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Substance use outcomes in cocaine-dependent tobacco smokers: A mediation analysis exploring the role of sleep disturbance, craving, anxiety, and depression

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Abstract

Background.—Sleep disturbance may play a role in cocaine use outcomes and, hence, may be a potential therapeutic target for cocaine use disorder (CUD). Research in this area, which has largely relied on resource-intensive polysomnography, would be facilitated by identifying a self-report sleep measure predictive of CUD outcomes and by a better understanding of the mechanisms by which sleep may impact CUD outcomes. This study tested the predictive validity of the Pittsburgh Sleep Quality Index (PSQI), a self-report assessment of past-month sleep quality. To better understand potential mechanisms, mediation models relating sleep disturbance to CUD outcomes were evaluated.

Methods.—This is a secondary analysis of data from cocaine-dependent (n=290) participants in a multi-site trial evaluating smoking-cessation treatment for stimulant-dependent patients. The PSQI was collected at baseline; the outcomes of interest were cocaine and drug abstinence at end-of-treatment (weeks 9–10). Potential mediators, measured in weeks 1–8, were: cocaine craving (Brief Substance Craving Scale); and anxiety and depression symptoms (Hospital Anxiety and Depression Scale). Mediation techniques were used to evaluate mediation effects separately and jointly.

Results.—The majority of participants (58.3%) had baseline sleep disturbance. Sleep disturbance was not a significant predictor of end-of-treatment abstinence when regressed without consideration of mediators. Cocaine craving, anxiety, and depression were significant mediators, both separately and jointly, of an effect of baseline sleep disturbance on end-of-treatment abstinence.

Conclusion.—This exploratory analysis suggests that there may be an indirect relationship between self-reported sleep quality and substance use outcomes in cocaine-dependent patients, mediated by craving, anxiety, and depression.

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Keywords

cocaine; sleep; mediation; craving; anxiety; depression

1. Introduction

Cocaine use disorder (CUD) has an estimated lifetime prevalence of 2.4% in the U.S. (Grant et al., 2016) and, despite extensive work, there are no FDA-approved interventions for its treatment. Thus, delineating modifiable factors that affect CUD outcomes and, hence, may be novel therapeutic targets, is of clinical import. Sleep disturbance may be of interest in this regard, with a recent imaging study finding that reduced sleep duration mediated the relationship between cocaine use and reduced dopamine D2/D3 receptors, which is predictive of relapse (Wiers et al., 2016). In addition, sleep disturbance, as measured by overnight polysomnographic sleep assessment, has been found to predict greater cocaine use in both human laboratory and outpatient studies (Angarita, Canavan, Forselius, Bessette, & Morgan, 2014). Furthermore, a recent study found that modafinil's effect in increasing cocaine-negative urine drug screens (UDSs) was mediated by an increase in slow-wave sleep (Morgan et al., 2016).

From the standpoint of clinical utility, a self-report measure would be preferable to the relatively resource-intensive polysomnographic sleep assessment. However, there is evidence that at least some self-report measures, such as visual analog scales, underestimate sleep disturbance, with cocaine users self-reporting sleep quality equivalent to normal volunteers despite polysomnographic evidence of sleep disturbance (Angarita, Emadi, Hodges, & Morgan, 2016). In contrast, cocaine users do report sleep disturbances on the Pittsburgh Sleep Quality Index (PSQI), a quasi-objective self-administered instrument (Angarita et al., 2016; Mahoney et al., 2014), and, thus, the PSQI may be less prone to underestimation of sleep disturbance in this population. However, to date, no published research has evaluated whether the PSQI is predictive of CUD outcomes. In addition to identifying a self-report sleep measure with predictive validity, the potential of sleep disturbance as a therapeutic target would be improved through a better understanding of the mechanisms by which it may impact CUD outcomes (Angarita et al., 2014).

A multi-site trial conducted by the National Institute on Drug Abuse (NIDA) National Drug Abuse Treatment Clinical Trials Network (CTN) evaluated the impact of concurrent substance use disorder (SUD) and nicotine dependence treatment for cocaine and/or methamphetamine-dependent patients who were also nicotine dependent (CTN-0046; [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01077024): NCT01077024). CTN-0046 included a baseline PSQI and measures of three constructs hypothesized to be mediators of the relationship between sleep quality and cocaine use outcomes: craving (Chen et al., 2015), depression (Angarita et al., 2014), and anxiety (Angarita et al., 2014). The present study utilized this dataset to conduct mediation analyses evaluating sleep as a potential therapeutic target by testing it as a predictor of substance use outcomes with mood and craving mediating the relationship. While sleep, craving, depression, and anxiety likely have bi-directional relationships, sleep was selected as the predictor variable since mood disorders (Pani, Trogu, Vecchi, & Amato, 2011) and

craving (Lin, 2014) have already received relatively extensive evaluation as therapeutic targets without yielding an FDA-approved medication for CUD. It was hypothesized that baseline sleep disturbance would be a negative predictor of end-of-treatment cocaine and drug abstinence and that the effect would be partially mediated by craving and mood.

