Interaction between cocaine use and sleep behavior: A comprehensive review of cocaine's disrupting influence on sleep behavior and sleep disruptions influence on reward seeking

Theresa E. Bjorness, Robert W. Greene

Dopamine, orexin (hypocretin), and adenosine systems have dual roles in reward and sleep/arousal suggesting possible mechanisms whereby drugs of abuse may influence both reward and sleep/arousal. While considerable variability exists across studies, drugs of abuse such as cocaine induce an acute sleep loss followed by an immediate recovery pattern that is consistent with a normal response to loss of sleep. Under more chronic cocaine exposure conditions, an abnormal recovery pattern is expressed that includes a retention of sleep disturbance under withdrawal and into abstinence conditions. Conversely, experimentally induced sleep disturbance can increase cocaine seeking. Thus, complementary, sleep-related therapeutic approaches may deserve further consideration along with development of non-human models to better characterize sleep disturbance-reward seeking interactions across drug experience.

1. General introduction

As a psychostimulant with strong reinforcing properties (Ritz et al., 1987), cocaine acutely increases behavioral arousal (Zubrycki et al., 1990; Kiyatkin and Smirnov, 2010). Accordingly, cocaine can induce sleep disruption if taken near the habitual bedtime (evening in humans and other primates, morning in most rodents). More chronic cocaine use has also been associated with sleep disturbance in people with cocaine use disorder (for review, Gawin, 1991; Morgan and Malison, 2007; Valladares and Irwin, 2007) with sleep disturbance persisting into withdrawal and abstinence suggesting that cocaine use may cause alterations in sleep/waking control beyond the direct pharmacological action of cocaine-induced psychostimulation. The mechanism by which cocaine alters sleep/waking control is yet unknown, but dopamine, orexin (hypocretin), and adenosine systems are well-positioned based on their dual roles in reward and sleep/arousal behavior. This review will begin with a description of the role of these neuromodulators in reward and sleep/arousal behavior. Next, the effect of acute or limited cocaine on sleep will be discussed followed by the effect of chronic cocaine on sleep. Most of the acute cocaine research has featured non-human animal models, while the chronic cocaine research has largely focused on cocaine-dependent human subjects. The ability of sleep disruption to modulate cocaine reward-related behavior will also be covered since long term changes in sleep behavior may influence reward responding thereby conferring possible vulnerability to addiction/relapse. Finally, the possibility of treating cocaine use disorder through sleep-based pharmaceuticals will be discussed followed by limitations and possible future directions.

Our goal was to include previous research articles describing sleep-related changes (or the absence thereof) following cocaine exposure in

**Abbreviations:** Abs, Abstinence; BDI, Beck Depression Inventory; CCQ, Cocaine Craving Questionnaire; DSM, Diagnostic and Statistical Manual of Mental Disorders; DA, Dopamine; DAT, Dopamine Transporter; ESS, Epworth Sleepiness Scale; HC, Healthy Control; IP, Intraperitoneally; IV, Intravenously; MSLT, Multiple Sleep Latency Test; NREM, N, Non-Rapid Eye Movement; PSG, Polysomnography; PTSD, Post-Traumatic Stress Disorder; PSQI, Pittsburgh Sleep Quality Index; REM, Rapid Eye Movement; REML, REM Sleep Latency; SD, Sleep Deprivation; SE, Sleep Efficiency; SL, Sleep Latency; SQQ, Sleep Quality Questionnaire; SWS, Slow Wave Sleep; TST, Total Sleep Time; TWT, Total Waking Time; WASO, Wake After Sleep Onset.

* Corresponding author at: Research Service, VA North Texas Health Care System, Dallas, TX 75126, USA.

**E-mail address:** theresa.bjorness@va.gov (T.E. Bjorness).

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both human and non-human models. These papers were collected via search of the Pubmed database using keywords ‘cocaine and sleep’, along with relevant papers cited within articles found by keyword search. Articles were excluded if they did not have an explicit sleep component, did not include cocaine exposure or cocaine-experienced participants, or were not written in English. Case reports, Letter to the Editor-style reports, and book chapters were excluded. For reward-related research, articles were excluded if they did not have an explicit reward component (for example, research describing sleep deprivation-related changes in locomotor sensitization are not reviewed here).

2. Dopamine, orexin, and adenosine systems involved in cocaine reward and modulated by cocaine exposure

Dopamine (DA) is a monoaminergic neurotransmitter with cell bodies primarily in the Ventral Tegmental Area (VTA) and Substantia Nigra (SN) of which the VTA located neurons have been heavily implicated in reward behavior, including for stimulant drugs of abuse such as cocaine (Baik, 2013; Volkow and Morales, 2015) with the mesocorticolumbic DA system hypothesized to be a common pathway for drug reinforcement (Wise, 1986; Koob, 1992). Cocaine, a psychostimulant with high abuse potential due to its strong reinforcing properties (Johanson et al., 1976; Bozarth and Wise, 1985), blocks monoaminergic transporters of which dopamine transporter (DAT) blockade is predominantly responsible for these reinforcing properties (Ritz et al., 1987). A full review of the role of DA in cocaine reward is beyond the scope of the current review, but has been previously reviewed (Kuhar et al., 1991; Kiyatkin, 1994; Baik, 2013; Volkow and Morales, 2015; Francis et al., 2019) as have alterations in the DA system in response to chronic cocaine exposure (for review, Porrino et al., 2004; Luscher, 2016; Wolf, 2016; Nestler and Luscher, 2019).

Orexin (also known as hypocretin) is a peptide expressed in a subset of glutamatergic neurons within the lateral hypothalamus and perifornical areas. These neurons send widespread projections throughout the brain, targeting various neuronal populations including those involved in motivation (Gonzalez et al., 2012). In rodents, orexin administration increases cocaine self-administration (España et al., 2011), while orexin antagonists decrease cocaine self-administration (Hollander et al., 2012; Gentile et al., 2018). Stimulation of orexin neurons is sufficient to induce conditioned place preference (Taslimi et al., 2011 [rodents]), while dual orexin receptor antagonism reduces expression of cocaine conditioned place preference (Steiner et al., 2013 [rodents]). Conversely, loss of orexin through genetic mutation in rodents prevents the acquisition of conditioned place preference to cocaine (Shaw et al., 2017), reduces cocaine self-administration at high doses (Steiner et al., 2018), and reduces DA response to cocaine (Shaw et al., 2017), as does orexin antagonism (Prince et al., 2015). Similar to the ability of chronic cocaine to modulate the DA system, chronic cocaine also modulates orexin signaling with changes persisting days to weeks following termination of exposure. Aston-Jones and colleagues, using a rodent model, reported that cocaine self-administration on an intermittent schedule increases orexin neuronal activity as determined by the number of neurons expressing orexin and co-expressing an immediate early gene with increases in response to re-exposure to the drug context lasting at least 5 months into withdrawal (James et al., 2019). Repeated cocaine exposure also increases experience-dependent potentiation of excitatory synapses on orexin neurons and facilitates induction of long term potentiation in orexin neurons, an effect that persists several days into withdrawal (Rao et al., 2013 [rodents]). Furthermore, stimuli previously conditioned to mark the availability of cocaine retain the ability to increase orexin neuronal activity at least three weeks following conditioning (Martin-Fardon et al., 2018 [rodents]).

