Normalizing Effects of Modafinil on Sleep in Chronic Cocaine Users

Peter T. Morgan, M.D., Ph.D.

Edward Pace-Schott, Ph.D.

Brian Pittman, M.S.

Robert Stickgold, Ph.D.

Robert T. Malison, M.D.

Objective: The purpose of the present study was to determine the effect of morning-dosed modafinil on sleep and daytime sleepiness in chronic cocaine users.

Method: Twenty cocaine-dependent participants were randomly assigned to receive modafinil, 400 mg (N=10), or placebo (N=10) every morning at 7:30 a.m. for 16 days in an inpatient, double-blind randomized trial. Participants underwent polysomnographic sleep recordings on days 1 to 3, 7 to 9, and 14 to 16 (first, second, and third weeks of abstinence). The Multiple Sleep Latency Test was performed at 11:30 a.m., 2:00 p.m., and 4:30 p.m. on days 2, 8, and 15. For comparison of sleep architecture variables, 12 healthy comparison participants underwent a single night of experimental polysomnography that followed 1 night of accommodation polysomnography.

Results: Progressive abstinence from cocaine was associated with worsening of all measured polysomnographic sleep outcomes. Compared with placebo, modafinil decreased nighttime sleep latency and increased slow-wave sleep time in cocaine-dependent participants. The effect of modafinil interacted with the abstinence week and was associated with longer total sleep time and shorter REM sleep latency in the third week of abstinence. Comparison of slow-wave sleep time, total sleep time, and sleep latency in cocaine-dependent and healthy participants revealed a normalizing effect of modafinil in cocaine-dependent participants. Modafinil was associated with increased daytime sleep latency, as measured by the Multiple Sleep Latency Test, and a nearly significant decrease in subjective daytime sleepiness.

Conclusions: Morning-dosed modafinil promotes nocturnal sleep, normalizes sleep architecture, and decreases daytime sleepiness in abstinent cocaine users. These effects may be relevant in the treatment of cocaine dependence.

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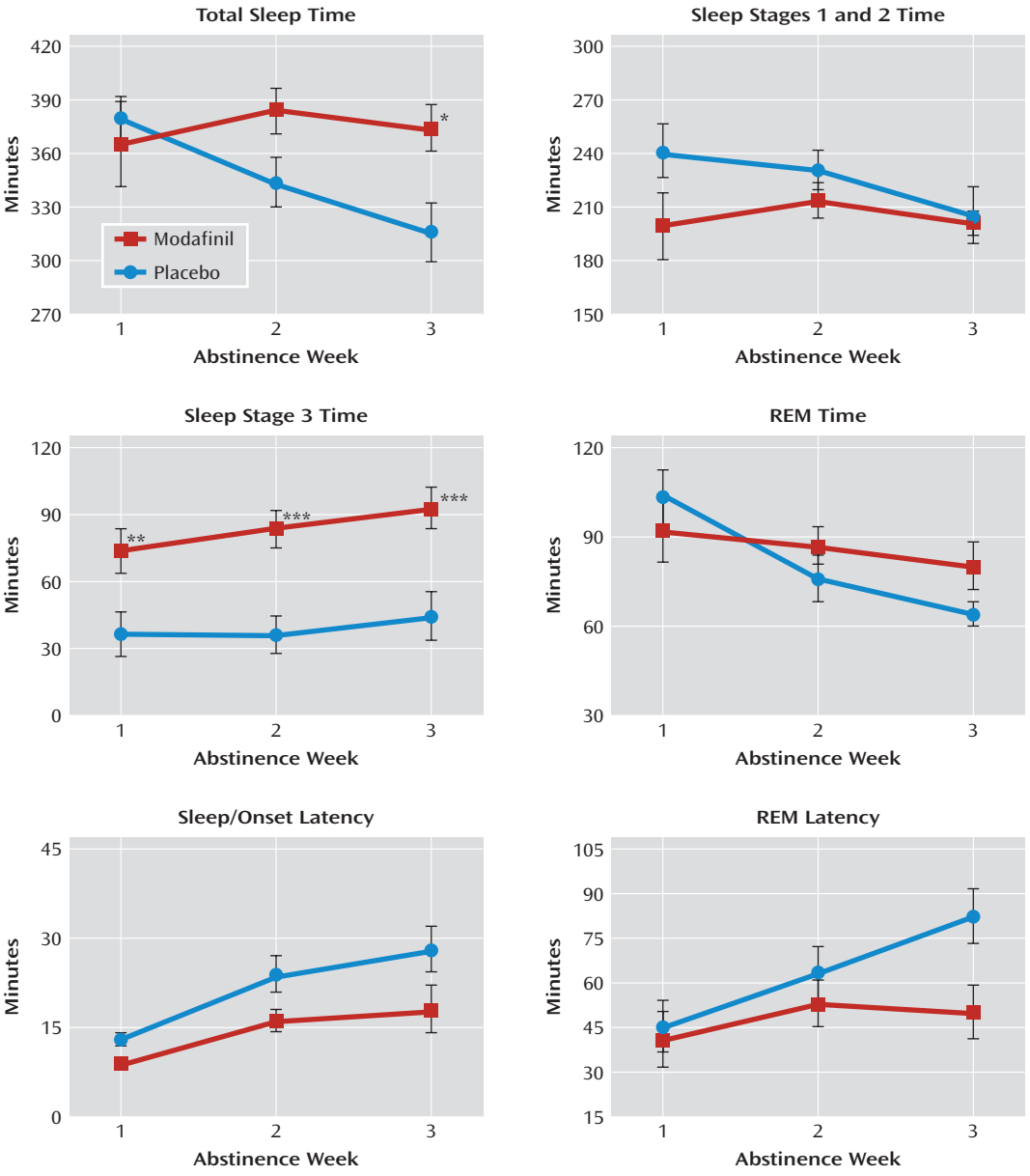
Sleep problems are a common and significant symptom of psychiatric illness (1). Evidence from the past two decades suggests that the sleep problems associated with psychiatric illnesses may be more than just symptomatic consequences of the underlying illness. Rather, the sleep disturbances associated with psychiatric illnesses may be integral to the underlying disease process (1–8). If this is the case, appropriate treatment of the sleep disturbance associated with the psychiatric illness would involve much more than symptom management, since treatment of the sleep problem may be essential to the full promotion of recovery. For cocaine dependence, this possibility may be particularly important. There is currently no Food and Drug Administration (FDA)-approved medication for the treatment of cocaine dependence despite many efforts toward this end, and thus the identification of a novel target for medicinal therapy, such as sleep architecture, could have far-reaching clinical implications.

