Drug and Alcohol Dependence xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Drug and Alcohol Dependence

journal homepage: www.elsevier.com/locate/drugalcdep

Correlates of polysomnographic sleep changes in cocaine dependence: Self-administration and clinical outcomes☆

Gustavo A. Angarita[a,b,*,1], Sofija V. Canavan[a,b,1,2], Erica Forselius[a,b], Andrew Bessette[a,b], Peter T. Morgan[a,b]

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

ARTICLE INFO

Article history:
Received 8 April 2014
Received in revised form 18 July 2014
Accepted 18 July 2014
Available online xxx

Keywords:
Cocaine
Sleep
Polysomnography
Clinical outcomes
Self-administration
Abstinence

ABSTRACT

Background: Abstinence from chronic cocaine use is associated with abnormal sleep architecture. As sleep abnormalities are associated with clinical outcome in alcohol dependence, we hypothesized a similar relationship in cocaine dependence.
Methods: We report data from a cocaine self-administration study ($N = 12$) and the placebo arm of a randomized clinical trial ($N = 20$). Self-administration participants underwent three cocaine self-administration sessions during a three-week inpatient stay. Treatment participants underwent two weeks of inpatient followed by six weeks of outpatient treatment including once-weekly cognitive behavioral therapy. Measurements included polysomnography from early and late in abstinence during the inpatient stays. Clinical outcomes included amount of cocaine self-administered, urine tests, and self-reported use and withdrawal symptoms.
Results: Change in slow-wave sleep from early to late abstinence (ΔSWS; $p = 0.05$), late abstinence rapid eye movement sleep (REM; $p = 0.002$), and late abstinence total sleep time ($p = 0.02$) were negatively correlated with the amount of cocaine self-administered. Early abstinence REM was positively correlated with withdrawal symptoms ($p = 0.02$). Late abstinence REM was positively correlated with percent negative urines and maximum consecutive number of days abstinent (both $p < 0.001$). ΔSWS was positively correlated with percent negative urines ($p = 0.03$) and participants with increased SWS had greater percent negative urines ($p = 0.008$) and maximum consecutive number of days abstinent ($p = 0.009$).
Conclusions: Correlations between sleep deficits and amount of cocaine self-administered, clinical outcomes, and severity of withdrawal symptoms underscore the relevance of sleep in clinical outcomes in the treatment of cocaine dependence.

1. Introduction

Cocaine use disorders exert a global impact. Not only has cocaine use increased in Europe and in some West African countries within the past decade (Degenhardt et al., 2011), but evidence-based ranking of addictive substances, using categories such as physical harm, dependence, and social stigma, has also listed cocaine as the second most harmful drug, after heroin (Nutt et al., 2007). North America has the world's highest prevalence rates for cocaine dependence, estimated at 1.6 million cases (Degenhardt et al., 2013). Despite reductions from peak use in the 1980s and 1990s, cocaine use remains a significant problem in the United States. In 2012, there were more current and more new users of cocaine than of heroin and methamphetamine combined (National Survey on Drug Use and Health, 2013). Despite decades of research into potential pharmacological treatment of cocaine dependence, no medication has been approved by the FDA to treat this condition.

In order to identify an effective pharmacotherapy that could be added to current psychosocial interventions (Simpson et al., 1999), one of the targets considered has been the disruption in sleep associated with chronic use of cocaine and withdrawal there from. This interest stems both from previous findings in cocaine users by our group and others, and from multiple findings on

☆ Supplementary material can be found by accessing the online version of this paper at http://dx.doi.org and by entering doi:. . ..

* Corresponding author at: Clinical Neuroscience Research Unit of the Connecticut Mental Health Center, New Haven, CT 06519.
E-mail address: Gustavo.angarita@yale.edu (G.A. Angarita).

[1] Indicates shared first authorship.

