HHS Public Access

Author manuscript

Pharmacol Biochem Behav. Author manuscript; available in PMC 2022 April 01.

Published in final edited form as:

Pharmacol Biochem Behav. 2021 April ; 203: 173153. doi:10.1016/j.pbb.2021.173153.

Sleep and Alertness Disturbance and Substance Use Disorders: A Bi-directional Relation

Timothy Roehrs[1,2,3], **Mohammad Sibai**[1,3], **Thomas Roth**[1,2]

[1]Sleep Medicine, Henry Ford Health System, Detroit Michigan

[2]Dept of Psychiatry & Behavioral Neuroscience, Wayne State University, SOM, Detroit Michigan

[3]Dept of Psychology, University of Detroit Mercy, Detroit Michigan

Abstract

The majority of the literature describing the relation of sleep/alertness disturbance and substance use disorders (SUD) has focused on the disruptive effects of substances with abuse liability on sleep and alertness. Rarely have studies or literature reviews assessed or discussed how sleep/alertness disturbance affects substance use. This paper focuses on the sleep/alertness disturbance side of the relation. We argue that the relation is bi-directional and review evidence showing that sleep/alertness disturbance affects all phases of the addiction cycle, including the initiation, maintenance and relapse of SUD. We review a variety of substances across all phases of the addiction cycle and conclude sleep/alertness disturbance is a critical factor in both understanding and treating SUD.

Keywords

substance use disorder; sleep disturbance; excessive daytime sleepiness; polysomnography; multiple sleep latency testing

Introduction

It is now becoming clearer that disturbances to sleep-wake functioning heighten risks to the development, maintenance, and relapse of substance use disorders (SUD). Research has shown that repeated exposure to addictive substances disrupts sleep-wake timing and the duration and continuity of sleep, while abstinence causes disturbed sleep and reports of insomnia and negative affect which tends to drive craving and impulsivity leading to relapse (1). Furthermore, these substances typically alter and disrupt the neurophysiology responsible for regulating the sleep-wake system (2). On the other hand, sleep/alertness disturbance often increases factors that drive substance use such as increased stress, mood

Corresponding Author: Timothy Roehrs, Ph.D., Sleep Disorders & Research Ctr, Henry Ford Hospital, 2799 West Grand Blvd, CPF-3, Detroit, Michigan 48202, Phn: (313) 916-5177, Fax: (313) 916-5167, troehrs1@hfhs.org.

disturbance, and greater sensitivity for pain. This suggests that sleep/alertness disturbance and SUD are bi-directionally related.

Much of the literature that has described the relation of sleep/alertness disturbance to SUD has focused on the disruptive effects of substances on sleep per se, rarely have studies or reviews looked at how sleep/alertness disturbance affects substance use. In this paper we will focus on the sleep-wake disturbance side of the relation. We will argue that sleep/alertness disturbance contributes to all phases of the addiction cycle (i.e. initiation, maintenance, and relapse) and that this bi-directional relation exists across a variety of drugs of abuse. We review examples from the major classes of drugs with known abuse liability and sleep/alertness effects; we do not intend to provide an exhaustive review of all drugs for which there are reports of abuse. Furthermore, in reviewing examples across all phases of the addiction cycle and with a variety of classes of drugs we argue that sleep/alertness disturbance is a critical factor to be considered in both understanding and treating SUD.

Basics of normal sleep/alertness relevant to SUD

To appreciate the hypothesized bi-directional relation of sleep/alertness and SUD, it is helpful to review some basics of sleep-wake phenomenology. The 24-hr sleep wake cycle is under complex and interacting homeostatic and circadian processes (3). Further, within the 24-hr sleep-wake cycle is a 90–120 min ultradian cycle (referred to as the basic rest-activity cycle), most clearly seen during sleep, but also hypothesized to exist during wakefulness. In sleep the ultradian cycle is expressed as the NREM-REM cycle and many drugs with abuse liability alter this cycle. NREM and REM sleep are two unique brain states each with a distinct physiology and neurobiology, which is discussed in the next section and is important in understanding addiction risks.

Homeostatic regulation of sleep is driven by the prior amount of wakefulness relative to the amount of sleep accumulated over days, termed Process S (4). The intensity of sleep drive can be inferred from the measurement of EEG slow wave activity during sleep, arousal threshold during sleep, the total duration and continuity of sleep and the speed of falling asleep at night and during the day. During nocturnal sleep the amount of slow wave activity diminishes during each successive NREM-REM cycle across the night and following development of enhanced sleep drive slow wave activity increases and extends to later NREM episodes. Speed of falling asleep during the day on repeated opportunities at two-hour intervals is used to measure the presence of an accumulated sleep drive; the method is termed the Multiple Sleep Latency Test (MSLT). Each of these various measures have shown parametric sensitivity to the accumulated prior daily amount of wakefulness, both acute and chronic.

Independent of homeostatic processes is a circadian process that organizes sleep and wake and other biological processes in synchrony with the light-dark cycle, termed Process C (4). Light-dark input from the retino-hypothalamic tract feeds to the supra-chiasmatic nucleus (SCN) which is considered the master biological clock. Efferents from the SCN convey circadian timing signals that synchronize a variety of physiological systems and organs. In some SUDs (i.e., opioids or stimulants) the substance self-administration pattern controls the

timing of sleep and wake irrespective of the environmental light-dark cycle and additionally within sleep can alter the ultradian NREM-REM cycle.

Neurobiological mechanisms common in both sleep/alertness and substance use.