Cocaine dependence is associated with severe disruptions in sleep, during both periods of use and, perhaps more surprisingly, extended abstinence (9). Early and influential studies of the subjective effects of cocaine withdrawal found that cocaine users reported poor sleep and fatigue in the first few days of abstinence but normal sleep shortly thereafter (10, 11). However, small polysomnographic studies of sleep suggested that the sleep disturbance associated with abstinence from chronic use worsened rather than improved after initial abstinence (12–17). In the largest polysomnographic study to date (18, 19), using laboratory cocaine administration and an inpatient setting to confirm abstinence, we demonstrated that the quality of sleep, measured polysomnographically, deteriorates from the first to third week of abstinence, with characteristic alterations in sleep architecture.

The changes in sleep architecture associated with chronic cocaine use include increases in sleep latency; decreases in total sleep time, slow-wave sleep time, and slow-wave activity; and alterations in REM sleep (12–20). These deficits are present initially and worsen over the course of 3 weeks of abstinence (18, 19), without signs of improvement, and are associated with sleep-related cognitive deficits (18) that may be sleep-stage dependent

This article is featured in this month's AJP Audio and is discussed in an editorial by Drs. Dackis and O'Brien (p. 248).

FIGURE 1. Polysomnographic Sleep Variables at Weeks 1, 2, and 3 of Abstinence Among Chronic Cocaine-Dependent Participants Randomly Assigned to Modafinil or Placebo for Treatment of Sleep Problems[a]

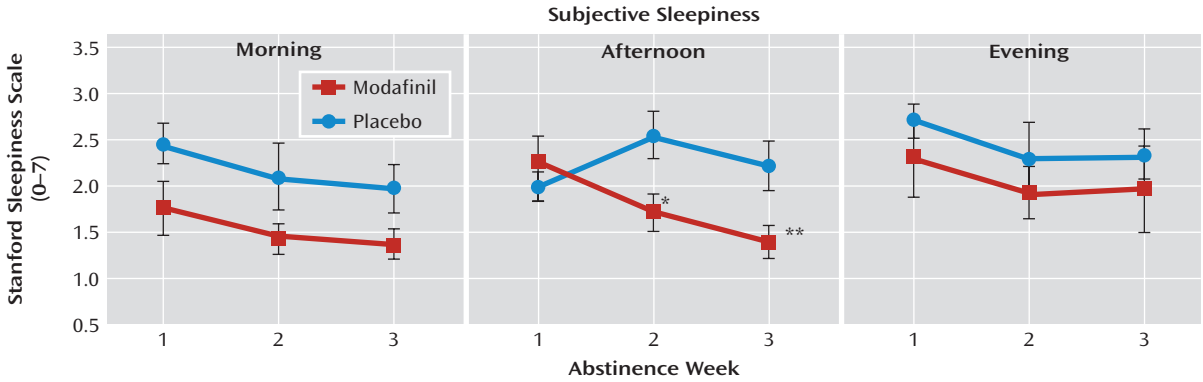


[a] Main effects of abstinence week and drug condition were present, as well as interactions between abstinence week and drug condition. Post hoc differences between placebo- and modafinil-treated cocaine-dependent participants at each time point are indicated (*p<0.05; **p<0.01; ***p<0.005). There were nearly significant post hoc differences at individual time points for total sleep time at abstinence week 2, sleep onset latency at each abstinence week, and sleep stages 1 and 2 time at abstinence week 1.

(19). The sleep deficits are likely the consequence of long-term use of cocaine and could increase the likelihood for relapse (21, 22). The concurrent improvement in self-reported sleep quality (18), consistent with earlier studies (10, 11), may contribute to these deficits escaping recognition as clinically relevant. Thus, the term "occult insomnia" was conceived to describe the discordance between self-reported and objectively measured sleep quality (18).