Adenosine is a purine neuromodulator and a component of ATP such that adenosine levels are influenced by metabolic activity, with adenosine, acting through adenosine A1 receptors, providing feedback inhibition to reduce subsequent neuronal activity (for review, Fredholm and Dunwiddie, 1988; Greene and Haas, 1991). All drugs of abuse directly or indirectly modulate adenosine signaling (Hack and Christie, 2003) with cocaine increasing adenosine tone (Bonci and Williams, 1996; Fiorillo and Williams, 2000). In turn, adenosine is thought to be able to increase DA release from the VTA by facilitating burst pause firing of glutamate afferents via inhibition of mGluR inhibitory postsynaptic potentials (Fiorillo and Williams, 2000). The effects of adenosine modulators on cocaine seeking behavior are quite complicated as multiple factors can influence outcomes. In rodents, acute caffeine (mixed A1 and A2 receptor antagonist) exposure increases responding for cocaine, while chronic caffeine exposure decreases responding (Kuzmin et al., 2000). Interestingly, cocaine dependent humans show lower caffeine use prevalence than the general public and caffeine use is associated with less frequent cocaine use (Budney et al., 1993), suggesting of substitution. Furthermore, caffeine and cocaine generalize to each other; in rodents trained to discriminate caffeine from saline, cocaine presentation results in caffeine-appropriate responding (Holtzman, 1986), while in cocaine experienced humans trained to discriminate cocaine from placebo, caffeine presentation results in cocaine-appropriate responding (Oliveto et al., 1998). Other non-caffeine A1 and A2 antagonists also partially substitute for cocaine in a discrimination task in rodents (Justinova et al., 2003). Another complicating factor is that A1 (Gi-coupled) and A2 (Gs-coupled) receptor modulators can have similar behavioral outcomes despite opposing effects on intracellular signaling as in the case of A1 and A2 agonists decreasing responding during extinction of cocaine self-administration (O’Neill et al., 2014 [rodents]). Furthermore, adenosine receptors directly influence DA signaling through the formation of heteromers (A1/D1, A2/D2, and less commonly, A1/D2; for review, Franco et al., 2007). As with DA and orexin systems, chronic cocaine also induces plastic changes in the adenosine system in terms of increases in adenosine A1 receptor expression in the nucleus accumbens (Toda et al., 2003) and decreases in adenosine-mediated inhibition of presynaptic glutamate release due to increases in adenosine uptake (Manzoni et al., 1998).

3. Dopamine, orexin, and adenosine systems influence sleep behavior

While the role of DA in reward behavior has been well-characterized, until recently a potential role of DA in sleep/waking behavior received much less attention. Dopaminergic neurons do not change firing rate across state (Trulson and Preussler, 1984), though the pattern of firing does change as demonstrated by prominent burst firing during REM sleep (Dahan et al., 2007) which would be expected to increase DA release. Additionally, there are brain region specific changes in DA level across states (Lena et al., 2005), increases in DA and metabolites in various brain regions following sleep deprivation (Asikainen et al., 1995; Farooqui et al., 1996; Zant et al., 2011), and reports that DA receptor agonists and antagonists influence sleep/waking state (for review, Monti and Monti, 2007). More recently, optogenetic and chemogenetic stimulation of dopaminergic VTA neurons was found to strongly promote arousal (Eban-Rothschild et al., 2016; Gishi et al., 2017). Classic and relatively new stimulants, such as methamphetamine and Modafinil respectively, require DA to promote waking (Wistrup et al., 2001). Furthermore, subjective sleep duration is shorter in cocaine users and D2/D3 receptor availability is reduced with a mediation analysis suggesting that sleep duration mediates the relationship between cocaine use and D2/D3 receptor availability (Wiers et al., 2016). In sum, cocaine-induced modulation of the DA system could underlie changes in sleep disturbance, particularly in regards to the increase in waking as a direct pharmacological effect, but also through alterations in the DA system in response to chronic cocaine exposure (for review, Porrino et al., 2004; Luscher, 2016).

In addition to orexin neuronal projections to motivation-related targets, orexin neurons also activate neuronal populations involved in...
Arousal/waking including, noradrenergic neurons in the locus coeruleus (Hagan et al., 1999), histaminergic neurons in the tuberomammillary nucleus (Erikkson et al., 2001), and cholinergic neurons in the ascending reticular activating system (Eggermann et al., 2001; Burlet et al., 2002). Orexin neuronal activity is high during waking (Lee et al., 2005) and increases further during sleep deprivation (Estabrooke et al., 2001). Similarly, orexin levels are high during typical waking and increase further during sleep deprivation (Yoshida et al., 2001). Furthermore, a subset of orexin neurons show increased excitability during sleep deprivation which may serve to promote continued arousal despite high sleep need (Briggs et al., 2019). Orexin administration increases waking (Akamnu and Honda, 2005), while orexin antagonist administration increases sleep (Winrow et al., 2011). Loss of orexin, through the disorder narcolepsy in humans or genetic modification in mice, causes sleep fragmentation (Chemelli et al., 1999; Hungs and Mignot, 2001) due to an inability to maintain waking. In sum, the orexin system has received widespread attention as a potential hub intermediating motivation and arousal (for review, Tyree et al., 2018).

