9	21	8	0.4
Current Use (\$/week)*	355	299	356	376	1
SDS (Cocaine)	9.8	2.9	9.8	3.3	1
Previous Treatment Episodes	2.8	3.2	1.9	1.5	0.2
Nicotine (cigarettes/day)	9	8	10	11	0.8
Caffeine (coffee cup equiv/week)	13	2	16	3	0.5
Days Abstinent (Study Day 4)	7.1	3.6	6.8	3	0.7

* , parameters on which urn randomization was based

Table 2A

Sleep architecture response to abstinence and modafinil treatment

Measure	Baseline				Between groups P	Within groups P	
	placebo	modafinil	placebo	modafinil		placebo	modafinil
TST	386 (9)	395 (11)	-52 (12)	-20 (13)	0.074	0.0001	0.1316
N1	28 (3)	34 (4)	+3 (4)	-6 (4)	0.12	0.4007	0.1657
N2	225 (7)	230 (10)	-32 (9)	-26 (10)	0.65	0.0013	0.0106
N3	38 (7)	33 (6)	-2 (4)	+16 (4)	0.0015	0.5198	0.0002
R	96 (6)	99 (6)	-18 (8)	-4 (8)	0.22	0.0225	0.5827
SL	19 (3)	18 (3)	+7 (5)	+4 (5)	0.64	0.165	0.4896
RL	45 (7)	60 (10)	+24 (10)	-1 (11)	0.11	0.0254	0.9461

All values are means shown in minutes (S.E.M.)

There were no statistically significant differences in baseline measures between groups.

is the difference from Night 4 (baseline) to Night 11.

'Within groups p' reflects the difference in from zero.

Table 2B

Correlations between sleep-response to abstinence and clinical outcomes

Parameter	Pearson				Spearman			
	%NegUrine		MaxConsDays		%NegUrine		MaxConsDays	
	R	p	R	p	R	p	R	p
TST	0.42	0.01	0.29	0.08	0.41	0.01	0.27	0.1
N2	0.19	0.3	0.11	0.5	0.17	0.3	0.1	0.6
N3	0.51	0.001	0.47	0.004	0.58	0.0001	0.55	0.0006
R	0.27	0.1	0.16	0.3	0.16	0.3	0.07	0.7
SL	-0.26	0.1	-0.27	0.1	-0.26	0.1	-0.25	0.1
RL	-0.23	0.2	-0.18	0.3	-0.35	0.03	-0.29	0.09