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Abstinence-related changes in sleep during treatment for cocaine dependence

G.A. Angarita[a,b,*], S.V. Canavan[a,b,1], E. Forselius[a,b,2], A. Bessette[a,b,2], B. Pittman[a,3], P.T. Morgan[a,b,2]

[a] Psychiatry, Yale University School of Medicine, New Haven, CT, United States
[b] Clinical Neuroscience Research Unit, Connecticut Mental Health Center, New Haven, CT, United States

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ABSTRACT

Background: Former sleep studies among non-treatment seeking chronic cocaine users had captured polysomnographic changes for as long as three weeks of abstinence.
Methods: 20 cocaine dependent participants, randomized to placebo in an ongoing clinical trial, received 12 days of inpatient substance abuse treatment followed by 6 weeks of outpatient cognitive behavioral therapy. Polysomnographic recording was performed on consecutive nights during the 1st and 2nd inpatient and 3rd and 6th outpatient weeks. Number of days abstinent was determined from thrice weekly urine toxicology and self-report. Polysomnographic sleep was compared between study week 1 and 2, using paired *t*-tests. Trajectory of total sleep time (TST) was modeled both as a linear and a quadratic function of days abstinent.
Results: Despite reporting an improvement in overall sleep quality, polysomnographic sleep worsened from week 1 to 2. Among all participants, TST and stage 2 sleep time decreased, while REM sleep latency increased. Among participants who began the study with a positive urine test, there was also a decrease in REM and a trend for decreased slow wave sleep. TST compared to number of days abstinent (up to 54 days) was best fit with a quadratic model ($p = 0.002$), suggesting the possibility of an improvement in total sleep time with extended abstinence.
Conclusions: This is the first polysomnographic characterization of sleep in a large sample of cocaine users in treatment. Present findings confirm earlier results of poor and deteriorating sleep early in abstinence, and raise the possibility of improvement after an extended abstinence.

1. Introduction

An important feature of cocaine use disorders is the increased vulnerability to relapse that patients undergo during the first weeks of abstinence. This phenomenon has been described in humans (Gawin and Kleber, 1986) in whom cue-induced craving increases after 2–10 weeks of abstinence, and in rodents, displaying not only a delay in the onset of craving, but also its progressive increment over a two months' period (Grimm et al., 2001).

Sleep dysfunction may be an important contributor to this pattern of relapse. As one of several commonly recognized abstinence/withdrawal symptoms, it may influence important endpoints such as capacity to complete treatment (Kampman et al., 2001). Early descriptions of cocaine abstinence discuss the normalization of sleep as an event that takes place in the transition between "the crash," or the first week after last cocaine use, and the "withdrawal phase" 2–10 weeks after last cocaine use. In addition, early qualitative studies observed improvement in self-reported sleep measures with abstinence (Weddington et al., 1990; Gawin and Kleber, 1986). Contrary to those initial descriptions and subjective reports, polysomnographic studies found worsening of sleep over the first 2–3 weeks of abstinence (for review see Morgan and Malison, 2007), introducing the possibility that persistent sleep abnormalities could have an effect on clinical outcomes, including, and in addition to, treatment completion.

A connection between sleep and treatment in drug dependence may not be surprising, given the intrinsic importance of sleep physiology to brain function and, in particular, the many overlapping neurotransmitter systems and brain regions that affect

* Corresponding author at: Clinical Neuroscience Research Unit, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519, United States. Tel.: +1 203 974 7536; fax: +1 203 974 7662.
E-mail address: Gustavo.angarita@yale.edu (G.A. Angarita).
[1] University of Chicago, 5841 S. Maryland Avenue, O-132, MC 2121, Chicago, IL 60637, United States.
[2] Clinical Neuroscience Research Unit, Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519, United States.
[3] Connecticut Mental Health Center, 34 Park Street, New Haven, CT 06519, United States.