As with orexin, adenosine is also modulated by cocaine exposure and, unlike orexin, is heavily implicated in the homeostatic control of sleep (Bjorness and Greene, 2009; Porkka-Heiskanen and Kalinichuk, 2011) which is the portion of sleep need that is influenced by prior waking time. Adenosine levels build up during waking (Porkka-Heiskanen et al., 1997); acting through Gi-coupled adenosine A1 receptors, adenosine inhibits wake active neurons in various brain regions (Rainnie et al., 1994; Alam et al., 1999; Thakkar et al., 2003; Liu and Gao, 2007) and disinhibits sleep active neurons (Chamberlin et al., 2003; Morairity et al., 2004), while acting through Gs-coupled adenosine A2 receptors adenosine excites sleep active neurons in the hypothalamus (Gallop et al., 2005) and disinhibits wake active neurons in the tuberomammillary nucleus (Hong et al., 2005), with all these actions promoting sleep. Homeostatic sleep rebound is absent in mutant mice that lack adenosine A1 receptors in forebrain glutamatergic neurons (Bjorness et al., 2009). Furthermore, increases in adenosine tone through reductions in adenosine kinase increase delta power under baseline conditions and slow the decay of delta power during NREM sleep indicative of enhanced sleep drive (Bjorness et al., 2016), while reductions in adenosine tone caused by overexpression of the cytoplasmic form of adenosine kinase reduce sleep and the homeostatic response to sleep deprivation (Palchykova et al., 2010). Interestingly, individual differences in the adenosine system of humans may be more pronounced than with other systems based on polymorphisms in adenosine A2a receptor (Retey et al., 2007; Erblang et al., 2019) and adenosine deaminase (Retey et al., 2005; Mazzotti et al., 2012) genes, which have functional consequences on sensitivity to caffeine and sleep loss. In sum, the adenosine system is positioned to influence and be influenced by prolonged waking and cocaine exposure, though interpretation of effects may be more complicated as compared to DA and orexin mechanisms.

4. Cocaine-induced alterations of sleep: limited exposure

Acute cocaine exposure increases sleep latency (SL) and REM sleep latency (REML) compared to vehicle or placebo in rodents (Hill et al., 1977; Bjorness and Greene, 2018; Dokkedal-Silva et al., 2020) and increases waking (Hill et al., 1977; Gruner et al., 2009) in a dose-dependent manner (Knapp et al., 2007; Bjorness and Greene, 2018 [rodents]) with higher doses increasing waking over longer durations, as expected, and cocaine and caffeine combinations increasing waking to a greater degree than cocaine alone (Schwarzkopf et al., 2018 [rodents]). Increased waking reflects decreases in both SWS and REM, though REM disruptions are prolonged compared to SWS (Knapp et al., 2007; Bjorness and Greene, 2018). Furthermore, this increase in waking is due to an increase in episode duration, while the decrease in SWS and REM is due to decreases in both episode duration and number (Bjorness and Greene, 2018). The immediate cocaine-induced increase in waking is followed by a delayed rebound in sleep resulting in modest wake surplus at 22 h post-injection (Gruner et al., 2009) and full recovery within the 24 h period (Bjorness and Greene, 2018). In rhesus monkeys, a primate species with consolidated night-time sleep patterns like that of humans, cocaine early in the day reduces sleep efficiency during the subsequent night, but only in response to the preferred dose (based on relative intake versus food reward) in that lower and higher doses do not significantly modulate sleep efficiency (Brutcher and Nader, 2013). Overall, these results indicate a direct pharmacological wake promotion that is non-linearly modulated by dose and subjective effects.

As determined by EEG spectral analysis, delta activity decreases and gamma (30-50 Hz) activity increases immediately following cocaine administration (Bjorness and Greene, 2018 [rodents]) with subsequent delta rebound over the next several hours. Protracted rebound increases in slow band power occur following binge cocaine (15 mg/kg delivered once per hour for 3 consecutive hours) with delta remaining elevated at 24 h post-injection (Porkka-Heiskanen et al., 2009 [rodents]) suggesting that while sleep time recovers within a 24 h period following cocaine, subtle alterations in neuronal activity during sleep states may show longer lasting alterations.

In humans, an evening of recreational cocaine use increases REML and decreases REM time compared to a pre-cocaine baseline night with subsequent rebound decreases in REML and increases in REM during recovery, while NREM and SWS are unchanged (Watson et al., 1992). Cocaine administration in non-users (severely depressed individuals) also decreases REM and total sleep time (TST), both of which subsequently rebound (Post et al., 1974a). These results are consistent with the pattern of sleep disturbance followed by recovery pattern observed following limited cocaine exposure in non-humans.

5. Cocaine-induced alterations of sleep: chronic exposure and withdrawal

In rodents, cocaine chronic exposure (20 mg/kg for 5d, 30 mg/kg for the next 5d), the pattern of increased waking immediately following cocaine administration with subsequent rebound resulting in unchanged sleep/waking time over the 24 h period persists (Dugovic et al., 1992). Conversely, across repeated cocaine self-administration exposures, sleep efficiency reductions moderate indicative of tolerance (Cortes et al., 2016 [rhesus macaque]). Discrepancy between these outcomes may be due to methodological differences, including route of administration (IP vs IV), volition (experimenter-administration vs self-administration), pattern (bolus vs repeated small volumes), relative timing (within subjective inactive phase vs within subjective active phase) along with species difference (rat vs rhesus macaque). Upon withdrawal from experimenter-delivered chronic cocaine, in which the term withdrawal refers to the termination of daily exposure and not a specific physiological state, increased waking in the light phase and increased SWS and REM in the dark phase continues for several days (Dugovic et al., 1992), while increased waking is observed following withdrawal from a combined cocaine plus caffeine exposure (Rivero-Echeto et al., 2021).

Persistent alterations in sleep/waking behavior following withdrawal from chronic self-administered cocaine (self-administration during the dark phase for 5d followed by weekly polysomnography at withdrawal days 1, 7, 14, 21; Chen et al., 2015 [rodents]) have also been demonstrated. Specifically, delayed decreases in NREM (withdrawal days 14, 21) and protracted decreases in REM (withdrawal days 1, 7, 14, 21) are seen (Chen et al., 2015) with shorter NREM and REM episode durations and fewer NREM to REM transitions alongside more NREM to waking transitions. Furthermore, spectral power including the delta band is unchanged at a time point when NREM and REM are decreased (withdrawal day 21, Chen et al., 2015) indicating that decreased sleep time is not counteracted by increased sleep intensity and thereby suggesting a net loss of absolute sleep activity. Thus, duration of cocaine exposure influences the pattern of sleep disturbance with more limited exposure resulting in a sleep disturbance-recovery pattern compared to protracted sleep disturbance (without demonstration of recovery within
the recording period) following longer cocaine exposure.

The effect of cocaine use or withdrawal/abstinence from cocaine use on sleep/waking behavior in humans has been investigated for decades, however, considerable variability in the design of experiments alongside variability in outcomes impedes conclusive interpretation of the literature as a whole. The majority of studies have found some measure of sleep disturbance, though the nature of the disturbance varies. In lieu of describing these disparate findings, details are summarized in a table. See Table 1 for a brief description of the experimental design with notable features, outcome measures used, population of cocaine use and control group details, and notable outcomes. This table includes published articles of original research or meta-analysis featuring human subjects with sleep-related outcomes under cocaine use/withdrawal/abstinence.