Intriguingly, one class of candidate pharmacotherapies for the treatment of cocaine dependence may positively affect sleep. These medications enhance γ-aminobutyric acid (GABA) neurotransmission and include vigabatrin (γ-vinyl GABA), tiagabine, and topiramate (23). For example, a small study has shown that tiagabine dramatically increases slow-wave sleep (sleep stages 3 and 4) in chronic cocaine users (24) at the expense of lighter sleep stages (sleep stages 1 and 2). Benzodiazepines (GABA active sedative/hypnotic agents that may be clinically harmful in the treatment of cocaine dependence) have the opposite effect, increasing time in the lighter sleep stage 2 (24), which suggests that the effects of these medications on sleep architecture may predict their clinical effectiveness. However, what may be the most promising medication (23, 25) for the treatment of stimulant dependence—

FIGURE 2. Subjective Sleepiness Among Chronic Cocaine-Dependent Participants Measured by the Stanford Sleepiness Scale[a]



[a] There were main effects of drug condition, abstinence week, and time of day as well as a drug-by-abstinence week-by-time of day interaction. There were statistically significant post hoc differences between modafinil- and placebo-treated cocaine-dependent participants at morning testing ($p<0.005$) and as shown at each time point (*$p<0.05$; **$p<0.005$). There were nearly significant post hoc differences at individual time points for subjective sleepiness at morning testing at each abstinence week.

modafinil—is not considered to be in the same class as vigabatrin, tiagabine, and topiramate, nor does it appear to have effects on sleep architecture in the populations in which it has been shown to be clinically effective (i.e., its effects on narcolepsy, obstructive sleep apnea, or shift work-related sleep disorder) (26–28).

Modafinil is a wakefulness promoting agent with effects on dopamine neurotransmission (29–33) and apparent effects on glutamate and other neurotransmitters (34). Modafinil is viewed as an abstinence initiation medication that may offset acute withdrawal symptoms (25), whereas the GABA active class of medications may reduce the reinforcing effects of cocaine and thus reduce the propensity for relapse. However, the mechanisms whereby any of these medications may help to reduce cocaine use are currently unknown. In prior investigations (18, 19, 24), we hypothesized that normalizing the aberrations in sleep architecture associated with abstinence may contribute to the efficacy of treatments for cocaine dependence, and we predicted that modafinil would have previously unrecognized positive effects on sleep and sleepiness in chronic cocaine users.

In the present study, we examined the effects of modafinil on objective and subjective measures of sleep and sleep-related outcomes in abstinent cocaine users. We hypothesized that morning-dosed modafinil would decrease nocturnal sleep latency, increase total sleep time, and decrease daytime sleepiness.

Method

Cocaine-Dependent Participants

Forty-four persons with self-identified cocaine problems responded to newspaper advertisements for cocaine research studies and passed the initial telephone screening. Of those who passed the telephone screening, 29 were found to be qualified for participation after in-person screening, and 21 entered the study. All participants met DSM-IV criteria for current cocaine dependence as determined by a clinical interview with an experienced psychiatrist. Potential participants who passed the telephone screening were excluded if they had chronic medical or neurological conditions (N=5), a history of dependence on substances other than cocaine and nicotine (N=3), nonsubstance-related axis I diagnoses (N=4), used psychoactive prescription medications within the past year (N=4), and/or urine toxicology results not positive for cocaine and negative for all other substances (N=5). Eight persons who were qualified chose not to participate in the study. None of the participants exhibited signs or symptoms of alcohol withdrawal during the study (35). All participants completed a sleep disorders screening questionnaire (used in prior studies [18, 19, 24]) to elicit a history of general sleep habits, symptoms related to general sleep habits and to the use of drugs or medications, primary sleep disorders (including psychophysiological insomnia, sleep-disordered breathing, narcolepsy, parasomnias, periodic limb movement, and restless leg syndrome), and sleep disorders related to other medical conditions and to psychiatric disorders and symptoms. No participant reported 1) having been evaluated for, diagnosed with, or treated for any sleep problem; 2) having a history consistent with a primary sleep disorder; or 3) regularly using the caffeine equivalent of more than one cup of coffee daily. All participants reviewed and signed an informed consent form, approved by the local institutional review board, before entering the study. Upon admission to the inpatient unit, all participants had a urine toxicology screen that was positive for cocaine metabolite (indicating likely use in the preceding 3 days) and negative for opiates, benzodiazepines, cannabis, phencyclidine, amphetamines, and barbiturates. Baseline assessments at the time of admission were conducted using the Pittsburgh Sleep Quality Index (36) and a 90-day Timeline-Follow-Back Interview (37) for all drug and alcohol use and typical daily nicotine use. Of the 21 persons who entered the study, 20 completed the study (one person dropped out voluntarily shortly after admission and was not included in the analysis). Participants who remained in the study until completion received compensation of $500.

Inpatient Facility

All cocaine-dependent participants were admitted to a 12-bed research facility (a full-service inpatient psychiatric unit with a structured daily routine, including individual and group therapy) and took part in individual and group therapy during their inpatient stay. Sixteen of the 20 participants who remained in the study until completion identified themselves as seeking treatment for cocaine dependence. They also attended substance abuse therapy groups and received individual therapy with a sub-

TABLE 1. Baseline and Demographic Characteristics of Chronic Cocaine-Dependent Participants Randomly Assigned to Modafinil or Placebo for Treatment of Sleep Problems