There are neurobiological processes that are common to control of sleep-wake, motivation and reward. Table 1 presents the primary brain origin and cell firing rates of important neurotransmitters involved in control of sleep and wake and the two distinct sleep states, NREM and REM (5). Without completely describing the complex interactions among these various transmitter systems it is clear that wake and arousal are controlled by multiple systems, while sleep is primarily controlled by GABA neurons in the hypothalamic preoptic area (POA, specifically ventral lateral, VLPO), which project to and inhibit the multiple wake promoting systems. NE, ACH, and 5-HT reciprocally inhibit GABA VLPO cells to promote wake. Uniquely opposed to GABA's sleep promoting effects is orexin and histamine, which project to and stimulate all the various wake promoting systems and additionally inhibit GABA, thereby stabilizing the maintenance of wakefulness. Thus, POA neurons active during sleep inhibit arousal systems and arousal systems inhibit sleep-active POA neurons.

From a SUD perspective, stimulation of the dopaminergic ventral tegmental-nucleus accumbens track (VTA-NAC), either directly or indirectly dependent on the specific drug, is recognized to be responsible for the reinforcing and rewarding effects of drugs of abuse. Given dopamine's moderate activity during wake and NREM, it is notable that dopamine activity increases during REM sleep (see Table 1). In addition, cholinergic activity is high both during wake and REM sleep. Basic animal studies document interaction of the peduculopontine tegmental nucleus (PPT), which is critical to maintaining arousal and REM sleep, with the ventral tegmental area (VTA) and in modulating stimulant self-administration (6,7). Many drugs of abuse (i.e. alcohol, stimulants, and opioids) suppress REM sleep and tolerance rapidly develops to their REM-suppressing effects. During drug discontinuation a REM rebound occurs, evident by reduced REM latency and enhanced REM percent, Eye Movements during REM, and wake intrusions into REM sleep. The nature of the specific REM-related alterations that have occurred during the addiction cycle is currently not completely clear. As discussed below these alterations may be especially important to the maintenance and relapse phases of the addiction cycle.

The relatively recent discovery of orexin (1998) is important regarding the bi-directional relation of sleep-wake and SUD. In 1998 two research groups simultaneously discovered a cluster of 50,000–80,000 neurons in the lateral hypothalamus that project throughout the brain and regulate sleep-wake, feeding, stress-reactivity, and drug-motivated behavior (8,9,10). These cells express two peptides, named hypocretin (HCT) by the sleep group and orexin (OX) by the feeding group. OX has now become the conventional designation for these peptides and their receptors. These neurons project from the lateral hypothalamus to cholinergic and monoaminergic systems thereby stimulating arousal and motivation. Orexin comes in 2 isoforms (Orexin A and B) derived from the same precursor protein, prepro-

orexin; these isoforms bind to two subtypes of G protein-coupled receptors, orexin-1 (OX-1) and orexin-2 (OX-2). Orexin A has slightly higher affinity for OX-1 than OX-2 receptors, whereas orexin B has much higher affinity for OX-2 than OX-1 receptors.

The functional/behavioral specificity of the two OX receptors is not completely defined (10). Pre-clinical models suggest OX-2 activation is primarily involved in maintaining wakefulness and arousal, while OX-1 activation promotes motivation and specifically drug reinforcement. An intriguing serendipitous discovery implicates an OX role in SUD (at least OUD). The sleep disorder narcolepsy, in which a primary symptom is excessive daytime sleepiness, is known to be associated with reduced CSF levels of orexin relative to normals and other CNS disorders of excessive daytime sleepiness. In search for evidence regarding deficiency in OX receptors in human narcolepsy, postmortem brains of people with narcolepsy were examined (11). Among the control brains examined for comparison was an individual that had a 54% greater number of OX receptors and that individual was found to have been a heroin addict. Elevation of the number of OX receptors was then confirmed in a larger sample of the decedent brains of heroin-addicts. Any number of compelling questions arise including: 1) is this evidence of a premorbid risk for development of OUD, or 2) a consequence of months of opioid use and 3) will post detoxification treatment via orexin antagonism improve sleep and relapse outcomes.

It is generally accepted that the sleep homeostat is extracellular adenosine, a naturally occurring purine nucleoside, which is found throughout the brain. It acts as a modulator of neurotransmission and behavior by generally exerting a depressant effect on neuronal firing. Adenosine acts primarily through A1 and $A2_A$ receptors that are widely distributed throughout the brain and relevant to sleep-wake control in the basal forebrain and the VPLO. Early research showed A1 receptors inhibit basal forebrain ACH wake promoting neurons (12). Later it was shown sleep-active GABA neurons of the VLPO, which are inhibited by the TMN HA neurons promoting wake, become disinhibited by $A2_A$ activation and thus promote sleep (13). With respect to SUD, $A2_A$ receptors are found in the striatum, clustered on dopaminergic and glutaminergic tracts projecting from the ventral tegmental area (VTA) to the nucleus accumbens (NA) (14). Whether the interaction of $A2_A$ modulation is synergistic or antagonistic, how that interaction may change with acute vs chronic drug use, and how it differs for various drugs of abuse has, as yet, not been clearly outlined (15,16,17). But, the intermingling of adenosinergic and dopaminergic/glutaminergic systems in the striatum may be important regarding the bi-directional relation of sleep-wake and SUD. Below we will describe EEG slow wave activity assessments done in people with various SUDs that suggest adenosinergic modulation of the dopaminergic/glutaminergic reward system is impaired in SUD.

Sleep/alertness disturbance and initiation of SUD

Alcohol

The strongest data showing that sleep/alertness disturbance is predictive of the development of a SUD comes from the alcohol literature. Cross-sectional studies of teens and young adults have shown insomnia symptoms and erratic sleep schedules are associated with early use of alcohol, cannabis, and nicotine (18,19). Prospective, longitudinal studies have also

shown an association between insomnia and substance use. Individuals with insomnia at time 1 were 7.2 times more likely to report alcohol and drug dependence 3.5 yrs later than those without time 1 insomnia (20). However, the relation, either cross-sectional or longitudinal, between sleep problems and substance use is not clearly independent of coexisting psychiatric problems (21).