A few brief notes on terminology: 1) several groups divide abstinence into early and late phases with early abstinence generally <2 weeks post cocaine and late abstinence generally 2–4 weeks post cocaine, 2) the terms withdrawal and abstinence are sometimes distinguished and other times used interchangeably with additional terms such as subacute used amongst other drugs of abuse (Schierenbeck et al., 2008; Garcia and Salloum, 2015; Valladares and Irwin, 2007) along with reviews featuring cocaine (Stage 4) with NREM3,4 (Stage 3) indicating that cocaine withdrawal is not consistently established articles of original research or meta-analysis featuring human variability in outcomes impedes conclusive interpretation of the literature as a whole. The majority of studies have found some measure of sleep disturbance, though the nature of the disturbance varies. In lieu of describing these disparate findings, details are summarized in a table. See Table 1 for a brief description of the experimental design with notable features, outcome measures used, population of cocaine use and control group details, and notable outcomes. This table includes published articles of original research or meta-analysis featuring human subjects with sleep-related outcomes under cocaine use/withdrawal/abstinence.

6. Sleep loss mediated alterations of cocaine reward

Sleep disruption has been indirectly linked to relapse behavior in humans in which an increase in N3 during abstinence is associated with percentage of urine screens negative for cocaine metabolites and maximum consecutive days abstinence (Angarita et al., 2014a). Direct tests of the ability of sleep disturbance to influence cocaine reward have been mixed suggesting that sleep disturbance can influence cocaine reward, but does not necessarily do so for every component of reward or in all individuals.

Using a conditioned place preference paradigm in which the rewarding properties of cocaine are inferred by time spent in a cocaine-paired context relative to time spent in a neutral (saline-paired) context, sleep deprivation prior to cocaine-conditioning trials or prior to the post-conditioning test enhances preference to the cocaine-paired location for a moderate dose of cocaine (8 mg/kg) and induces preference to a low dose of cocaine (3 mg/kg) when deprivation occurs prior to cocaine-conditioning trials (Bjorness and Greene, 2020 [rodents]). Sleep deprivation-induced preference to a low dose of cocaine is consistent with reports that sleep deprivation induces preference to a low dose of amphetamine (Berro et al., 2018 [rodents]) or methylphenidate (Roehrs et al., 1999 [humans]) and that one night of sleep deprivation increases the perception of the strength of cocaine and reverses sleep deprivation-induced vigilance impairments in humans (Fischman and Schuster, 1980), effects that are lost with two nights of sleep deprivation.

Several experiments have used self-administration, in which non-humans lever-press or nose-poke to receive cocaine rewards, to assess the effect of sleep disturbance on cocaine reward. Acute sleep deprivation of 4–8 h reduces reinstatement (a model for relapse [for review, Shabam et al., 2003]) in a population of rats that self-administer relatively low amounts of cocaine, but not high amounts of cocaine (Puhl et al., 2009; rats are divided into high or low cocaine taking based on their self-administrative behavior relative to the entire population). Furthermore, sleep deprivation reduces inter-infusion interval and increases active/inactive lever press ratio in low cocaine-taking animals (Puhl et al., 2009) indicating that acute sleep deprivation can subtly influence cocaine seeking behavior. Acute sleep deprivation does not influence motivation to seek cocaine as determined by a progressive
Table 1
Experimental design with notable features, outcomes measures, population details, and notable outcomes.

| Citation            | Experimental design [binge refers to multiple uses within session] and notable features | Outcome measures reported (sleep) | Population (number cocaine use group and healthy control [HC] group) | Notable outcomes                                                                 |
|---------------------|----------------------------------------------------------------------------------------|----------------------------------|-----------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Angarita et al., 2014a | Non-treatment group design: accommodation (cocaine tolerance test plus off days) – binge cocaine or placebo (midday for 3d) – abstinence – placebo or binge cocaine – abstinence (some subjects accommodation – binge cocaine – early abstinence – placebo – late abstinence, others accommodation – placebo/early abstinence – late abstinence – binge cocaine – early abstinence). PSG 16× over 23d which were binned into accommodation, binge days, and 5 bins of abstinence. | Time in REM, N1, N2, N3, SL, REMI, TST, % change SWS and % change REMI from abstinence week 1 to 2 | 12 cocaine-dependent non-treatment seeking individuals, 20 cocaine-dependent treatment-seeking individuals | Non-treatment group: REM and TST late in abstinence negatively correlated with fraction of available cocaine used, while those whose SWS increased from early to late abstinence showed a trend towards less cocaine self-administered. In treatment-seeking group: REM time late in abstinence positively correlated with negative urine screens and max consecutive days abstinent, percent change SWS from early to late abstinence positively correlated with percentage of negative urine screens, and those whose SWS time increased from early to late abstinence had higher percentage of negative urine screens and higher max consecutive abstinence days than those whose SWS did not increase. |
| Angarita et al., 2014b | Inpatient on Caffeine Free Unit 12d inpatient, 6 week outpatient with PSG measured during inpatient week 1 and 2 and outpatient week 3 and 6, subjective overall sleep quality on 0–100 measured scale during inpatient phase. Treatment consisted of individual and group therapy (inpatient) and cognitive behavioral therapy (outpatient), contingency management. | Time in REM, N1, N2, N3, SL, REMI, TST, subjective sleep quality | 20 cocaine-dependent treatment-seeking individuals | Compared to historical healthy control data (Morgan et al., 2010) From week 1 to week 2, TST and N2 decreased, REMI and subjective sleep quality increased with a trend towards increased REM. |
| Brower et al., 1988 | Inpatient on Caffeine Free Unit. Questionnaire for cocaine use and withdrawal symptoms (including sleep disturbance) given to Veterans seeking treatment for psychiatric problems. | Self-reported sleep disturbance and dreaming | 75 cocaine users | No HC Of those respondents in which cocaine withdrawal symptoms occurred, 70.7% reported sleep disturbance. |
| Coffey et al., 2000 | St. Mary’s Hospital Sleep questionnaire completed 2d/week for 3 weeks and divided into 3 blocks (1/week). 50% subjects also alcohol-dependent, 25% subjects diagnosed with PTSD, compared abstainers throughout and those relapsing during study. | Self-reported depth of sleep, number of times awake, hours of sleep/night, hours of sleep/day, quality of sleep, clear-headedness upon arising, satisfaction with sleep, difficulty falling asleep | 24, cocaine dependent individuals | Last cocaine within past 48 h No HC Across 3 blocks of abstinence, no difference in subjective sleep outcomes between those who abstained and those who relapsed nor difference across time. |
| Cottler et al., 1993 | Structured interview based on list of withdrawal symptoms in a field study and outreach program targeting substance users. Divided respondents based on past cocaine vs cocaine and opiate use. | Self-reported insomnia (as trouble sleeping) and hypersomnia (as tired, sleepy, or weak) | 533 respondents who had used cocaine at least once (218 had experience with cocaine and opiates, 315 had experience with cocaine but not opiates) | Insomnia and hypersomnia were affirmed as cocaine withdrawal symptoms in cocaine and opiate experienced individuals (42% and 41%, respectively) and in cocaine but not opiate experienced individuals (34 and 37%, respectively) suggesting that sleep disturbance is a useful diagnostic criteria for cocaine withdrawal. |
| Dudish-Poulsen and Hatsukami, 2000 | Binge cocaine or placebo (morning) and within day abstinence, repeated 4×, completed Leeds Sleep Questionnaire at 25% subjects diagnosed with PTSD, 50% subjects also alcohol-dependent, divided into 3 blocks (1/week). | Self-reported ease of getting to sleep, sleep quality, awakening from sleep, behavior following wakefulness | 12, cocaine users | Following morning cocaine exposure, getting to sleep was reportedly easier the evening of (continued on next page) |
Table 1 (continued)