Characteristic	Cocaine-Dependent Group				Analysis
	Placebo (N=10)		Modafinil (N=10)		
	Mean	SD	Mean	SD	p
Age (years)	44	7	40	5	0.26
Cocaine use in last 90 days					
Number of days	44	29	31	16	0.25
Grams	50	39	40	25	0.47
Days abstinent at first study day	3.2	1.9	3.3	1.3	0.89
Alcohol use in last 90 days (number of drinks)	117	133	75	86	0.42
Cannabis use in last 90 days (number of joints)	2.6	7.9	3.0	8.2	0.91
Daily nicotine use (number of cigarettes)	3.6	2.5	4.2	1.4	0.51
Pittsburgh Sleep Quality Index baseline score	4.3	2.1	3.5	2.1	0.40
	N	%	N	%	p
Sex					0.26
Men	9	90	7	70	
Women	1	10	3	30	
Race					0.64
African American	6	60	7	70	
Caucasian	4	40	3	30	
Seeking treatment	8	80	8	80	

stance abuse focus. All meals and snacks were served three times each day (at 8:45 a.m., 12:45 p.m., and 5:45 p.m.) in a caffeine-free unit. Fifteen-minute outdoor breaks were allowed for smoking. Participants were checked by staff every 15 minutes daily, from 7:00 a.m. to 11:00 p.m. Daytime napping was not permitted. Urine toxicology screens were administered three times per week. All participants spent at least 1 day and 1 night in the inpatient unit before starting the first day of the study. Lighting conditions in the unit consisted of mixed artificial and subdued natural light and thus varied somewhat with the season. Participants were exposed to outdoor light during the outdoor (smoking) breaks.

Modafinil Administration

Participants were randomly assigned (1:1) to receive modafinil, 400 mg, or placebo every morning at 7:30 a.m. for 16 days (study days 1 to 16), starting within 3 days of their admission to the inpatient unit and therefore between the second and sixth day of abstinence from cocaine (based on the positive urine toxicology screen at admission). The dose of modafinil could be lowered to 200 mg for lack of tolerance to side effects. One participant did have the dose lowered on days 3 and 4, secondary to palpitations (experienced without apparent electrocardiogram [ECG] changes), but returned to the full 400 mg (38).

Sleep Measurement

Participants maintained an 11:00 p.m. to 7:00 a.m. time-in-bed schedule for the duration of the study. They were accommodated to the sleep laboratory on the night prior to the first study day. Experimental polysomnographic sleep measurement was performed on the following three study night blocks: 1 to 3, 7 to 9, and 14 to 16. Data from each three-night block were averaged and reported as "abstinence weeks" 1, 2, and 3, respectively. Polysomnographic measurement was performed using a TEMEC 8 Channel Universal system (TEMEC Instrument B.V., Kerkrade, the Netherlands) in a dedicated sleep laboratory bedroom and included two EEG channels (C3–A2, C4–A1), right and left electrooculogram, chin electromyogram, and ECG. Polysomnographic recordings were scored according to the American Academy of Sleep Medicine criteria (39) by a single individual who was blind to the study day and treatment group. Reported sleep variables were defined in the typical fashion as follows: Sleep-onset latency was defined as the time from "lights out" until the appearance of the first epoch of sleep; REM latency was defined as the time from sleep onset to the first epoch of REM sleep; and total sleep time was defined as the time from sleep onset until final awakening minus the time awake after sleep onset. Time spent in sleep stages 1 and 2 and stage 3 as well as REM sleep is also reported.

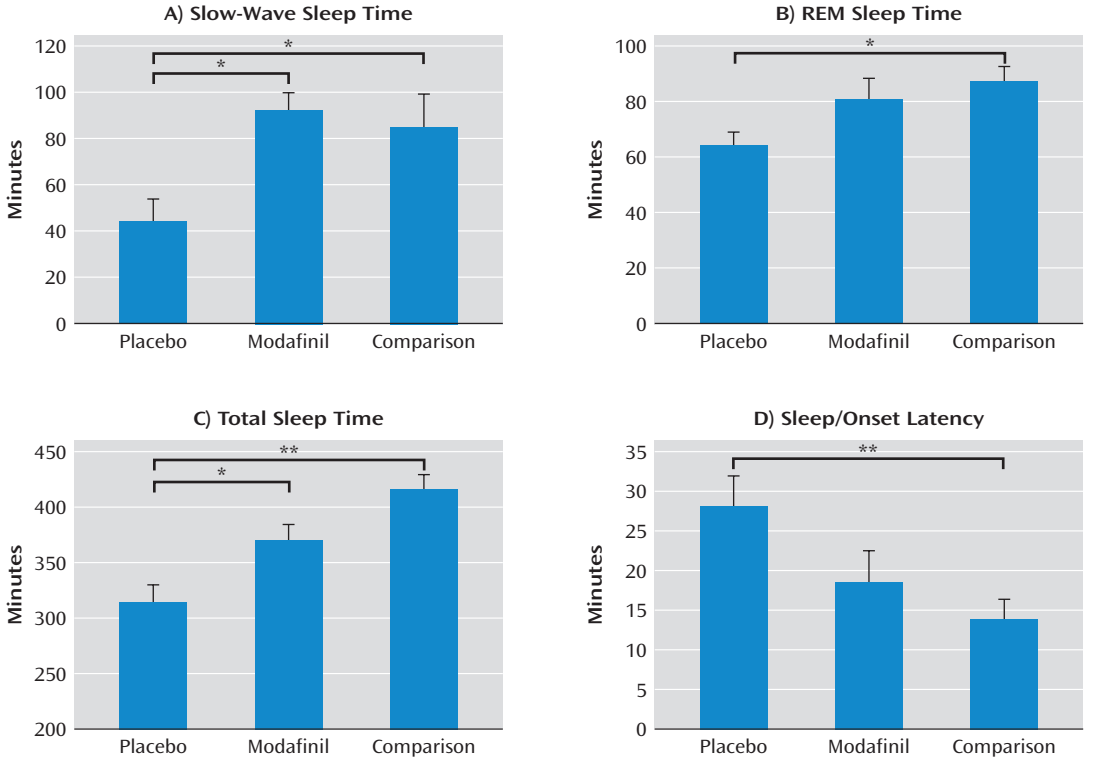
The Multiple Sleep Latency Test

Sleep latency tests were performed at 11:30 a.m., 2:00 p.m., and 4:30 p.m. on days 2, 8, and 15, using a Grass Colleague polysomnographic system (Grass Technologies, West Warwick, R.I.). The sleep latency protocol followed typical practice (40, 41), except that the first nap opportunity was more than 3 hours after the conclusion of the polysomnographic measure on the previous night. Additionally, to reduce the effect of the Multiple Sleep Latency Test on subsequent nocturnal sleep, only three nap opportunities were used (instead of four), and the test was terminated after three consecutive 30-second epochs of sleep (instead of 15 minutes following sleep onset). This method precluded the normal assessment of sleep-onset REM periods.