Laboratory, alcohol self-administration studies in people with insomnia without co-existing psychiatric disorders and reported light to moderate social drinking self-administer alcohol vs placebo before sleep, while age-matched controls prefer placebo (22,23). Initially, a low dose (0.045% BrEC) alcohol normalizes percentage of slow-wave sleep to that of the controls without disrupting sleep the last four hours of the sleep period. However, by night 6 of nightly alcohol tolerance developed.to the slow wave sleep enhancement and alcohol reduced sleep efficiency (23). On subjective effects assessment alcohol was initially rated for its sedative effects, which was lost by night 6 and replaced by enhanced beverage “liked” ratings. In a follow-up study people with insomnia were randomized to 6 nights of alcohol or placebo before sleep and then given an opportunity to self-administer multiple alcohol doses before sleep (23). Those with 6 nights of prior alcohol exposure selected higher alcohol doses before sleep compared to those with prior placebo exposure.

The specific sleep disturbance that may increase the risk of development of AUD is apparently a dysfunction of the sleep homeostat, as measured by slow wave activity. Spectral EEG analyses of sleep in alcohol dependent and abstinent persons with AUD have shown reduced spectral power in the delta band relative to healthy controls (24,25). A classic approach to assessing the function of the sleep homeostat is to deprive sleep or delay sleep onset which in healthy control subjects produces a robust enhancement of slow wave activity during recovery sleep. A study of the effects of a phase delay showed people with AUD relative to controls had a blunted slow wave sleep response to the delay (26). Yet, these studies do not exclude the possibility that the sleep homeostat disturbance is the result of the excessive alcohol intake inherent in AUD.

The participants with insomnia in the self-administration studies cited above, who were without AUD and had a history of moderate social alcohol use, had reduced amounts of slow wave sleep at baseline relative to the age-matched controls and alcohol normalized their slow wave sleep (22,23). Genetic and familial aggregation studies support the hypothesis that sleep homeostat dysfunction is linked to AUD onset. The $PER3^{4/4}$ polymorphism, which is a genotype associated with lower homeostatic sleep drive, had the strongest association with the severity of insomnia in AUD patients (25). Finally, 9–10 yr old children with a family history of AUD had lower delta and theta power on NPSGs compared to family history negative children (26). Taken together, these data suggest sleep homeostat dysfunction represents a risk of the development of AUD.

Cannabinoids

The cannabinoids remain illegal at the federal level, but now are legal in a majority of states for therapeutic use and in some states for social use. As such, cannabis is readily available to many adolescents. The cross-sectional studies cited above, regarding sleep disturbance in teens and young adults being associated with early onset alcohol use, also included early use

of cannabinoids (18,19). We are aware of one prospective longitudinal study showing sleep disturbance is predictive of higher risk of developing cannabis use, but the relation was only present in males (18). Further, the self-report of insomnia and cannabis use at both time points was dichotomized (yes/no), which can-not be interpreted as the presence of either insomnia or cannabinoid use disorder (CanUD).

Several studies discussed below report insomnia and cannabis use are associated and cannabis users report using cannabis as a sleep aid (29). There is a neurobiology supporting the association of sleep disturbance and CanUD. Two cannabinoid receptors CB1 and CB2 have been identified and CB1 agonists promote sleep, while CB1 antagonists increase wake (30). Basic research has suggested that the cannabis sedative effect occurs through release of adenosine in the basal forebrain (31). There also is evidence that cannabis is involved in the control of the circadian sleep wake rhythm. A study in healthy volunteers showed plasma concentrations of anandamide exhibited a circadian rhythm with concentrations three times higher at awakening from sleep than before sleep and that sleep deprivation disrupted that rhythm (32). A recent twin study suggests insomnia and regular cannabis use are shared genetic traits (33). In a study of 472 monozygotic and 304 dizygotic twins there were higher cross-twin correlations for regular cannabis use, insomnia, and short weekday sleep (< 6 hrs nightly) than for the dizygotic pairs. However, while all this evidence suggests an association of sleep/circadian disturbance and cannabis use, it does not indicate that sleep disturbance leads to the initiation of CanUD.

Sedative-Hypnotics

While it is generally considered that sedative-hypnotics have a relatively high abuse liability, the scientific evidence from epidemiological and laboratory studies indicate the abuse liability of modern sedative-hypnotics is relatively low. The distinction “modern” is critical in that, the early sedative-hypnotics, barbiturates and ethanol-based drugs (i.e., ethchlorvynol, choral hydrate); clearly produce tolerance, as well as both physical and behavioral dependence. But, the modern benzodiazepine receptor agonists (BzRA) are not as likely to do such.

In the 1980s, daytime self-administration studies were done in normals, persons with substance abuse histories and patients with anxiety disorders and the results showed a generally low behavioral dependence liability. BzRAs were self-administered by people with a substance abuse history at low and declining rates over time (34) and were not differentially self-administered relative to placebo by normals or patients with anxiety disorders (35,36). These studies were conducted during the daytime and used long-acting anxiolytic BzRAs.

Short term pre-sleep self-administration studies of BzRA hypnotics in volunteers with insomnia found that triazolam and placebo were self-administered at similar rates (67–88%) in a single-choice paradigm (i.e., choice of taking the available capsule or not), which is the clinical situation) (37–39). When forced to choose between triazolam and placebo on a given night, triazolam was preferred eighty percent of the time (39). Most importantly, when given an opportunity, in a single-choice paradigm, to self-administer multiple capsules on the same night, a 0.27 mg average nightly triazolam dose was self-administered (i.e., close to the 0.25

mg clinical dose), while the placebo dose was escalated to the three capsule maximum. Finally, when given an opportunity to self-administer triazolam or placebo during the daytime a minority of the insomnia volunteers choose triazolam relative to placebo. Those preferring daytime triazolam were hyper-aroused as reflected in unusually high MSLT scores (40).