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sleep. Regulation of sleep and wakefulness involves structures such as the brain stem, hypothalamus, basal forebrain, preoptic area of the hypothalamus, the thalamus and the cortex, and is influenced by the actions of GABA, glutamate, adenosine, nitric oxide, acetylcholine, dopamine, serotonin, norepinephrine, histamine, orexin/hypocretin, and neuropeptide S, among other neurotransmitters (Brown et al., 2012). The action of cocaine on these systems produces several changes that can affect sleep. For instance, blocking uptake of not only dopamine but also serotonin and norepinephrine by cocaine may disrupt the balance between sleep and wakefulness, given that these amines promote wake and suppress sleep (Baumann et al., 1995; Koob and Nestler, 1997). In addition, cocaine intake can also lead to enduring changes in the cholinergic (Heidbreder and Shippenberg, 1996), adenosinergic (Toda et al., 2003), glutamatergic (Kalivas et al., 2003), and GABAergic (Xi et al., 2003) systems, all known to be involved in the regulation of the sleep- wake cycle (Brown et al., 2012).

The changes in sleep and sleep architecture associated with cocaine use and abstinence may be particularly relevant to understanding the potential impact of sleep abnormalities on treatment outcomes. Changes in sleep architecture observed during early withdrawal include shortened sleep onset latency, decreased rapid eye movement (REM) sleep latency, and increased REM sleep time and total sleep time (TST; Morgan et al., 2006, 2008). After 2–3 weeks of abstinence, however, TST appears shortened (5–6 h), latency to sleep onset is delayed (by 10–50 min), and REM sleep time is reduced despite decreased REM latency (Morgan and Malison, 2007). Perhaps most striking, however, is the finding that slow-wave sleep (SWS) time appears dramatically reduced compared to age matched-controls (Morgan et al., 2010). This change may be particularly important given the evolutionary value of SWS (Rattenborg, 2006), its preservation despite chronic sleep restriction (Van Dongen et al., 2003) or, in response to sleep deprivation (Borbely et al., 1981), the multiple cognitive functions that appear to rely on it (Stickgold et al., 2000), and evidence suggesting that promoting SWS with a medication such as tiagabine can improve cognitive performance in sleep restricted individuals (Walsh et al., 2006).

Unfortunately, there have been relatively few studies of appreciable size that have examined sleep deficits objectively in abstinent cocaine users, owing to the difficulty of such studies. In addition, these studies have been limited in the duration of abstinence in which sleep is measured. For example, previous work from our laboratory on this question has been restricted to fully inpatient studies of not more than 3 weeks (Morgan et al., 2006, 2008, 2010), with a mix of treatment and non-treatment seeking participants, and without directed treatment being offered. Here we present objective and self-report sleep measurement from an ongoing, randomized controlled trial for the treatment of cocaine dependence. In particular, we are presenting sleep data from the placebo arm of this trial, which to date constitutes the largest sample of cocaine dependent persons in whom polysomnographic sleep has been measured, and a sample in which extended periods of outpatient abstinence were achieved.

2. Methods

2.1. Cocaine dependent participants

Chronic cocaine users were recruited to participate in an ongoing randomized placebo-controlled trial of modafinil.

In order to be eligible for all study procedures, participants underwent a screening in three phases. The first phase included a telephone interview, assessing whether potential participants were likely to qualify, their desire for treatment and interest in the study, basic demographic questions, and severity of cocaine use. The second phase entailed an in depth medical, psychiatric, and substance abuse screening. For the medical evaluation, an experienced physician obtained a medical history, performed a physical exam, reviewed medical records when available, and reviewed results of basic blood and urine laboratory work and an electrocardiogram. Psychiatric and substance abuse assessment consisted of an unstructured clinical interview performed by a psychiatrist and other instruments to determine additional substance/alcohol use, such as the Substance Use Calendar. Psychiatric interview of this phase was conducted on either an outpatient basis or upon admission to the research unit. The third and final screening phase was conducted upon admission, and included a new urine toxicology screening, a breath alcohol test, and a final recapitulation of drug and alcohol use since outpatient screening or in the past 30 days prior to inpatient admission. On the third inpatient night and as the last step on the screening process, participants underwent a clinical polysomnography in order to identify previously undiagnosed sleep disorders.