[2] University of Chicago, 5841 S. Maryland Avenue, O-132, MC 2121, Chicago, IL 60637, United States.

http://dx.doi.org/10.1016/j.drugalcdep.2014.07.025
0376-8716/

alcohol use disorders dating back to the 1970s (Allen et al., 1971, 1977; Allen and Wagman, 1975). One of the earliest studies on sleep in alcoholics found that rapid eye movement sleep, measured as a percentage of total sleep (REM%) decreased after 2–3 days of withdrawal but rebounded after 5–6 days (Allen et al., 1971). Later, this group demonstrated the potential clinical value of objectively measured sleep abnormalities: low REM% was positively correlated with response rate in a button-press task to obtain an alcoholic drink faster (Allen and Wagman, 1975). While some of the above findings on REM have been difficult to replicate, new findings have emerged. For instance, one study showed that persons with alcohol dependence who relapsed within 3 months of an inpatient admission had increased REM%, rather than decreased, and had shorter REM latency upon admission and upon discharge, in comparison with persons who remained abstinent (Gillin et al., 1994).

Other work has examined changes in the slow wave sleep (SWS) of alcohol users. This work ranges from documenting the potential ability of acute alcohol use to increase SWS (Gross and Hastey, 1975) to several reports of abnormally low SWS among alcohol users, an effect that may remain for months (Brower, 2003). When it comes to the potential clinical relevance of SWS, Allen and colleagues examined SWS% in nine inpatients and found that subjects with poor outcomes had lower levels of SWS% at baseline, in comparison with the subjects who had good outcomes (Allen et al., 1977). Nevertheless, similar to the literature on REM, some findings on SWS have not been strongly replicated. For instance, study by Gillin et al. (1994) showed no differences in Stage 3 or Stage 4 NREM sleep between abstainers and relapsers. In another study, subjects who relapsed had lower percentages of Stage 4 NREM sleep, but not SWS overall (Brower et al., 1998).

Intriguingly, deficits in SWS have been observed in chronic users of other addictive substances including central nervous system depressants such as heroin (Schierenbeck et al., 2008), stimulants such as amphetamines and cocaine (Thompson et al., 1995), and cannabis (Barratt et al., 1974; Bolla et al., 2008). Decreased SWS has been found early in abstinence and during sub-acute withdrawal from cocaine use (Angarita et al., 2014; Morgan et al., 2010; Schierenbeck et al., 2008) in addition to other polysomnographic changes present during the first weeks of abstinence from cocaine (Matuskey et al., 2011; Morgan et al., 2006, 2008, 2010). These changes include early REM rebound (Pace-Schott et al., 2005), prolongation of REM latency (Angarita et al., 2014), and decreases in REM, SWS, and total sleep time (TST) during the first 3 weeks of abstinence (Angarita et al., 2014; Morgan et al., 2006, 2008, 2010; Pace-Schott et al., 2005; Thompson et al., 1995).

Lastly, subjective self-reports of sleep may impact clinical outcomes in chronic substance users. For example, answering yes to the statement, "it takes me a long time to fall asleep" on the Nottingham Health Profile (NHP) questionnaire differentiated those who relapsed from those who abstained from alcohol (Foster et al., 1998). Another study, also among alcohol dependent subjects, demonstrated that the presence of subjective sleep disruption increased the likelihood of relapse (Brower et al., 2001). However, cocaine users exhibit the opposite trend of alcoholics when it comes to the clinical utility of subjective sleep measurements. Early work on inpatient cocaine dependent subjects studied for 28 days found conflicting subjective reports such as improvement on several sleep measurements (e.g., sleep quality) on one hand, and difficulties falling asleep, on the other (Weddington et al., 1990). Our group has shown that cocaine users report experiencing better sleep as abstinence progresses, despite the objective deterioration of multiple sleep measures along with worsening sleep-related cognitive function (Morgan et al., 2006). This discrepancy between subjective self-report and objective polysomnographic measurements has been replicated (Angarita et al., 2014).

However; in spite of the prior research on subjective and objective sleep abnormalities in chronic cocaine users, no work to date has associated sleep parameters during the initial abstinence period with later cocaine use or relapse.