Recent long-term studies of nightly use of zolpidem or placebo for 1 yr showed that 1) zolpidem was preferred to placebo by people with insomnia, but its overall rate of self-administration did not increase over 12 months of nightly use (i.e., a stable average nightly dose of 9.5 mg was self-administered, similar to the clinical dose, 10 mg), while placebo self-administration did increase over the 12 months, again to the maximum three capsules, implying an ineffective hypnotic (i.e. placebo) is dose-escalated (41); 2) 12 months of nightly zolpidem use did not produce rebound insomnia or withdrawal signs and symptoms after chronic use (42); and 3) relative to placebo zolpidem increased total sleep time and this hypnotic efficacy did not diminish over 8 months of nightly use (43).

Finally, to characterize those people with insomnia who self-administer at high rates in short-term studies and who dose-escalated in long-term studies, it was found that they were hyperaroused with lower percentages of stage 3/4 sleep (44) and elevated MSLT scores during the daytime (45). Interestingly, among the signs identified in case reports of hypnotic abuse are rapid shifts from nighttime use to daytime use and escalation of dose (46). Thus, overall, sleep/alertness disturbance leads to abuse in a small subset of individuals who use hypnotics.

Opioids

One route through which sleep disturbance may lead to OUD is pain. It is well established that acute and chronic pain is associated with shortened and disrupted sleep and daytime sleepiness/fatigue (47). In healthy volunteers reducing bedtime enhances pain sensitivity and in sleepy, otherwise healthy, volunteers increasing bedtime reduces pain sensitivity (48,49). But, most importantly as regards a pain path to OUD, improving sleep leads to reduced pain and reduced opioid use. A study in joint replacement patients, randomized the patients to one week of a nightly increase in bedtime vs continuation of habitual bedtime. This sleep time manipulation was done over the week immediately prior to hip or knee joint replacement (50). During the pre-surgery week the sleep extension group slept one hour longer nightly vs the habitual sleep group and then reported less daily pain over the three, post-surgery, in-patient days and used 48% less daily morphine mg equivalents. Although the mechanisms are not well understood, it has been shown that the suboptimal management of postoperative pain increases the risk of transition to chronic pain and opiate abuse (51, 52). The joint-patient study suggests optimal management of postoperative pain should include attention to a patient’s sleep.

Among opioid pain medication dependent patients, pain severity scores were related to Insomnia Severity Index scores (53). In other OUD studies a large proportion of patients report initiating opioid use for pain management and then subsequently using the medication for other reasons including to “get high” or “for sleep” (54–56). In summary, sleep

insufficiency enhances pain and thus increases the risk for opioid dependence, while improving sleep decreases opioid use.

Psychomotor Stimulants

The sleep/alertness disturbance mediator of stimulant dependence is likely excessive daytime sleepiness. We noted above that excessive daytime sleepiness is the consequence of inadequate sleep due to reductions in the opportunity to sleep, or the presence of sleep disorders disturbing the continuity of sleep, or sleep that is scheduled in opposition to the light-dark cycle (i.e., shift workers). We are unaware of prospective studies showing daytime sleepiness precedes development of a stimulant use disorder.

There are laboratory studies that suggest use of stimulants to reverse sleepiness may increase the risk of development of a stimulant use disorder. In healthy people methylphenidate is self-administered relative to placebo after four hours in bed the previous night, but not after eight hours in bed (57). Methamphetamine is self-administered relative to placebo during work periods after an abrupt shift in sleep schedule, but not after a normal sleep schedule (58). In both studies subjective effect ratings of amphetamine-like effects or “desire to take the drug” were not different in the rested versus sleepy state. As tolerance development to the psychomotor stimulants is well documented, the critical question is whether and how the positive rewarding effects of these stimulants, experienced in both the alert and sleepy state, change as tolerance to the sleepiness reversing effects develops.

Sleep/alertness disturbance and maintenance of SUD

Once a SUD has developed sleep/alertness disturbance can contribute to the maintenance of the disorder. In discussing sleep/alertness disturbance and maintenance of SUD we make a distinction between relapse after prolonged abstinence (treated in the next section) vs continued daily use or brief discontinuations followed by resumption of substance use. We suggest that in patients with SUD, in addition to the positive rewarding effects of the substance important to initiation of the SUD, negative reinforcing effects are added as the addiction cycle progresses. In other words, the substance now is used to reverse a sleep/alertness disturbance that developed in association with the excessive use of the substance.

It is important to note that beyond showing sleep/alertness disturbance is present during acute or chronic use and acute discontinuation, it is necessary to show that the sleep/alertness disturbance itself is maintaining the continued use. There are numerous review articles reporting sleep/alertness disturbance is present in SUD, but in few cases has it been shown that the disturbance leads to continued use. The argument for this association can be strengthened by showing neurobiological changes in sleep-wake control as a result of sustained substance use. Such neurobiological changes have been shown in a few SUDs.

Caffeine

Caffeine is the best example of negative reinforcement maintaining substance use. Caffeine, the most widely used stimulant in society, is generally not considered a drug of abuse, and even within the medical community, its potential for abuse is not fully appreciated. As with the psychomotor stimulants, there are no prospective studies showing use of caffeine to

reverse sleepiness can lead to abuse. But, laboratory data indicate there are conditions under which caffeine is persistently self-administered and that caffeine does have abuse liability, albeit a relatively low liability compared with other recognized drugs of abuse (59). A withdrawal syndrome was observed after a double-blind, placebo-controlled cessation of chronic but moderate (235 mg daily on average) caffeine consumption (60). Putting this dose in context, an 8-ounce cup of coffee contains 100 mg of caffeine. On the second day of caffeine cessation (20 hours after the last caffeine use), in addition to the ubiquitous headache, reduced vigor and increases in sleepiness, fatigue, and drowsiness were experienced. For moderate to heavy caffeine users, the morning cup of coffee immediately after arising probably restores caffeine levels and alertness, as the 8-hour sleep period is essentially a caffeine discontinuation given caffeine's pharmacokinetics. These data would suggest that caffeine is operating as a negative reinforcer, as opposed to a positive reinforcer; that is the caffeine use reverses the withdrawal syndrome which includes excessive sleepiness. However, as yet it has not been directly shown in laboratory studies that caffeine vs placebo is self-administrated to reverse excessive sleepiness.