2. Methods

2.1 Study Design

Design considerations for the CTN-0046 trial have been published previously (Winhusen, Stitzer, et al., 2012). The trial was a 10-week, intent-to-treat, 2-group randomized controlled trial. Participating sites included 12 outpatient SUD treatment programs that did not provide smoking-cessation treatment. Eligible participants were randomized in a 1:1 ratio to treatment as usual (TAU) or TAU with smoking-cessation treatment (TAU+SCT). During the treatment phase, participants attended twice-weekly research visits. Participants randomized to TAU+SCT participated in the SUD treatment as typically provided by the site and also received SCT, which included bupropion XL (300mg/day), nicotine inhaler (6–16 cartridges/day, ad lib), weekly brief counseling, and prize-based contingency management for smoking abstinence. The results of the trial revealed no significant treatment effect on stimulant- and drug-use outcomes during active treatment (Winhusen et al., 2014) and, thus, the present analyses were conducted without regard to treatment arm.

2.2 Participants

Participants were adult cigarette smokers interested in quitting smoking and enrolled in outpatient SUD treatment for stimulant dependence. Eligible participants were in good physical health, not currently being treated for nicotine dependence, and had no medical or psychiatric conditions that would make study participation unsafe. The exclusively cocaine-dependent participants (N=290) were included in the present analyses.

2.3 Measures

The Pittsburgh Sleep Quality Index (PSQI), a 19-item, validated, self-administered instrument that measures sleep quality (e.g., sleep duration, latency, etc.) over the past 30 days, was obtained at baseline; a PSQI global score > 5 is suggestive of significant sleep disturbance (Buysse, Reynolds, Monk, Berman, & Kupfer, 1989). The Hospital Anxiety and Depression Scale (HADS), a 14-item, validated self-administered instrument with subscales measuring depression and anxiety symptoms over the past 7 days (Zigmond & Snaith, 1983), was collected weekly; a subscale score ≥ 8 indicates elevated depression/anxiety (Bjelland, Dahl, Haug, & Neckelmann, 2002). Cocaine craving was assessed weekly using the Brief Substance Craving Scale (BSCS; (Mezinskas, Dyrenforth, Goldsmith, Cohen, & Somoza, 1998). The BSCS instructs the participant to use a five-point scale to rate three aspects of craving: intensity, frequency, and length of time spent craving during the past 24 hours. A rapid UDS system that screened for cocaine, methamphetamine, amphetamine, opioids, benzodiazepines, and marijuana was completed twice weekly. Urine samples were collected using temperature monitoring and were validated with a commercially available adulterant test. Self-report of substance use was assessed twice weekly using the Timeline Follow-back (Fals-Stewart, O'Farrell, Freitas, McFarlin, & Rutigliano, 2000), which is

widely employed and well-validated. Cocaine abstinence was defined by cocaine-negative UDSs and self-report of no cocaine use. The more general outcome, drug abstinence, was defined by UDSs negative for all screened substances and self-report of no substance use other than nicotine.

2.4. Data analysis

Mediation effects were tested using standard mediation analysis techniques (Herr; Kenny, 2016; Mackinnon & Dwyer, 1993). In mediation analysis, the “total effect” is the effect of a predictor on an outcome without considering mediators. A “mediation effect” is the effect presumably caused by the predictor affecting a mediator, which in turn affects the response. The “direct effect” is the effect remaining after accounting for mediation effects. All regressions either had binary outcomes and used logistic models, or had ordered categorical outcomes and used proportional odds logistic models. All effects and respective 95% confidence intervals were estimated using bootstrap procedures. All calculations used SAS 9.4.

The predictor, mediator, and outcome variables were defined prior to undertaking the analysis. The predictor variable (X) was baseline sleep disturbance (PSQI total score > 5 vs. 5). As mediators (M), we tested the following HADS and BSCS results for study weeks 1–8: proportion of HADS anxiety scores > 8, proportion of HADS depression scores > 8, and proportion of BSCS cocaine craving scores > 0. The BSCS cutoff was set to zero due to zero-inflated data. For each of the three measures (craving, anxiety, and depression), the value used in the analysis was the number of weeks out of eight for which the participant’s score was significant based on the given cutoff. As outcomes (Y), we used cocaine abstinence and drug abstinence for weeks 9–10. Abstinence during the final two weeks of the active treatment phase (end-of-treatment abstinence) is consistent with cocaine research outcomes (Somoza et al., 2013).