Subjective Measures

Subjective measures of sleep quality and alertness were assessed with previously used visual analogue scales (15) that were based on the Likert scales utilized in the St. Mary's Hospital Sleep Questionnaire (42). Upon awakening (and hence prior to receiving the daily dose of study medication), participants rated their "overall quality of sleep," "depth of sleep," "feeling well-rested," and "mental alertness." Ratings were indicated by the participant marking an "X" on 100 mm lines, with the extreme points anchored by text descriptions (i.e., "worst/best," "not at all deep/very deep," "not at all rested/very well-rested," and "most drowsy/most alert," respectively). The placement of the "X" was measured, using a ruler, to the nearest millimeter and thus ranged from 0 mm to 100 mm. In the evening just prior to going to sleep, participants retrospectively rated their "level of alertness today" using the same visual analogue scale. Subjective daytime sleepiness was assessed with the Stanford Sleepiness Scale (range: 0–7, with 7 being the most sleepy) at 10:00 a.m., 3:30 p.m., and 9:00 p.m. Subjective measures from days 1 to 3, 7 to 9, and 14 to 16 were averaged to correspond to abstinence weeks 1, 2, and 3.

FIGURE 3. Normalizing Effects of Modafinil on Polysomnographic Sleep Variables Among Chronic Cocaine-Dependent Participants in Abstinence Week 3 and Healthy Comparison Participants[a]



[a] A) Modafinil increased slow-wave sleep time in chronic cocaine-dependent participants to be indistinguishable from that of healthy comparison participants. B) REM sleep time was significantly less in the placebo-treated cocaine-dependent group (but not the modafinil-treated cocaine-dependent group) than it was in the healthy comparison group. C) Modafinil increased the total sleep time for cocaine-dependent participants but was still less (nonsignificantly) than the total sleep time for healthy comparison participants. D) Sleep-onset latency was significantly longer in the placebo-treated cocaine-dependent group (but not the modafinil-treated cocaine-dependent group) relative to the healthy comparison group, and there were nearly significant differences in improved sleep latency in modafinil-treated cocaine-dependent participants. Statistically significant, independent sample ANOVA was followed by post hoc Tukey's honestly significant difference (*$p<0.05$; **$p<0.01$).

Healthy Comparison Participants

Twelve healthy male participants, age 30–50 years (mean age: 39 years [SD=9]), were recruited to match the typical age range of the cocaine-dependent participants. Healthy participants represented the following ethnic groups: Caucasian (N=9), Asian (N=2), and African American (N=1). These individuals had no history of any chronic medical, neurological, or psychiatric illness; no history of any substance abuse or dependence, including nicotine dependence; no condition that precipitated medicinal treatment in the 3 months prior to participation; no history of any sleep disorder; and no history of the use of any substance for the purpose of promoting sleep in the 6 months prior to participation. None endorsed napping more than once per month in the 6 months prior to participation, and all had Pittsburgh Sleep Quality Index (36) scores ≤5. These participants were excluded for the caffeine equivalent of more than three cups of coffee per day in the past month. Exclusion criteria were assessed by open-ended screening interviews and questionnaires, a salivary cotinine test, urine drug screen, and blood screening. All healthy participants reviewed and signed an informed consent form, approved by the local institutional review board, before involvement in the study. Starting 1 week before their nights in the sleep laboratory, they monitored their daily sleep and activity patterns with twice-daily questionnaires and 24-hour actigraphy. The objective of this monitoring was to encourage these participants to maintain regular habits in the week prior to formal testing. During this period, they were required to 1) keep their bedtime within a 1-hour window, 2) not nap, 3) refrain from drinking alcoholic beverages, and 4) not drink caffeine after 6:00 p.m. All healthy participants reported adhering to these requirements, and actigraphy data were consistent with the reported bedtimes and a lack of daytime napping. The healthy comparison group reported to the sleep laboratory no later than 8:00 p.m. on consecutive nights. Data were collected under the same conditions as for the cocaine-dependent group, except that the comparison group 1) spent their days outside of the research unit and 2) did not receive morning medication or placebo. In addition, data from a single experimental night (following an accommodation night) were used for the comparison group, whereas data from three experimental nights were averaged for each time point for the cocaine-dependent group.

Statistical Considerations

All data were approximately normal according to Kolmogorov-Smirnov test statistics and normal probability plots. Linear-mixed models were used to evaluate the effects of modafinil treatment on polysomnographic sleep measurements, Multiple Sleep Latency Test scores, and subjective measures of sleep. For these models, treatment (modafinil versus placebo) was used as a between-subjects effect, while the time abstinent (weeks 1, 2, and 3) was used as a within-subjects explanatory variable. The interaction between treatment and time was modeled and explained by appropriate post hoc tests. The correlation structure of the data was modeled by structured variance-covariance matrix for repeated observations over time. The latter variance-covariance

structure was the best fitting according to information criterion. Stanford Sleepiness Scale measures were evaluated using the same aforementioned model but included time of day (morning, afternoon, evening) as an additional within-subjects effect and a random subject effect. Sleep data measured at abstinence week 3 were compared between treatment groups and the healthy comparison group using one-way analysis of variance (ANOVA). All data were analyzed using SAS, Version 9.1 (SAS Institute, Inc., Cary, N.C.).