Nicotine

Nicotine is a well-known addictive drug, but the role of sleep/alertness disturbance in the initiation of nicotine addiction has not been assessed. On the other hand, sleep/alertness disturbance may be involved in the maintenance of nicotine addiction. As with caffeine, the 8-hour sleep period is essentially a nicotine discontinuation. Given nicotine's even shorter half-life than that of caffeine, the frequently reported middle-of-night awakening or early morning awakening to smoke is necessary to restore nicotine plasma levels. It has been reported that the often-reported nighttime awakening is due to nicotine craving in 20% of heavy smokers (61). In a longitudinal study compared to non-smokers, smokers had an increased risk of difficulty falling asleep and daytime sleepiness (62). PSG and MSLT studies have documented the sleep disturbance and the excessive daytime sleep (63). However, in their extensive and critical review, Jaehne and associates point out that other factors such as anxiety or depression could be important mediators to the role of sleep/alertness disturbance in maintaining nicotine addiction (63). In a large sample of smokers it was shown that emotional dysregulation mediated the relation between sleep/alertness disturbance and nicotine addiction (64). Despite being a stimulant, heavy smokers typically report smoking relaxes them.

Alcohol

In AUD research it has been demonstrated that individuals who use alcohol for long periods of time tend to develop difficulty sleeping. One study examined the prevalence of insomnia and self-medication with alcohol in a sample of AUD patients (65). Results demonstrated that compared to patients without insomnia, patients with insomnia reported more frequent use of alcohol to aid in falling asleep. These patients also reported greater severity scores for alcohol dependence and depression. An inpatient study of 56 males diagnosed with alcohol use disorder (AUD) assessed alcohol's effect on subjective sleep during one week in which they were abstinent from alcohol as well as the 4 following weeks during which they had the opportunity to drink (66). Results showed that participants who chose to drink had worse sleep quality at the abstinent baseline than participants who did not drink during the four-

week optional period. Alcohol temporarily improved sleep quality in those patients who used alcohol after the abstinent week. However, improvement in sleep quality was only observed during the first week of optional alcohol use (i.e., tolerance developed).

Some studies have suggested there are important mediator/moderators of the sleep/alertness disturbance and continued alcohol use relation. There is an indication that age may moderate the association found between alcohol and sleep (67). One study investigated the main and interactive effects of diagnostic group and age group on sleep. Results showed that both older (greater than 55 years of age) AUD participants and non-AUD participants had significantly decreased total sleep time as well as an increase in stage 1 sleep percent, respiratory distress, and periodic limb movements relative to the young non-AUD participants. When compared, older AUD participants had the highest mean values for latency and the lowest mean values for sleep efficiency, as well as delta sleep percentage when compared with the other three groups (younger control, younger AUD, and older control). A recent study in 123 patients with AUD assessed severity of alcohol use and insomnia and as well assessed indices of depression and anxiety (68). Structural equation modeling showed severity of insomnia and alcohol use was linked via the psychiatric symptoms.

Finally, there is animal research suggesting mechanisms that may mediate the disruptive effects of protracted alcohol use on control of sleep and wakefulness in AUD (69). Acute alcohol administration inhibits the basal forebrain ACH wake-promoting neurons through activation of adenosine A1R receptors (10). Using an animal model of alcohol addiction that mimics the high and sustained blood alcohol levels followed by the signs of a withdrawal syndrome seen in human AUD, it was shown that BF ACH activation was increased, while adenosinergic inhibition was downregulated (69). These studies suggest the sleep disturbance in AUD that maintains the AUD disorder is disruption of sleep homeostatic mechanisms.

Cannabis

Research has demonstrated that heavy marijuana users tend to show reduced total sleep times as well as less slow wave sleep than non-users upon discontinuation of the drug (70). Cannabis users also showed worse sleep efficiency, longer sleep onset, as well as shorter NREM-REM cycles compared to non-marijuana users. PTSD is known to be associated with sleep disturbance and among medical cannabis users with PTSD those with higher PTSD scores used cannabis at a higher frequency than those with lower PTSD scores and were more likely to report using cannabis as a sleep aid (71). These findings suggest that use or discontinuation of cannabis is associated with sleep disturbance which may in turn lead the individual to continue using cannabis to induce sleep.

During withdrawal, cannabis users often report an increased level of anger, irritability, as well as sleep difficulty (72). Difficulty sleeping can occur within 24–72 hours of discontinuation of marijuana use and can persist for 6–7 weeks. Withdrawal symptoms are felt in a relatively short period of time while their persistence for more than a month can make it difficult to remain abstinent. However, studies have shown that the desired hypnotic effect of cannabis tends to deteriorate slowly over several years of use due to tolerance

development (73). As yet it has not been directly shown that this sleep disturbance leads to further self-administration or use of cannabis.