| Citation | Experimental design ([binge refers to multiple uses within session] and notable features) | Outcome measures reported (sleep) | Population (number cocaine use group and healthy control [HC] group) | Notable outcomes |
|----------|--------------------------------------------------------------------------------------|----------------------------------|--------------------------------------------------------|------------------|
| Epstein and Hodges et al., 2017 | Placebo group (11d placebo), Modafinil (atypical, weak dopamine reuptake inhibitor; 100–400 mg/d). Inpatient on Caffeine Free Unit. | Self-reported resting/sleeping as select response to “what were you doing when the beep occurred”, with responses divided into “using” and “abstaining” bins based on urine screens. | 112, cocaine dependent, Methadone maintained individuals; No HC | Self-reported sleeping/resting was higher mid-morning to early afternoon in ‘using’ bins compared to ‘abstaining’ bins and was bracketed by responses of at work during the early morning and evening. The authors raise the possibility of increased early daytime sleeping likelihood bracketed by work as cocaine being used in the context of shift work, though sleeping was not distinguished from resting. Sleep disturbance was a predictor of subsequent substance use disorder, with co-morbid sleep disturbance and mental health disorder more prevalent in subsequent substance use disorder than sleep disturbance alone. Of the illicit substances driving substance use disorder, cocaine was the most common. During withdrawal, subjective report of insomnia followed by hypersomnia. |
| Fortuna et al., 2018 | Investigation of electronic health records from patients in the Boston area over a 32 month period with an inclusion criteria of at least 3 visits over this period, used International Classification of Diseases codes to identify sleep disturbance, mental health disorder, illicit use disorder, alcohol use disorder. | Presence or absence of sleep, mental health, illicit use, or alcohol use disorders | 83,920 patients (Placebo dose; no HC) | TST and REM time. |
| Gavin and Kleber, 1986 | Repeated structured clinical interviews. Participants received therapy. | Self-report, with hypersonomlence and normal sleep | 30, cocaine dependent individuals; No HC | Sleep difficulties endorsed by 82% of individuals, insomnia endorsed by 91% of upper income users, sleep problems endorsed by 78% of adolescent callers. |
| Gillin et al., 1994 | Baseline (placebo, 2-6d) – treatment (Lisuride or placebo, 21d) with PSG sleep assessment 2d/week. All participants received therapy, some received Lisuride (dopamine D2-type receptor agonist; 0.4-4 mg/d). | WASO, REM density, REM, Delta (Stage 3 + 4), SL, TST, REML | 21, cocaine and/or amphetamine dependent (male only) | Lisuride increased REML, non-significantly increased WASO, and decreased %REM in stimulant users. No change in craving via a self-rating craving scale. |
| Gold et al., 1985 | Telephone interview based on callers to a cocaine abuse helpline. Some analysis with subgroups such as upper income callers and adolescent callers. | SL, time awake after sleep onset, time awake after final awakening. Self-reported time went to bed, SL, WASO, TST, time of awakening, time got out of bed | 500, cocaine users; No HC | Sleep difficulties endorsed by 82% of individuals, insomnia endorsed by 91% of upper income users, sleep problems endorsed by 78% of adolescent callers. |
| Hodges et al., 2017 | Placebo group (1d placebo), Modafinil group (4d placebo, 7d Modafinil), PSG for 2d/week for 2 weeks (2nd day of each used for analysis), subjective measures through Evening-Morning Sleep Questionnaire and PSQI (baseline). Modafinil (atypical, weak dopamine reuptake inhibitor; 100–400 mg/d). Inpatient on Caffeine Free Unit. | Self-reported sleep problems included as a checklist item | 23 cocaine-dependent individuals [placebo], 20 cocaine-dependent individuals [Modafinil] | Time-dependent sleep state misperception in abstinent cocaine users was reported. TST values from self-report and PSG correlated more strongly during week 1 vs week 2 and there was a significant difference in TST values between these sources (PSG TST decreased from week 1 to 2 while self-report TST did not. During week 2, self-report SL and WASO were underestimated compared to PSG measures). A median split for high and low mis-reporters resulted in no difference in baseline PSQI between groups, but REM minutes were lower during week 2 of the high mis-reporters. There was also a correlation between minutes misreported during week 2 and both TST and REM time. (continued on next page) |
| Citation                | Experimental design (binge refers to multiple uses within session) and notable features | Outcome measures reported (sleep) | Population (number cocaine use group and healthy control [HC] group) | Notable outcomes |
|------------------------|--------------------------------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------------|------------------|
| Irwin et al., 2016     | PSG 2d (2nd day used for analysis), subjective assessment with PSGI. Included alcohol use disorder group (n = 73) and age stratified controls. | SE, SL, TST, Min and %Stage 1, 2, 3, 4, SWS (stage 3 + 4), REM, REML, REM density, duration of 1st REM, self-reported sleep quality. | 32, cocaine-dependent individuals | Objective sleep time [PSG] was higher with Modafinil compared to placebo with no difference in subjective [self-report] sleep time between conditions. |
| Johanson et al., 1999  | Phase 1: (8-10d, divided into 2 time points) - Phase 2: morning placebo and evening cocaine (5d, divided into 2 time points) - Phase 3: abstinence (15-16d, divided into 3 time points). MSLT during both abstinence phases. Cocaine exposure was once every 30 min for 3 h. Placebo dose was 4 mg/70 kg cocaine +96 mg lactate by same route. Inpatient, some polydrug use. | SE, SL, SL during MSLT, REML, %REM, occurrence of REM during MSLT | 12, HC [with single 8 h night recording] | Associated with years of cocaine, SL and REML remained different than values gathered from age-matched controls. Daytime SL (from MSLT), was initially shorter than control values during abstinence but became longer by the end of 2 weeks of abstinence. Early in abstinence there were numerous occurrences of REM during the MSLT, returning to control levels by the end. |
| Kowatch et al., 1992   | PSG repeated across 3 weeks (4d week 1, 2d/week for week 2 and 3). Self-reported sleep quality on 4 point scale. Participants received individual and group therapy. | TST, SE, SL, TWT, %Stage 1, 2, 3, 4, REM, REML, Number of REM periods, REM activity, REM density | 9, cocaine dependent individuals | TST increased during the first 2 weeks following heavy binge cocaine cessation becoming near normal by week 3. At week 3, SL was long, WASO increased, SE was poor. Early in withdrawal, percentage of Stage 3 and 4 was low, with Stage 4 nearly absent, while %REM was increased. By the end of week 3, %REM normalized, while Stage 3 and 4 were still low. Initially self-reported sleep quality was “worse than usual” but became “same as usual” later. |
| Mahoney 3rd et al., 2014 | Single subjective assessment with PSQI and ESS. Additional methamphetamine use disorder group. | Self-reported sleep quality, daytime sleepiness | 51, individuals with cocaine use disorder | Cocaine users reported values in the poor sleep range for both instruments with no correlation between sleep instrument scores and cocaine intake (amount, frequency, time since start). |
| Matsuney et al., 2011 (compilation of 3 previously published studies) | PSG and subjective measures through Sleep Quality Questionnaire (sleep quality and alertness measured in morning, daytime alertness measured in evening), averaged each week for 3 weeks. Inpatient on Caffeine Free Unit. | SL, REML, TST, time in N1–2, time in N3 (SWS), REM, SE, self-reported overall quality, depth of sleep, feeling well-rested, mental alertness, daytime sleepiness | No HC | Across 3 weeks of abstinence, TST, REM, N1, N2, and SE decreased while SL, REML and SWS increased. There were some differences in SE and SL outcomes between studies. Subjective sleep measures improved across the 3 weeks. Using covariate analysis, TST was negatively associated with years of cocaine, REM was greater in female subjects, SWS time was negatively associated with years of cocaine and age. |
| Morgan et al., 2006 | Accommodation (cocaine tolerance test plus off days) – binge cocaine or placebo (midday for 3d) – abstinence – placebo or binge cocaine – abstinence (some subjects accommodation – binge cocaine – abstinence – placebo – abstinence, others accommodation – placebo – abstinence – binge cocaine – abstinence. PSG 16– over 23d was | TST, SL, WASO, arousal index, # of awakenings (2 durations), SE, SWS time (Stage 3 + 4), spectral activity, self-reported overall quality, depth of sleep, feeling well rested, mental alertness | 12, cocaine dependent individuals | Overall, from binge through the 5 abstinence (abs) bins, TST had a U shaped curve, SL and slow spectral band power (0.5-8 Hz) an inverted U shaped curves, while subjective sleep quality had a linear increase, though due to variability only a subset of bins showed a statistically significant differences (TST: 2nd abs |