Analysis began with separate, independent tests of each mediator. Because the tested mediation effects were co-occurring and likely related, we supplemented our separate analyses by jointly testing all mediators in one parallel multiple-mediator model to more accurately assess simultaneous mediation effects (MacKinnon, 2000; MacKinnon, Fairchild, & Fritz, 2007). However, it was suspected that collinearity between the mediators may obscure the hypothesized relationships. Thus, we first transformed the potential mediator variables into their independent principal components (Jolliffe, 2002) and performed our joint analysis, evaluating the principal components as mediators.

3. Results

Table 1 summarizes participants’ demographic and baseline characteristics. The majority of participants (58.3%) had a PSQI global score > 5, indicating significant sleep disturbance. As can be seen, the groups were generally comparable, though participants with significant sleep disturbance were less likely to be Hispanic. The groups did not differ significantly on the proportion of cocaine-abstinent participants; in the subset of non-abstinent participants, the frequency of cocaine use days was higher in those with significant sleep disturbance.

At end-of-treatment, there was no significant group difference for either cocaine abstinence, which was achieved by 63.5% of participants, or drug abstinence, which was achieved by 45.0% of participants. Table 2 summarizes the separate mediation analysis results, which were similar for both end-of-treatment cocaine abstinence and drug abstinence. Contrary to prediction, baseline sleep disturbance did not show significance as a predictor of end-of-treatment abstinence when regressed without consideration of mediators (see Table 2, “Total Effect”). However, it was shown to be a significant positive predictor of all three mediators (cocaine craving, anxiety, and depression); the mediators were shown to be significant negative predictors of end-of-treatment cocaine and drug abstinence. When tested separately, each potential mediator was consistently a significant mediator of an effect of baseline sleep disturbance on end-of-treatment abstinence. When included in the joint principal components mediation analysis, cocaine craving, anxiety, and depression showed significance as joint, consistent, and approximately equal contributors to a common mediation effect (see Table 3, “Principal Component M1”).

4. Discussion

This study evaluated the ability of the PSQI, a self-report assessment of sleep quality, to predict outcomes in patients with CUD and evaluated cocaine craving, anxiety, and depression as mediators of the hypothesized relationship between baseline sleep quality and CUD outcomes. Approximately 58% of the sample had significant sleep disturbance at baseline, as measured by the PSQI. The results did not reveal a significant association between sleep quality and cocaine and drug abstinence outcomes. Both the independent mediation analyses and the joint principal components mediation analysis indicated with statistical significance that cocaine craving, anxiety, and depression were instrumental in mediating a relationship between sleep disturbance and substance use outcomes. These mediation results reveal a relationship between sleep quality and substance use outcomes that would not have appeared using only simple regression analysis. This pattern of results suggests that this may be an indirect relationship (Hayes, 2009; Shrout & Bolger, 2002), mediated by increased craving, anxiety, and depression.

While the importance of understanding the factors mediating the potential relationship between sleep and cocaine use outcomes has been noted (Angarita et al., 2014), this is, to our knowledge, the first study evaluating potential mediators. When substance use outcomes were regressed against sleep quality without regard for mediators, no relationship was found; this is inconsistent with past research finding such a relationship (Angarita et al., 2014). The difference in results may be due to several factors. First, studies finding a significant relationship have utilized polysomnographic sleep assessments (Angarita et al., 2014) whereas the present study utilized the PSQI, which is a self-report assessment; polysomnographic sleep assessments may be a more sensitive measure of sleep deficits (Angarita et al., 2016). Second, our study sample consisted of cocaine-dependent tobacco smokers in an outpatient SUD treatment setting, whereas patients in the study by Angarita and colleagues (Angarita et al., 2014) were observed in an inpatient setting.

The finding of a significant association between baseline sleep quality and cocaine craving, anxiety, and depression during the active study is consistent with past research suggesting

that poorer sleep quality is associated with cocaine craving and mood problems (Carpenter & Andrykowski, 1998; Chen et al., 2015; Grandner, Kripke, Yoon, & Youngstedt, 2006; Hinz et al., 2017). The small, but statistically significant relationships between craving (Sinha, Garcia, Paliwal, Kreek, & Rounsaville, 2006; Weiss et al., 2003), depression (Stulz, Thase, Gallop, & Crits-Christoph, 2011), anxiety (Buffalari, Baldwin, & See, 2012) and SUD outcomes in CUD is also consistent with research suggesting similar associations.