Opioids

In early rat studies of opioid dependence and discontinuation, in which morphine methadone, and l-alpha-acetyl-methadol were self-administered IV while EEG sleep and wake were continuously recorded across the 24-hr day; these opioids disrupted timing and normal staging of sleep (74). Sleep and wake were systematically distributed within each inter-injection interval (≈3-hr with morphine and 8 injections per day) irrespective of the 12/12 light-dark cycle. Within each interval initial wake was followed solely by NREM sleep, and then REM sleep intermixed with NREM and wake, and the next injection followed a brief awakening. During opioid discontinuation a protracted rebound of REM sleep lasting 12 days was seen (75).

Clinical studies similarly indicate chronic opioid use/exposure disrupts sleep. In 3 separate double-blind placebo-controlled studies, morphine (76), heroin (77) or methadone (78) administered to abstinent opioid-dependent participants dose-dependently decreased total sleep time, stage 3–4 sleep, and REM sleep. All these opioids also increased arousals and frequent sleep stage changes (i.e. sleep fragmentation).

Tolerance to opioid-induced sleep disruption often develops within weeks (78,79); fragmentation is lessened, and REM sleep suppressive effects tend to diminish. However, some studies in methadone- or buprenorphine-treated patients suggest REM sleep remains suppressed (80,81).

Opioid agonist-related sleep disruptions may also occur by disturbing respiratory mechanisms (82). Opioids cause hypoventilation and reduce hypoxic and hypercapnic drive during wake. Sleep itself normally reduces respiratory drive and, combined with opioids, the risk of sleep-disordered breathing (i.e. central sleep apnea) and the consequent disruption and fragmentation of sleep is heightened. In contrast to obstructive sleep apnea, which predominates in obese men and is related to excessive daytime sleepiness, central apnea most typically is associated with insomnia. Central apnea is characterized by cessation of both respiratory effort and airflow and is associated with awakening and not the brief EEG arousal of obstructed breathing.

Furthermore, discontinuation of chronic opioid use is associated with disturbance of sleep efficiency and staging that lasts several weeks. Heroin-dependent people maintained on buprenorphine in an outpatient program were discontinued from their treatment; sleep latency and latency to REM sleep were prolonged and percent stage 3–4 sleep was reduced compared to healthy controls (83). Thus, continuation of opioid use is likely associated with extensive sleep disturbance and sleep-related breathing disturbance associated with its use. However, again this has not been directly demonstrated.

Sleep/alertness disturbance and relapse in SUD

Relapse after a period of extended abstinence is the defining characteristic of SUD and research suggests sleep/alertness disturbance is a predictor of relapse. A recent retrospective chart review was conducted of patients in an outpatient treatment program which included a pre-treatment assessment of insomnia and daytime sleepiness using validated self-report scales (84). Patients represented a diverse range of SUDs, including alcohol, cannabis, opioids, stimulants, and sedative/hypnotic/anxiolytics. The study did not analyze by specific type of SUD, as the study hypothesis tested was that sleep disturbance is a "universal risk factor" for relapse. Among the 110 patients clinically significant insomnia was predictive of inability to complete the 20-day treatment, while excessive sleepiness was not predictive. Longer-term abstinence studies of specific SUDs present a similar picture.

Alcohol

Both objective and subjective measures of sleep after acute detoxification predict the likelihood of relapse during long-term abstinence. Based on sleep laboratory NPSG studies, disturbed sleep can persist for up to 3 years in alcoholism. Sleep time remains shortened and REM sleep pressure elevated as reflected in elevated REM percentages, shortened latencies to REM sleep and higher REM densities (85). Other studies have identified deficiencies in slow wave sleep as predictive of relapse (86, 87). While it is tempting to attribute these sleep abnormalities to the excessive alcohol drinking of the patients and alcohol's REM suppressive effects and the consequent buildup of REM pressure, the sleep problems could have preceded the development of the alcoholism (see the initiation section above) or they could be secondary to the development of other medical and psychiatric disorders that have developed during the excessive alcohol drinking. However, in one study sleep-related relapse risk was greater than that associated with other variables such as age, marital status, employment, duration and severity of alcoholism, hepatic enzymes, and depression ratings (88).

Nicotine

Any number of studies have shown that sleep is disturbed during nicotine abstinence and there is daytime sleepiness (64). It has been shown that nicotine plasma levels are associated with time awake at night and other withdrawal symptoms. A study of treatment-seeking smokers found that self-reported sleep disturbance was associated with lower quit self-efficacy, a measure of confidence of successful abstinence (89). Furthermore, insomnia symptoms were predictive of quitting failure in another study, specifically pre-quit insomnia as opposed to postquit insomnia (90).

Cocaine

There are studies linking sleep/alertness disturbance to cocaine use disorder (CocUD) relapse. Discontinuation of cocaine use is followed by both sleep and alertness disturbance (91). After 5 evenings of in-laboratory insufflation of cocaine (6–9 pm) by non-treatment seeking volunteers with CocUD, NPSG sleep efficiency was in the low normal range, which after two weeks of discontinuation dropped to levels seen in people with severe insomnia. Excessive daytime sleepiness, measured by MSLT, was evident on the first two days with

multiple sleep onset REM periods each day, which returned to normal levels after two weeks. A larger NPSG study (n=28) in cocaine-dependent participants initially showed increased sleep time and REM time and reduced slow wave sleep (SWS), which was reversed by week 3 of abstinence (92). Sleep time and SWS were negatively correlated with prior years of cocaine use.

Two studies have assessed the role of these clear sleep/alertness disturbances on cocaine relapse. The life-time history of insomnia and hypersomnia was assessed by self-report in 7168 adults at SUD treatment entry and at 12 months post treatment entry. Sleep/alertness disturbance was associated with cocaine use at the 12-month post treatment assessment with odds ratios of 1.3 to 1.6, meaning that with the disturbance there was a 30–60% chance of relapsing (93). A NPSG study of CocUD patients undergoing treatment was done during nights 3–4 and 10–11 of a 2 week in-patient phase and over the 6 week out-patient phase percentage of cocaine-negative urine and maximum consecutive days of abstinence were assessed (94). Overall increase in SWS from the early to late in-patient abstinence was positively correlated with the percentage of out-patient negative urines and those with no SWS change had significantly fewer negative urines and consecutive days of abstinence compared to those with increased SWS. As with AUD, normalization of REM sleep measures was also predictive of the ability to maintain abstinence.