Results

Demographic Characteristics

Demographic data for cocaine-dependent participants are presented in Table 1. There were no statistically significant differences between the modafinil and placebo groups with regard to age, gender, and race. Self-reported cocaine, alcohol, cannabis, and cigarette use were similar between these two groups as well as the self-reported number of days abstinent from cocaine on day 1 of the study, which was the first day of modafinil administration.

Polysomnographic Sleep Measurement

Polysomnographic sleep data are illustrated in Figure 1. There were main effects of modafinil on sleep-onset latency ($F=5.8$, $df=1, 18$, $p=0.03$) and time spent in sleep stage 3 ($F=11.9$, $df=1, 18$, $p=0.003$). In addition, there were main effects of abstinence week on all assessed polysomnographic sleep measures as follows: total sleep time ($F=4.1$, $df=2, 36$, $p=0.03$), sleep latency ($F=20.0$, $df=2, 36$, $p<0.0001$), time in sleep stages 1 and 2 ($F=5.2$, $df=2, 36$, $p=0.01$), time in sleep stage 3 ($F=6.3$, $df=2, 36$, $p=0.005$), REM sleep time ($F=8.4$, $df=2, 36$, $p=0.0002$), and REM latency ($F=11.1$, $df=2, 36$, $p=0.001$). Post hoc differences between abstinence weeks 1 and 3 reflected increases in sleep-onset latency ($t=-4.9$, $df=36$, $p<0.0001$), time in sleep stage 3 ($t=-3.5$, $df=36$, $p=0.001$), and REM latency ($t=-4.0$, $df=36$, $p=0.0003$) and decreases in total sleep time ($t=2.8$, $df=36$, $p=0.008$) and REM sleep time ($t=3.0$, $df=36$, $p=0.005$).

Significant interactions were observed between drug condition and abstinence week in total sleep time ($F=7.4$, $df=2, 36$, $p=0.002$), REM latency ($F=3.6$, $df=2, 36$, $p=0.03$), and REM sleep time ($F=3.5$, $df=2, 36$, $p=0.04$). There was a nearly significant difference in the interaction in sleep time for sleep stages 1 and 2 ($F=2.6$, $df=2, 36$, $p=0.09$). Post hoc assessment of these interactions revealed increases in total sleep time ($F=6.7$, $df=1, 36$, $p=0.01$) and decreases in REM latency ($F=6.9$, $df=1, 36$, $p=0.01$) as the result of modafinil treatment at week 3. No treatment differences were observed in REM sleep time at any time point.

The Multiple Sleep Latency Test

There were no main effects of modafinil or abstinence week on daytime sleep latency. However, there was a significant interaction between abstinence week and drug condition, with modafinil associated with longer mean sleep latency (modafinil, 15 minutes [SD=2]) versus placebo, 10 minutes [SD=2]) during the first week of abstinence only ($F=4.4$, $df=1, 36$, $p=0.04$).

Subjective Sleep, Alertness, and Sleepiness Measures

Participants reported progressively improving subjective sleep and alertness with abstinence. The following improvements were statistically significant: main effects of abstinence week on overall sleep quality ($F=9.0$, $df=2, 36$, $p=0.0007$), depth of sleep ($F=6.3$, $df=2, 36$, $p=0.004$), feeling well-rested upon awakening ($F=5.9$, $df=2, 36$, $p=0.006$), alertness upon awakening ($F=8.3$, $df=2, 36$, $p=0.001$), and retrospective daytime alertness ($F=7.2$, $df=2, 36$, $p=0.0023$). There were no statistically significant effects of modafinil on any of these measures.

Results from Stanford Sleepiness Scale measures, assessed in the morning, afternoon, and evening, are illustrated in Figure 2. Nearly significant differences were observed for drug condition ($F=3.4$, $df=1, 144$, $p=0.07$) and abstinence week ($F=3.0$, $df=2, 144$, $p=0.06$). There was a main effect for time of day ($F=5.1$, $df=2, 144$, $p=0.007$) and a significant interaction among drug condition, abstinence week, and time of day ($F=2.7$, $df=4, 144$, $p=0.04$). Statistically significant post hoc comparisons revealed an association between modafinil and decreased sleepiness during morning and afternoon testing at weeks 2 and 3. No modafinil effects were observed for evening sleepiness. Sleepiness at abstinence week 3 was less than at abstinence week 1 ($t=2.4$, $df=144$, $p=0.02$).