This report includes data from all participants who were found to have received placebo ($n = 20$) at a preliminary unblinding point.

Participants were required to meet DSM-IV criteria for cocaine dependence with a duration of at least 2 years, current criteria for dependence as measured by a score ≥ 3 on the severity of dependence scale (Kaye and Darke, 2002), and have a positive urine test for cocaine (benzoylecgonine) during the screening process.

Potential participants were excluded if they had a medical condition that would render study participation unsafe; a chronic primary sleep disorder; a known hypersensitivity to modafinil; current dependence on any drugs other than cocaine or nicotine; lifetime dependence on alcohol, benzodiazepines, or opiates; current, non-substance related Axis I disorder; current use of alcohol in excess of 21 standard drinks/week in the past month or non-zero breathalyzer at screening or study start; or a positive urine toxicology test for opiates, methadone, amphetamines, barbiturates, benzodiazepines, PCP, methaquolone, and propoxyphene at the time of screening, or a positive test for any of those listed plus cannabis at the time of study start. Individuals were also excluded if they were taking psychiatric medications, medications that affect sleep, or medications not safe to take with modafinil; or, if female and of childbearing potential, if they were pregnant, lactating, or unwilling to use contraceptives for the duration of the study.

All individuals reviewed and signed a consent form approved by the local institutional review board, with understanding assessed by a quiz.

2.2. Study design

The study consisted of a 12-day inpatient stay followed by a six-week outpatient phase with appointments three times per week. Inpatient treatment for substance abuse included both individual and group therapy, and outpatient treatment consisted of weekly, manual guided cognitive behavioral therapy (Kadden et al., 1992), and thrice-weekly urine toxicology screening. Adherence to study participation was promoted through contingency management (Budney and Higgins, 1998; Petry, 2000) wherein keeping appointments and participating in study related duties (but not abstinence) were rewarded. In week 3 and week 6 of the outpatient phase, participants returned for additional inpatient stays of two nights each.

Participants were compensated by check after the end of the study, including $200 for the initial inpatient stay, $50 for each readmission, and $200 for participating in the entire study. They also earned up to $10 in cash each week for returning their empty pill pack, and depending on their adherence to the outpatient portion of the study (not related to abstinence), they earned contingency management prizes adding up to a mean of $234.

2.3. Inpatient environment

Participants were admitted to an inpatient psychiatry research unit. Participants slept in a single room every night and were not allowed to sleep, nap, or lie in a recumbent position between 7 am and 11 pm. The unit provided all meals and snacks as part of a caffeine free diet. In addition, fresh air breaks outside of the building were allowed with staff members three times a day, during which time smokers had the opportunity to smoke 1–2 cigarettes.

2.4. Polysomnographic sleep measures

Overnight polysomnographic sleep studies (PSG) were conducted eight times total: during the inpatient portion on the nights of days 3, 4, 10, and 11; and during outpatient weeks 3 and 6 on both nights of the 2-day admissions. The first night of each consecutive day set was used as an accommodation night to acclimate the participant to wearing the polysomnographic equipment, while data from the second night was used for analyses and is reported here. For all PSG studies, a strict 11 pm to 7 am time in bed was followed.

Polysomnography was performed using a TEMEC 8 Channel Universal system (TEMEC Instrument B.V., Kerkrade, the Netherlands) and consisted of two electrographic (EEG) leads (C3-A2 and C4-A1), left and right electrooculogram (EOG) referenced to the opposite mastoid, a two-lead chin electromyogram (EMG), and a two-lead electrocardiogram (ECG).

On the first night of recording (night 3), a more extensive clinical sleep study was carried out (Siesta; Compumedics, Abbotsford, Australia) to screen for sleep disorders. In addition to the above leads, this setup included four more EEG leads (F3-A2, F4-A1, O1-A2, and O2-A1), right and left leg EMGs, finger pulse oximeter, plethysomographic thoracic and abdominal belts, airflow sensor, and snore microphone.