The results of the present study suggest that patients with CUD reporting sleep disturbance, as measured by the PSQI, may need additional intervention to achieve cocaine and drug abstinence, relative to those without reported sleep disturbance. These results, taken together with past findings (Angarita et al., 2014; Morgan et al., 2016; Wiers et al., 2016), support sleep disturbance as a potential therapeutic target in the treatment of CUD. The present study has several strengths and a few limitations. First, this study included a relatively large sample of individuals with CUD, which helps to ensure the reliability of the results. Second, the sample was comprised of cocaine-dependent patients seeking treatment at community treatment programs located in multiple states; thus, the results are likely generalizable to individuals seeking treatment for CUD (Winhusen, Winstanley, Somoza, & Brigham, 2012). A limitation is that mediation analyses are correlational in nature and, thus, cause-and-effect determinations cannot be made. Second, the mediators evaluated were limited to the assessments included in the parent trial, which was not designed to address this question. For example, we were unable to assess cognitive function and stress reactivity as potential mediators (Angarita et al., 2014) since these constructs were not assessed in the parent trial.

4.1 Conclusions

In conclusion, the results of this exploratory analysis suggest that there may be an indirect relationship between sleep disturbance and SUD outcomes, mediated by cocaine craving, anxiety, and depression in cocaine-dependent tobacco smokers in outpatient SUD treatment. Future research to: 1) replicate and extend the evaluation of mediators to objective measures of sleep quality; and 2) evaluate the potential of sleep disturbance as a therapeutic target for CUD may be of interest.

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Highlights

Sleep disturbance has been associated with cocaine use disorder (CUD) outcomes.

A self-report sleep measure predictive of CUD outcomes could be clinically useful.

Cocaine users self-report sleep disturbances on the Pittsburgh Sleep Quality Index.

Baseline sleep disturbance, mediated by mood and craving, predicted worse outcomes.

Sleep disturbance as a potential therapeutic target for CUD may be of interest.

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Table 1.

Participant demographic and baseline characteristics as a function of baseline sleep quality

	Normal Sleep at Baseline (N=121)	Disturbed Sleep at Baseline (N=169)	Statistical Analysis ^a
Age, mean (SD), y	40.7 (9.7)	39.6 (10.0)	W=0.2
Sex, male, n (%)	73 (60.3%)	93 (55.0%)	X ² (1)=0.8
Race, n (%)			X ² (2)=1.6
African-American	66 (55.0%)	92 (54.4%)	
Caucasian	46 (38.3%)	71 (42.0%)	
Other/mixed	8 (6.7%)	6 (3.6%)	
Ethnicity, Hispanic, n (%)	16 (13.3%)	9 (5.4%)	X ² (1)=5.5 *
Baseline use (prior 28 days)			
Cocaine-abstinent, n (%)	82 (67.8%)	98 (58.0%)	X ² (1)= 2.9
Cocaine use days ⁺	3.7 (4.5)	6.8 (7.2)	T (105.7)=2.8 *
Drug-abstinent, n (%)	74 (61.2%)	84 (49.7%)	X ² (1)=3.7
Alcohol use days ⁺	4.3 (4.9)	4.5 (5.9)	W=0.3
Cannabis use days ⁺	2.7 (7.2)	5.3 (9.8)	T (120)=1.8
Opioid use days ⁺	0.8 (4.1)	0.6 (3.2)	W=0.2
Sedative use days ⁺	0.9 (4.6)	0.2 (1.3)	T (50.3)=1.1
No. of cigarettes/day	15.9 (7.7)	17.4 (7.7)	W=1.7
Diagnoses, n (%)			
Major Depression	5 (12.8%)	12 (16.9%)	X ² (1)= 0.3
Alcohol abuse/dependence	31 (63.3%)	65(75.6%)	X ² (1)= 2.3
Cannabis abuse/dependence	15 (30.6%)	22 (25.6%)	X ² (1)= 0.4
Opioid abuse/dependence	10 (20.4%)	11 (12.8%)	X ² (1)= 1.4
Sedative abuse/dependence	3 (6.1%)	15 (17.4%)	X ² (1)= 3.5

Note. Disturbed sleep defined as scoring > 5 on the Pittsburgh Sleep Quality Index^aW= Wilcoxon rank-sum test; X²(df)= Pearson chi-square test (degrees of freedom); T=T-test (degrees of freedom).*
p<.05.