(continued on next page)
Table 1 (continued)

| Citation            | Experimental design [binge refers to multiple uses within session] and notable features | Outcome measures reported (sleep) | Population (number cocaine use group and healthy control [HC] group) | Notable outcomes |
|---------------------|--------------------------------------------------------------------------------------------|----------------------------------|--------------------------------------------------------------------|-----------------|
| Morgan et al., 2008 | Accommodation (cocaine tolerance test plus off days) – binge cocaine or placebo (midday for 3d) – abstinence – placebo or binge cocaine – abstinence (some subjects accommodation – binge cocaine – abstinence – placebo – abstinence, others accommodation – placebo – abstinence – binge cocaine – abstinence. PSG 16-× over 23d was binned into accommodation, binge days, and 5 bins of abstinence. | SL, WASO, TST, SE, SWS time (Stage 3 + 4), REM, REM time, REM time each quarter, SWA each quarter | 12, cocaine dependent individuals No HC | REM time was higher during the 2nd and 3rd abstinence (abs) bins compared to the 4th and 5th abs bins, while REM was higher during binge bin compared to the 1st and 2nd abs bins and higher during the 5th abs bin compared to the 3rd abs bin. SWA (0.5-3 Hz) was higher during the first quarter of the night in the binge bin compared to the 1st abs bin, while REM was lower in the binge bin compared to the 1st abs bin. For procedural learning with a visual texture discrimination task, 6 h of sleep was insufficient for overnight improvement during early or late cocaine abstinence, though overnight learning did occur following binge cocaine exposure and was greater than during early and late abstinence. |
| Morgan and Malison, 2008 | Inpatient on Caffeine Free Unit. Binge cocaine (midday for 3d) – abstinence (2 week) with placebo, Tiagabine, Lorazepam 2d of each abstinence week, PSG 3d/week, Sleep Quality Questionnaire 2×/d (morning, evening) and Stanford Sleepiness Scale daily (morning). | SL, SE, % time Stage 1–2, % time Stage 3 – 4, %REM, self-reported overall quality, mental alertness, sleepiness | 6, cocaine dependent individuals Placebo group; no HC | Statistical trend for decreasing SE, TST, and %REM from abstinence week 1 to week 2. Tiagabine increased %Stage 3–4 and decreased %Stage 2. Lorazepam increased % Stages 1 and 2 and initially decreased %REM. No difference in subjective sleepiness between Tiagabine, Lorazepam, and placebo use. Lorazepam resulted in more inappropriate responses on a continuous performance task. |
| Morgan et al., 2008 | PL by Nightcap 1d/week for 3 weeks. Subjects participated in substance use treatment (not described). | TST, SE, SL, WASO | 26, cocaine dependent individuals -divided subjects by sex (12 male, 14 female) 19, HC [outpatient] | During week 3 of abstinence, male cocaine users showed significantly lower SE compared to female cocaine users. SE decreased over abstinence to this point in males while staying stable in females. TST during week 3 of abstinence, though it was noted that several subjects had little SWS. Digit vigilance reaction times were faster during binge compared to all abs bins, but slower during the 5th abs bin compared to 4th abs bin. |
### Table 1 (continued)

| Citation | Experimental design [binge refers to multiple uses within session] and notable features | Outcome measures reported (sleep) | Population (number cocaine use group and healthy control [HC group]) | Notable outcomes |
|----------|--------------------------------------------------------------------------------------|-----------------------------------|-------------------------------------------------|-----------------|
| Pace-Schott et al., 2005 | Initial abstinence (3d) – binge cocaine (midday for 3d) – abstinence (15d divided into early and late phases). PSG 12+ over 21d with Nightcap monitoring every night, subjective sleep measures with Sleep Quality Questionnaire and Beck Depression Index every morning. Cocaine dose was 50 mg/opportunity and was self-administered by smoking. Binge consisted of 2 sessions with 6 cocaine opportunities per session [max daily 600 m]. | TST, SE, SL, SL stage 2, SL to 10 min continuous sleep, WASO, REMLAT [REML], %REM, %SWS (stage 3 + 4), self-reported increase or decrease in sleep, onset, middle, terminal sleep difficulty, overall quality, how well rested, mental alertness upon awakening | 5, cocaine users | 5, moderate to severely depressed non-users | REM and TST were decreased followed by subsequent rebound. |
| Post et al., 1974a | Placebo (average 4d) – cocaine (average 6d) – placebo (average 3d). Cocaine dose varied across days | REM, TST, SL, REMLAT, NREM, Stage3, Intermediate wakefulness, movement time, early morning awakening, total recording period, REM activity, REM latency, sleep efficiency, REM index, percentage of total sleep time spent in REM sleep. | 5, moderate to severely depressed non-users | No HC | No effect on mood as described in a (continued on next page) |