Comparisons With Healthy Participants

Compared with cocaine-dependent participants (Table 1), healthy comparison participants were similar in age (39 years [SD=9]), had nonsignificantly lower baseline Pittsburgh Sleep Quality Index scores (3 [SD=1.5]), and drank significantly less alcohol (19 drinks in the past 90 days [SD=15], $p<0.05$). Data for healthy comparison participants on polysomnographic- and subjective-measured sleep were compared with these data for cocaine-dependent participants in the following three-group comparison: healthy comparison group, cocaine-dependent group receiving placebo, and cocaine-dependent group receiving modafinil. Data from abstinence week 3 were used in the assessment of cocaine-dependent participants. There were statistically significant group differences in slow-wave sleep (sleep stage 3) time ($F=4.9$, $df=2, 29$, $p=0.02$), REM sleep time ($F=3.5$, $df=2, 29$, $p=0.04$), total sleep time ($F=12.1$, $df=2, 29$, $p<0.0001$), sleep-onset latency ($F=4.7$, $df=2, 29$, $p=0.02$), time in sleep stages 1 and 2 ($F=3.6$, $df=2, 29$, $p=0.04$), and REM latency ($F=3.5$, $df=2, 29$, $p=0.04$). There was no statistically significant difference in self-reported overall sleep quality (cocaine-dependent placebo group, 77 [SD=5]; cocaine-dependent modafinil group, 81 [SD=5]; healthy comparison group, 67 [SD=6]). Post hoc comparisons showed statistically significant normalizing effects of modafinil on slow-wave

sleep time and modafinil-associated decreases in differences in REM sleep time, total sleep time, and sleep-onset latency between the placebo-treated group and healthy comparison group (Figure 3). REM latency was not significantly different between either of the cocaine-dependent groups and the healthy comparison group, and there were no post hoc differences in the time in sleep stages 1 and 2.

Adverse Events

Six cocaine-dependent participants receiving modafinil and two receiving placebo experienced a total of nine adverse events. Four participants receiving modafinil and one receiving placebo reported headaches. Two participants receiving modafinil reported nausea without vomiting. One of the participants who experienced nausea also experienced palpitations and was evaluated in the local emergency department and had the dose of modafinil lowered on days 3 and 4 before returning to the full dose (38). One participant receiving placebo developed conjunctivitis (possibly related to the polysomnographic setup procedure). All of the other adverse events were considered mild and did not require medical intervention or reduction in the modafinil dose.

Discussion

To our knowledge, this is the largest study of polysomnographically measured sleep in chronic cocaine users to date and the first study of the effects of modafinil on sleep in this population. The most intriguing finding is the dramatic and therapeutically suggestive effect of modafinil on objective measures of sleep and daytime sleepiness in chronic cocaine users. Additionally, these results confirm earlier studies showing severe disruptions of sleep in abstinent cocaine users and a lack of subjective awareness of those disruptions.

Previous polysomnographic studies (12–16, 18, 19, 24) suggested that cocaine-related sleep disturbances extend beyond the acute and early withdrawal effects of cocaine (10, 11). In the present study, we report that abstinence from chronic cocaine use is indeed associated with disruptions of sleep that are present within the first week of abstinence (e.g., disruptions in sleep stage 3 time) and worsen over 3 weeks of abstinence (e.g., disruptions in sleep-onset latency, REM sleep time, time in sleep stages 1 and 2, total sleep time). However, prior studies that used only self-reported sleep measures typically reported improvement in sleep during abstinence (10, 11, 43). In a previous investigation (18), we demonstrated this discrepancy explicitly and found that polysomnographically measured sleep and sleep-related cognitive performance deteriorated over 2 to 3 weeks of abstinence, while self-reported sleep quality improved. These findings were interpreted as a possible dysregulation of the homeostatic sleep drive and were termed "occult insomnia." The present findings reproduce our previous findings in both the objective deterioration and subjective improvement in sleep quality during abstinence. However, the novel findings of the present study are the striking effects of modafinil on sleep latency, sleep duration, sleep architecture, and daytime sleepiness.

Patient Perspectives

Most participants sought participation in a research study as the only way to receive inpatient treatment for their cocaine addiction. Except for persons with the ability to self-pay, inpatient treatment of cocaine addiction in adults is typically available only in the context of a severe co-occurring psychiatric illness, during alcohol or opiate withdrawal, or when a court mandate is issued. Many participants reported that in prior outpatient treatments they were not able to achieve more than 1 week of abstinence, and nearly all used the personalized social work services available to them in the present study to help arrange outpatient follow-up treatment and to help with social and financial issues. Difficulties staying in the inpatient environment for 3 weeks were reported infrequently and were at least superficially related to strict rules about meals, visitors, and the scarcity of opportunities to go on staffed excursions outside of the unit.

We found that modafinil, 400 mg, given in a single, early morning dose, leads to improvements in sleep and decreases in objective and subjective measures of daytime sleepiness. The improvements in sleep occurred as either overall drug effects (sleep latency decreased and time in sleep stage 3 increased) or interactions with abstinence week, where the improvements reflected a reversal of the deterioration that developed over 3 weeks of abstinence in placebo-treated participants (in total sleep time and REM sleep time).

The modafinil-related improvement in objective daytime sleepiness, as measured by the Multiple Sleep Latency Test, was present only in abstinence week 1, when excessive somnolence is a well-known clinical feature of cocaine withdrawal (10). One interpretation of this finding is that modafinil's dopaminergic effects (31–33) on wakefulness are more apparent during the relatively hypodopaminergic state of early abstinence from cocaine. This interpretation is consistent with an overall decreased propensity to sleep (i.e., increased sleep-onset latency and decreased total sleep time) in the second and third weeks of abstinence. Subjective sleepiness was also improved with modafinil, with statistically significant effects 2.5 and 8 hours after dosing but no effect 13.5 hours after dosing. Unlike objectively measured sleepiness, these effects were observed in the second and third weeks of abstinence. This difference may reflect several factors. As mentioned earlier, the propensity toward sleep diminishes as abstinence progresses, and therefore the objective effect of modafinil on reducing daytime sleep latency may be limited. However, subjective symptoms of reduced sleep time, such as diminished cognitive performance, may worsen with continued absti-

nence (18) and thus may be more responsive to modafinil treatment as abstinence progresses. The absence of a subjective effect of modafinil on nighttime sleepiness may reflect the lower concentration of modafinil at that time (modafinil half-life: approximately 10 to 15 hours [44]) and is consistent with its positive, objective effects on nocturnal sleep latency and sleep architecture.