The purpose of this work was to test for such an association by measuring sleep during confirmed abstinence in an inpatient setting as a predictor of two clinical phenotypes: laboratory cocaine self-administration (number of doses delivered) and use-related clinical outcome during treatment (i.e., percentage of urine tests negative for cocaine and maximum consecutive number of days abstinent). To that end, we performed secondary analyses from two cohorts of participants: the first was a group of non-treatment seeking, cocaine dependent participants who self-administered cocaine during a period of inpatient abstinence; the second was a group participating in a combined inpatient-outpatient treatment protocol. Given that baseline sleep measures such as TST, SWS, and REM are perturbed in abstinent cocaine users relative to age matched controls, and considering that normalization of sleep measures have shown to be related to clinical outcomes in alcohol dependent patients, we hypothesized that decreased TST, SWS, and REM sleep measurements during abstinence, and the lack of normalization in those measurements in response to further abstinence, would positively correlate with worse clinical outcomes (e.g., more cocaine self-administration and lower percentage of negative urines/maximum number of consecutive days abstinent).

2. Methods

2.1. Participants

Data is presented from two groups: (1) a "self-administration group" consisting of non-treatment seeking cocaine dependent individuals ($N = 12$) who participated in a laboratory study of intravenous cocaine self-administration (Morgan et al., 2008) and (2) a "treatment group" consisting of treatment-seeking cocaine dependent individuals enrolled in an ongoing clinical trial on modafinil who were randomized to receive placebo ($N = 20$).

All participants met DSM-IV criteria for cocaine dependence, had been using cocaine for at least two years, were not taking any psychiatric medication, and were not dependent on any other drugs (except nicotine).

Potential participants were excluded if they had a medical condition that would render study participation unsafe, a chronic primary sleep disorder, a current non-substance/alcohol related axis I psychiatric disorder, or if taking either psychiatric medications or medications known to affect sleep. Female of childbearing potential were excluded if pregnant, lactating, or unwilling to use effective forms of contraception.

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

Self-administration group: Detailed methods and outline of the self-administration study design were published previously (Morgan et al., 2006) and are summarized here in Fig. 1. Briefly, 12 participants stayed inpatient for 23 days and were randomized to either an "early binge" group ($N = 6$) or a "late binge" group ($N = 6$) in a placebo-controlled manner to control for potential confounding effects of both inpatient hospitalization and potential subclinical withdrawal from other substances (e.g., alcohol, benzodiazepine, or cannabis). Both subgroups underwent an initial cocaine self-administration session on day 0 to assess safety and eligibility. The early binge subgroup completed 3 days of laboratory cocaine self-administration on study days 4–6 and 3 days of placebo (saline) self-administration on study days 18–20. The late binge subgroup completed the 3 days of placebo self-administration on study days 4–6 and the 3 days of cocaine self-administration on study days 18–20. Participants were not aware of the early binge/late binge design, were not exposed to any medications during study days 1–3, 7–17, and 21–23, and were blinded as to whether they were receiving placebo or cocaine during any given session.

During each experimental self-administration day, participants were allowed to administer, ad libitum, up to 12 cocaine doses of 32 mg/70 kg over a 2-h binge period from 12 P.M. to 2 P.M. A 5-min lockout period following each bolus dose and a 384 mg/70 kg total daily limit were imposed. Safety cut-offs, based on heart rate and blood pressure, were also imposed.

Both subgroups underwent polysomnography (PSG) to measure their sleep on sixteen nights out of the 22-day protocol. Participants were allowed to sleep ad libitum between 9:30 P.M. and 7:45 A.M. every night while on the unit.

Treatment group: Participants in this randomized clinical trial first completed an initial 2-week inpatient phase, followed by a 6-week outpatient phase with thrice-weekly appointments. Inpatient treatment included both individual and group therapy, while outpatient treatment consisted of once-weekly, manual-guided

Please cite this article in press as: Angarita, G.A., et al., Correlates of polysomnographic sleep changes in cocaine dependence: Self-administration and clinical outcomes. Drug Alcohol Depend. (2014), http://dx.doi.org/10.1016/j.drugalcdep.2014.07.025