Cannabinoids

There are equivocal data suggesting that insomnia is predictive of relapse in cannabinoid use disorder (CanUD). Among veterans self-reported sleep difficulty on the Pittsburgh Sleep Quality Index (PSQI), a validated self-report measure, predicted relapse over the first two days of a quit attempt and predicted a heightened amount of cannabis use over 6 months after the quit attempt (95). In a laboratory self-administration model of a two-day abstinence, a number of medications that improved sleep did not led to reductions in the risk of relapse to cannabinoid use (96–99). The one NPSG study we are aware of recorded adolescents with alcohol and cannabis use histories on nts 1–2 and 27–28 of abstinence (64). Night 2 REM % related positively to past month alcohol use and night 2 SWS % to past month cannabis use. But, these sleep stage findings did not differentiate those who were able to abstain the full 28 days of abstinence from those that did not. It should be noted these adolescents were mild to moderate substance users. Furthermore, in most of these studies the studied period of abstinence was two days, which can’t be considered an adequate assessment of the role of sleep disturbance in CanUD relapse.

Treatment of Sleep/alertness disturbance to prevent relapse in SUD.

Given sleep/alertness disturbance is predictive of relapse (at least for some substances), it follows that treatment of the disturbance should improve SUD relapse outcomes. Due to space limitation we will not conduct a comprehensive review of the treatment literature. To briefly summarize, treatments for insomnia, including a variety of pharmacological treatments and several cognitive-behavioral treatments have been studied in SUD, primarily AUD. The treatments, all focused on sleep disturbance, generally do improve sleep, but have no impact on rates of alcohol abstinence (92–94). We are aware of one treatment study in CocUD in which daytime modafinil improved abstinence outcomes and increased nighttime

SWS (95). The improved nighttime sleep associated with daytime short-acting stimulant use needs explanation. It is hypothesized that by reducing sleepiness and napping during the daytime homeostatic sleep drive is enhanced and thus nighttime sleep is improved, specifically SWS. Treatments that focus on orexin antagonism, as discussed in the neurobiology section above, may be important given orexin's role in both sleep wake and in motivation and reward.

Summary

We have argued that sleep/alertness disturbance affects all phases of the addition cycle and is found with a variety of drug classes that have known abuse liability. We have shown data suggesting that sleep/alertness disturbance plays a role in the initiation, the maintenance, and relapse in SUD. It is critically important to further investigate how sleep/alertness disturbance enhances the likelihood of developing a SUD and how sleep/alertness disturbance treatment may improve abstinence and relapse outcomes.

Funding Support:

Supported by NIDA, grant #: R01DA038177 and NHLBI, grant # U01HL150551 awarded to T. Roehrs, PhD

References

1). Valentino RJ, Volkow ND. Drugs, sleep, and the addicted brain. Neuropsychopharm 2020; 45:3–5.

2). Conroy DA, Arnedt JT. Sleep and substance use disorders: an update. Curr Psychiat Reports, 2014:16:487 10.1007/s11920-014-0487-3.

3). Roehrs T, Roth T. The sleep-wake cycle: An overview. In Murillo-Rodrigues E (Ed). The Behavioral, Molecular, Pharmacological and Clinical Basis of the Sleep-Wake Cycle. Philadelphia PA: Elsevier: 2019, pg1–15.

4). Borbely AA, Daan S, Wirz-Justice A, Deboer T. The two-process model of sleep regulation: a reappraisal. J Sleep Res 2016;25:131–143. [PubMed: 26762182]

5). Schwartz MD, Kilduff TS. The neurobiology of sleep and wakefulness. Psychiatr Clin N Am 2015;38:615–644.

6). Urbano FJ, Bisagno V, Gonzalez B, Rivero-Echeto MC, Muniz JA, Luster B, D'Onofrio S, Mahaffey S, Garcia-Rill E. Pedunculopontine arousal system psysiology-Effects of psychostimulant abuse. Sleep Sci 2015;8:162–168. [PubMed: 26779323]

7). Urbano FJ, Bisagno V, Garcia-Rill E. Arousal and drug abuse. Behav Brain Res 2017;333:276–281. [PubMed: 28729115]

8). De Lecea L, Kilduff TS, Peyron C, Gao XB, Foye PE, Danielson PE, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA 1988;95: 322–327.

9). Sakurai T, Amemiya A, Ishii M, Matuzaki I, Chemelli RM, Tanka H, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell 1988;92:573–585.

10). Tyree SM, Borniger JC, de Lecea L Hypocretin as a hub for arousal and motivation. Front Neurology 2018;9:1–16.

11). Thannickal TC, John J, Shan L, Swaab DF, Wu MF, Ramanathan L, McGregor R, Chew KT, Cornford M, Yamanaka A, Inutsuka A, Fronczek R, Lammers GJ, Worley PF, Siegel JM. Opiates increase the number of hypocretin-producing cells in human and mouse brain and reverse cataplexy in a mouse model of narcolepsy. Sci Tansi Med 2018;10:1–13.

12). Bjorness TE, Kelly CL, Gao T, Poffenberger V, Greene RW. Control and function of the homeostatic sleep response by adenosine A1receptors. J Neurosci 2009;29:1267–1276. [PubMed: 19193874]

13). Morairity S, Rainnie D, McCarley R, Green R. Disinhibition of ventrolateral preoptic area sleep-active neurons by adensosine: A new mechanism for sleep promotion. Neurosci 2004;123:451–457.