The strongest effect of modafinil on sleep architecture appears to be the increase in the time in sleep stage 3 (slow-wave sleep). Slow-wave sleep was significantly higher in the modafinil group, more than double that of the placebo group, at all time points. From a clinical perspective, this effect may also be particularly relevant. Slow-wave sleep is a highly protected stage of sleep. In healthy individuals who are limited to 4 or 6 hours in bed, slow-wave sleep time is not reduced (45) and is dramatically increased following total sleep deprivation (e.g., reference 46). In addition, there is evidence that increasing slow-wave sleep time may improve cognitive performance (47). Nevertheless, slow-wave sleep time in chronic cocaine users is markedly decreased (18), and deficits in slow-wave sleep are also associated with chronic use of other addictive substances (e.g., reference 48). Indeed, the observed deficits in slow-wave sleep may be necessary to see such an effect from modafinil, since large studies of modafinil in other populations have not reported such effects (26–28). However, stimulant effects on slow-wave sleep are not unprecedented, since, for example, cocaine given early in the day increases nocturnal slow-wave activity (18).

The present study suggests that modafinil exhibits its greatest objective effects on sleep and sleepiness when the inherent abnormality is greatest. Hence, objective daytime sleepiness was improved with modafinil during the first week of abstinence (when sleepiness is greatest), and sleep latency decreased and total sleep time increased with modafinil later in abstinence when these measures were most abnormal. Although slow-wave sleep increased somewhat with abstinence, deficits in slow-wave sleep time in cocaine-dependent participants were prominent throughout abstinence, and the increase in slow-wave sleep caused by modafinil was similarly stable across the study. Consistent with the notion that modafinil reverses sleep deficits, modafinil appeared to normalize sleep in cocaine-dependent participants relative to healthy comparison participants. Indeed, modafinil-treated cocaine-dependent participants had normal slow-wave sleep time, a significant improvement in total sleep time, and apparent reductions in deficits in REM sleep time and sleep-onset latency. In contrast, self-reported sleep quality among cocaine-dependent participants (both modafinil- and placebo-treated) was not significantly different from that among healthy comparison participants, nor was it numerically better than that among healthy comparison participants, supporting the previous finding of "occult insomnia" (18).

Strengths of the present study, compared with previous polysomnographic studies of sleep in cocaine users, are the relatively large number of participants and the use of a fixed time in bed for all participants. However, the number of participants was still small for a placebo-controlled trial and was powered only to detect the previously observed changes in sleep during abstinence in each group separately (18, 19, 24). Another limitation of the study design was the lack of occipital EEG leads for nocturnal polysomnography. Although this limitation may not have affected the experimental groups differently, it may have caused a small systematic difference in the observed nocturnal sleep latencies. In addition, the use of the fixed time in bed, while a strength, introduced the possibility of an unforeseen group difference. In particular, some participants may have had more difficulty adapting to the 11:00 p.m. bedtime than others, and formal assessment of "morningness/eveningness" was not conducted (and possible differences between groups in "morningness/eveningness" are not known). However, the sleep results for the placebo group of this study match well with our prior study in which bedtime was flexible (18, 19), suggesting that any difficulty adapting to the fixed schedule did not likely affect this aspect of the results. Although cocaine use immediately prior to the start of the study was not normalized through the use of laboratory cocaine administration, the accuracy of observed urine toxicology screens at the time of admission provided reasonable assurance that all participants were between 2 and 6 days of abstinence, consistent with their self-report. Other limitations include the lack of control over daytime lighting conditions, the lack of a substantial number of nontreatment seeking cocaine users, and the possibility of withdrawal from other substances influencing the measured outcomes. The latter two concerns were largely addressed in our previous studies, where we found similar changes in sleep during abstinence in nontreatment seeking participants, and in a study design that controlled for withdrawal from other substances (18, 19).

The present results suggest that modafinil, given early in the morning, has positive effects on sleep and sleepiness in chronic cocaine users. In early abstinence, modafinil decreases the objective and subjective sleepiness associated with withdrawal from cocaine. Throughout 3 weeks of abstinence, it decreases subjective afternoon sleepiness. Nocturnally, latency to sleep onset is decreased with modafinil and sleep architecture is improved, with severe deficits in slow-wave sleep reversed and the development of REM sleep and total sleep time deficiencies during abstinence reduced. These effects are likely mediated in large part by the cocaine-like effects of modafinil on dopamine neurotransmission (29–33, 49). Cocaine given approximately 9 hours prior to sleep, for example, has similar effects, including an increase in slow-wave sleep activity on the same night and rebounds in REM sleep and total sleep time that develop the next day (18, 19). We hypothesize that the apparent clinical effectiveness of modafinil given in the morning (25) is in part due to these effects on daytime sleepiness

and nocturnal sleep. Finding such a connection between sleep improvement and clinical effectiveness in cocaine dependence, a condition that is not intrinsically a sleep disorder, is also relevant to the treatment of other conditions in which sleep abnormalities may contribute to morbidity, inhibit recovery, and, indeed, may be closely related to the disease process (e.g., major depression [2]). This connection should be explicitly and prospectively tested in a controlled clinical study.

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