Where not specifically indicated, numbers represent means (standard deviations).

⁺
In non-abstinent participants

Table 2.

Summary of separate analyses testing cocaine craving, anxiety, and depression as mediators of the hypothesized relationship between baseline sleep disturbance and substance use outcomes

		Baseline Sleep Disturbance (X)	
		Cocaine Abstinence (Y)	Drug Abstinence (Y)
BSCS Cocaine Craving (M)	Total Effect	−0.138 (−0.278, 0.007)	−0.134 (−0.265, 0.001)
	Effect of X on M	0.202 (0.084, 0.314) *	0.193 (0.075, 0.300) *
	Effect M on Y	−0.400 (−0.517, −0.268) *	−0.402 (−0.523, −0.268) *
	Direct Effect	−0.044 (−0.185, 0.108)	−0.054 (−0.185, 0.078)
	Mediation Effect	−0.081 (−0.142, −0.035) *	−0.077 (−0.135, −0.031) *
HADS Anxiety (M)	Total Effect	−0.138 (−0.280, 0.009)	−0.134 (−0.263, 0.008)
	Effect of X on M	0.304 (0.186, 0.412) *	0.295 (0.176, 0.394) *
	Effect M on Y	−0.255 (−0.391, −0.108) *	−0.237 (−0.381, −0.090) *
	Direct Effect	−0.057 (−0.210, 0.099)	−0.067 (−0.204, 0.078)
	Mediation Effect	−0.078 (−0.139, −0.031) *	−0.070 (−0.132, −0.026) *
HADS Depression (M)	Total Effect	−0.138 (−0.276, 0.005)	−0.134 (−0.260, 0.002)
	Effect of X on M	0.280 (0.142, 0.412) *	0.289 (0.151, 0.421) *
	Effect M on Y	−0.299 (−0.458, −0.153) *	−0.303 (−0.486, −0.126) *
	Direct Effect	−0.061 (−0.204, 0.084)	−0.066 (−0.206, 0.067)
	Mediation Effect	−0.084 (−0.156, −0.036) *	−0.087 (−0.172, −0.030) *

All effect estimates are accompanied by respective 95% confidence intervals. Bolded entries represent the mediation effects of interest.

* Confidence intervals indicate statistical significance ($\alpha = 0.05$).

Table 3.

Summary of analysis jointly testing the principal components of cocaine craving, anxiety, and depression as mediators of the hypothesized relationship between baseline sleep disturbance and substance use outcomes. The lower half shows the weights of each variable within each principal component (M1-M3)

		Baseline Sleep Disturbance (X)	
		Cocaine Abstinence (Y)	Drug Abstinence (Y)
Principal Components (M1, M2, M3)	Total Effect	−0.138 (−0.276, 0.009)	−0.134 (−0.258, 0.001)
	Effect of X on M1	0.241 (0.164, 0.316) *	0.242 (0.165, 0.315) *
	Effect of X on M2	−0.001 (−0.054, 0.053)	−0.006 (−0.059, 0.047)
	Effect of X on M3	−0.015 (−0.053, 0.026)	−0.008 (−0.045, 0.030)
	Effect M1 on Y	−0.412 (−0.547, −0.261) *	−0.408 (−0.559, −0.250) *
	Effect M2 on Y	−0.155 (−0.298, −0.008) *	−0.162 (−0.315, −0.005) *
	Effect M3 on Y	−0.140 (−0.285, 0.011)	−0.148 (−0.291, 0.002)
	Direct Effect	−0.003 (−0.148, 0.144)	−0.020 (−0.150, 0.119)
	Med. Effect (M1)	−0.099 (−0.158, −0.055) *	−0.099 (−0.161, −0.052) *
	Med. Effect (M2)	0.000 (−0.009, 0.011)	0.001 (−0.007, 0.013)
	Med. Effect (M3)	0.002 (−0.003, 0.012)	0.001 (−0.004, 0.010)
	M1 Principal Component Weights		
	Cocaine Craving	0.510	0.511
	Anxiety	0.630	0.631
	Depression	0.586	0.583
	M2 Principal Component Weights		
	Cocaine Craving	0.826	0.821
	Anxiety	−0.170	−0.157
	Depression	−0.537	−0.550
	M3 Principal Component Weights		
	Cocaine Craving	0.238	0.255
	Anxiety	−0.758	−0.759
	Depression	0.608	0.598

All effect estimates are accompanied by respective 95% confidence intervals. Bolded entries represent the mediation effects of interest.

* Confidence intervals indicate statistical significance ($\alpha = 0.05$).