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Morgan et al., 2010 | PSG 3d/week for 3 weeks, MSLT 1/week for 3 weeks, subjective measures through St. Mary’s Hospital Sleep Questionnaire (morning) and Stanford Sleepiness Scale (evening). Some participants received daily Modafinil (400 mg, [one individual temporarily at 200 mg due to side effects]). | SL, REMLAT, TST, time in N1–2, time in N3 (SWS), REM, self-reported overall quality, depth of sleep, feeling well-rested, mental alertness, daytime sleepiness | 20, cocaine-dependent individuals (10 received Modafinil) | 12, HC [outpatient] | [placebo group compared to HC] during week 3 of abstinence, cocaine users showed less TST, N3, and REM sleep and increased SL. Modafinil normalized SWS time, REM time, TST, and SL at abstinence week 3 [not different than healthy control]. During abstinence weeks 2 and 3, sleepiness during the afternoon was reduced compared to placebo control. An increase in N3 from abstinent week 2 to 3 was associated with percentage of urine screens negative for cocaine metabolites and maximum consecutive days abstinence. |

Morgan et al., 2016 | Inpatient with PSG for 2d/week for 2 weeks (2nd day of each used for analysis), outpatient 6 weeks. Based on cited previous experience, study week 1 is considered abstinence week 2. Participants received Psycho-education, individual and group therapy, contingency management, one group also received Modafinil (100–400 mg/d) starting on study day 5. | Time in REM, N1, N2, N3, SL, TST, REMLAT | 27, cocaine-dependent individuals [placebo], 30, cocaine-dependent individuals [Modafinil] With post-hoc assessment separated male (21 placebo, 23 Modafinil) and female (6 placebo, 7 Modafinil) participants | No HC | Modafinil increased N3 from abstinence week 2 to 3 and resulted in a higher mean rate of cocaine negative urine screens. When dividing participants by sex, sleep outcomes and differences between Modafinil and placebo remained in males, but not females. Female participants showed a similar increase in N3 time following Modafinil, but had more N3 during baseline compared to male participants which likely explains the lack of significant increase. However, Modafinil also did not increase mean rate of cocaine negative urine screens in female participants suggesting that the positive group-level clinical outcome was driven by male participants. SL decreased from binge cocaine exposure to late abstinence, with a non-significant trend towards decreased TST and REMLAT and increased SL. SL and REMLAT were significantly different between binge cocaine and early abstinence (decreased and increased, respectively). Subjective SL was stable across binge through abstinence, but compared to objective SL individuals overestimated SL during binge phase but underestimated SL during abstinence. This is similar to the ‘occult insomnia’ described by Morgan et al., 2006, during abstinence, but compared to objective SL individuals. |
| Citation                  | Experimental design [binge refers to multiple uses within session] and notable features                                                                 | Outcome measures reported (sleep)                                                                 | Population (number cocaine use group and healthy control [HC group]) | Notable outcomes                                                                 |
|--------------------------|---------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------|---------------------------------------------------------------------|----------------------------------------------------------------------------------|
| Trksak et al., 2013      | Baseline (1d with PSG) – sleep deprivation (SD; 1d without PSG) – recovery (1d with PSG). Subjective measures through Stanford Sleepiness Scale and a Visual analog scale (anchors – sleepy, alert) each morning and evening. | WASO, SE, TST, SWS, REM, self-reported tiredness, sleepiness, fatigue, difficulty waking          | 8, cocaine dependent individuals                                          | No difference in sleep response or subjective sleepiness following 1 night of SD between cocaine users and non-users and no difference in sleep between groups prior to SD. In response to SD, SL and WASO decreased while SE, TST, Stage 2, and REM increased suggesting sleep time homeostasis was maintained in a population of cocaine users in which sleep was similar to control values. Cocaine users showed lower evening sleepiness and higher difficulty waking under the baseline conditions, but showed similar sleepiness responses as controls following SD. Performance on a continuous performance task and digit symbol substitution task was impaired in cocaine users under non-deprived conditions, but SD did not influence performance. |
| Walsh et al., 2009       | Binge cocaine (morning for 4d) – placebo (4d, considered acute withdrawal) – binge cocaine (morning for 4d) – placebo (26d, considered protracted withdrawal). Subjective | Self-reported TST, time to wake up, time to get up                                               | 9, cocaine users                                                      | Placebo condition; no HC. Subjective TST decreased on the placebo condition. Possible explanation for differences in subjective measures between conditions, study design or duration of withdrawal. |
ratio schedule in which progressively more lever presses are needed to acquire successive infusions (Puhl et al., 2009) nor does overnight sleep disturbance (hourly awakening) increase cocaine choice relative to food reward in rhesus monkeys (Brutcher and Nader, 2013). However, recently it was shown that pharmacodynamics influence food vs drug choice in non-humans with faster dynamics supporting relative preference for food rewards (Canchy et al., 2021) suggesting the reward timing is an important consideration of choice designs.

With chronic sleep reduction (40% reduction of sleep during light phase, 80% reduction of sleep during dark phase, for two sessions of 4d sleep restriction separated by 2d recovery), motivation to seek cocaine increases in high cocaine-taking rats during the second sleep restriction period with near significant increases in seeking during the first sleep restriction period (Puhl et al., 2013). Chronic sleep restriction did not influence motivation for cocaine in low cocaine-taking rats. Reduction of cocaine withdrawal-induced REM sleep fragmentation (via sleep restriction during the dark phase) decreases cocaine craving as determined by cue-induced cocaine seeking, while chronic sleep fragmentation across the 24 h period for 7d accelerates the time-dependent incubation of cocaine craving (Chen et al., 2015 [rodents]).

In sum, there is both direct and indirect support for the ability of sleep disturbance to influence cocaine reward behavior. Interestingly, with self-administration, acute sleep deprivation modulates cocaine seeking in low taking animals, while chronic sleep disruption modulates...
coke seeking in high taking animals suggesting differential sensitivity to differing amounts of sleep loss within subpopulations.

7. Therapeutics targeting sleep disturbance and their reward outcomes

There is currently no FDA approved pharmacotherapy for cocaine use treatment, though dopaminergic, GABAergic, and orexinergic agents have been investigated for efficacy in modulating sleep in cocaine dependent individuals or maintenance of abstinence. See Table 1 for full details. Modafinil (weak, selective DAT inhibitor used to treat excessive daytime sleepiness) has been shown to improve sleep during abstinence (Morgan et al., 2010, 2016) and provides some useful secondary abstinence outcomes such as reducing the number of cocaine use days, though it does not improve cocaine abstinence or treatment retention rates (meta-analysis, Sangroula et al., 2017). Recently, a small pilot experiment has provided preliminary support for use of Suvorexant (dual orexin receptor antagonist approved for insomnia treatment), in cocaine-dependent individuals finding a slight increase in sleep via actigraphy and a decrease in craving (Suchting et al., 2020). A Phase I clinical trial investigating the effects of Suvorexant on cocaine reinforcement in humans is ongoing (PI, Dr. William Stoops, University of Kentucky). Orexin receptor antagonism (SB-334867, selective orexin receptor 1 antagonist) reduces sleep deprivation-induced enhancement of cocaine conditioned place preference in rodents (Bjorness and Greene, 2020). While outside the scope of the current review focusing on cocaine reward, orexin receptor antagonists may also provide therapeutic benefits for alcohol, opioid, and polydrug abuse (for review, Moorman, 2018; James et al., 2020; Zarribian et al., 2020). Currently, dual orexin receptor antagonists are promising with a clinical trial currently underway.

Adenosinergic modulators have been tested for sleep-related therapeutic effects in disorders such as restless leg syndrome (Decerce et al., 2007) and Parkinson’s disease (Suzuki et al., 2017), with subjective improvements in sleep-related symptoms. These modulators have not been investigated for sleep-related treatment to reduce relapse rates in a cocaine experienced population. Targeting the adenosine system brings challenges due to issues such as tolerance, receptor heterodimerization, and caffeine use (for review, Chen et al., 2013). Nevertheless, alternate mechanisms of adenosine modulation including allosteric modulators or indirect modulation of the adenosine system have gained attention as possible therapeutic avenues (Peleli et al., 2017; Jacobson et al., 2019). Modulation of the adenosine system may be particularly useful in promoting delta activity within SWS thereby increasing the intensity of SWS; low levels of SWS (N3) have been reported in a subset of cocaine-dependent individuals (Morgan et al., 2006; Irwin et al., 2016), while increases in SWS over the course of abstinence have been correlated with reduced relapse risk (Angarita et al., 2014a). It is currently unclear whether increasing delta activity alone is sufficient to reduce relapse risk; however, modulators that either increase adenosine tone or activity through A1 receptors could provide a direct test. Thus, as yet, cocaine use outcomes following sleep interventions are encouraging based on reductions in cocaine use days and craving.

8. Limitations and future directions

A main limitation for interpreting the body of work investigating changes in sleep following cocaine use/withdrawal/abstinence is the wide variability in experimental designs used across experiments. While results in human subjects have an advantage in relevancy to the human condition, there are myriad challenges in designing experiments due to the variability in cocaine use patterns, polydrug issues, and genetic variability. Additionally, long term objective sleep measurements are expensive to conduct and difficult to control in humans. Thus, non-human experiments would be useful to characterize long term changes in sleep (and the response to challenges such as sleep deprivation in order to assess possible changes in homeostatic sleep control) and would provide the additional benefit of being able to use within-subjects designs by comparing drug naïve and post-chronic cocaine exposure sleep parameters, which is precluded in human subjects. Rodent studies provide the advantages of being comparatively less expensive, easier to control, and include the option for genetic sameness; however, while many sleep parameters are similar across rodent and primate species, one major difference is the timing of sleep across the 24 h period. Excluding early development, primates are largely diurnal, while rodents are typically nocturnal dominant and polyphasic. Furthermore, humans may face social pressures (work/school timing) that are not easily modeled in non-humans which may limit interpretation of cocaine-mediated changes in the circadian timing of sleep.

Additionally, investigation of sleep/waking behavior following drug combination exposure such as cocaine with caffeine (coca paste formulations as in Schwarzkopf et al., 2018 and Rivero-Echeto et al., 2021) and cocaine with heroin (“speedball” as in Duvachele et al., 1998), which represent cocaine use variations that occur in the human population, would be informative based on the opposing influence (stimulant vs sedative) of the co-factors with respect to sleep. Polydrug exposure may also provide insight into different potential mechanisms by which drug use can influence sleep behavior and may explain some population-level variability in sleep outcomes under drug use and withdrawal.

In regards to the ability of sleep disturbance to influence cocaine reward, additional studies are necessary to provide a mechanistic understanding and to better characterize the conditions under which sleep disturbance alters cocaine reward. Determining the mechanism/s by which cocaine alters sleep and sleep disturbance alters cocaine reward may provide insight into possible novel therapeutic options to reduce the vulnerability to addiction or reduce relapse risk. Here, the use of non-human subjects provides advantages in terms of types of data that can be collected (such as brain tissue), but has the disadvantage that reward may be in some ways fundamentally different in humans and in non-humans, particularly rodents, (for example, the timescale of delay discounting influencing food vs drug choices as hypothesized by Ahmed (2018)).

Finally, while this review was intended to be comprehensive for sleep-related cocaine research, the constraint of English-only papers and use of a Pubmed-based keyword search may have missed important contributions. As interest in research involving sleep and cocaine use increases future reviews will be warranted.

9. Conclusions

Based on their dual roles in sleep/arousal and reward behaviors, DA, orexin, and adenosine systems are well placed to mediate cocaine-induced alterations of reward and sleep behavior. Further, cocaine-induced plasticity of the DA, orexin, and adenosine systems may be the means by which sleep disturbance continues into withdrawal and abstinence conditions, long after any disturbance can be attributed to direct cocaine effects. The protracted sleep disturbance has implications for maintenance of abstinence based on correlational evidence of long-lasting risk for relapse (measured up to 6 weeks; Angarita et al., 2014a). We now have direct evidence that this sleep disturbance increases the rewarding properties of cocaine (Bjorness and Greene, 2020). Thus, treatment of sleep disturbance, including with dopaminergic, orexinergic, or adenosinergic modulators, may be expected to have potential for reducing the risks of relapse, a highly valued clinical outcome for the patient with cocaine use disorder.

Declaration of competing interest

The authors have nothing to declare.
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