14). Brown RM, Short JL. Adenosine A2A receptors and their role in drug addiction. J Pharmacy & Pharmacol 2008;60:1409–1430.

15). Shen HY, Chen JF. Adenosine A2A receptors in sychopharmacology: Modulators of behavior, mood and cognition. Curr Peuropharmac 2009;7:195–206.

16). Kavanagh KA, Schreiner DC, Levis SC, O'Neill CE, Bachtell RK. Role of adensonine receptor subtypes in methamphetamine reward and reinforcement. Neuropharm 2015;89:265–273.

17). Ferre S, Diamond I, Goldberg SR, Yoa L, Hourani SMO, Huang ZL, Urade Y, Kitchen I. Adenosine $A2_A$ receptors in ventral striatum, hypothalamus and nociceptive circuitry: Implications for drug addiction, sleep and pain. Prog Neurobiol 2007;83:332–347. [PubMed: 17532111]

18). Roane BM, Taylor DJ. Adolescent insomnia as a risk factor for early adult depression and substance abuse. Sleep 2008;31:1351–1356. [PubMed: 18853932]

19). O'Brien EM, Mindell JA. Sleep and risk-taking behavior in adolescents. Behav Sleep Med 2005;3:113–133. [PubMed: 15984914]

20). Breslau N, Roth T, Rosenthal L, Andreski P. Sleep disturbance and psychiatric disorders: A longitudinal epidemiological study of you adults. Biol Psychiatry 1996;39:411–418. [PubMed: 8679786]

21). Johnson EO, Breslau N. Sleep problems and substance in adolescence. Drug Alcohol Dep 2001;64:1–7.

22). Roehrs T, Papineau K, Rosenthal L, Roth T, 1999. Ethanol as a hypnotic in insomniacs: self administration and effects on sleep and mood. Neuropsychopharm 1999;20:279–286.

23). Roehrs T, Roth T. Insomnia as a path to alcoholism: tolerance development and dose escalation. Sleep 2018;

24). Irwin M, Miller C, Gillin JC, Demodena A, Ehlers CL. Polysomnographic and spectral sleep EEG in primary alcoholics: an interaction between alcohol dependence and African-American ethnicity. Alcohol Clin Exp Res 200;24:1376–1384.

25). Gillin JC, Smith TL, Irwin M, Kripke DF, Schuckit M. EEG sleep studies in pure primary alcoholism during subacute withdrawal: relationships to normal controls, age, and other clinical variables. Biol Psychiatry 1990;27:477–488. [PubMed: 2310803]

26). Armitage R, Hoffmann R, Conroy DA, Arnedt JT, Brower KJ. Effects of a 3-hour sleep delay on sleep homeostasis in alcohol dependent adults. Sleep 2012;35:273–278. [PubMed: 22294818]

27). Brower KJ, Wojnar M,Sliwerska E, Armitage R, Burmeister M. PER3 polymorphism and insomnia severity in alcohol dependence. Sleep 2012;35:571–577. [PubMed: 22467995]

28). Tarokh L, Carskadon MA. Sleep electroencephalogram in children with a paraental history of alcohol abuse/dependence. J Sleep Res 2010;19:165–174. [PubMed: 19735444]

29). Babson KA, Scottile, Morabito D. Cannabis, cannabinoids, and sleep: a review of the literature. Curr Psychiatty Rep 2017;19:23–35.

30). Valentino RJ, Volkow ND. Drugs, sleep, and the addicted brain. Neuropsychopharm 2020;45:3–5.

31). Murillo-Rodriguez E, Blanco-Centurion C, Sanchez C, Piomelli D, Shiromani P. Anaandamide enhances extracellular levels of adenosine and induces sleep: An in vivo microdiolysis study. Sleep 2003;26:943–947. [PubMed: 14746372]

32). Vaughn LK, Denning G, Stuhr KL, deWit H, Hill MN, Hillard CJ. Endocannabinoid signalling: has it got rhythm? Br J Pharmacol. 2010;160:530–543. [PubMed: 20590563]

33). Winiger EA, Huggett SB, Hatoum AS, Friedman NP, Drake CL, Wright KP, Hewitt JK. Onset of regular cannabis use and young adult insomnia: an analysis of shared genetic liability. Sleep 2000; 1–1 10.1093/sleep/zsz293.

34). Griffiths RR, Weerts EM. Benzodiazepine self-administration in humans and laboratory animals. Implications for problems of long-term use and abuse. Psychopharmacology 1997;134:1–37. [PubMed: 9399364]

35). deWit H, Pierri J, Johanson CE. Reinforcing and subjective effects of diazepam in nondrug-abusing volunteers. Pharm Biochem Behav 1989;33;205–213.

36). deWit H, Uhlenhuth EH, Hedeker D, McCracken SG, Johanson CE. Lack of preference for diazepam in anxious volunteers. Arch Gen Psychiatry 1986;43:533–541. [PubMed: 3707286]

37). Roehrs T, Merlotti L, Zorick F, Roth T. Rebound insomnia and hypnotic self administration. Psychopharmacology 1992;107:480–484. [PubMed: 1603890]

38). Roehrs T, Pedrosi B, Rosenthal L, Zorick F, Roth T. Hypnotic self administration and dose escalation. Psychopharmacology 1996;127:150–154. [PubMed: 8888381]

39). Roehrs T, Pedrosi B, Rosenthal L, Zorick F, Roth T. Hypnotic self administration: Forced-choice versus single-choice. Psychopharmacology 1997;133:121–126. [PubMed: 9342777]

40). Roehrs T, Bonahoom A, Pedrosi B, Zorick F, Roth T, Nighttime versus daytime hypnotic self-administration. Psychopharmacology 2002;161:137–142 [PubMed: 11981593]

41). Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to dose escalation: A prospective placebo-controlled study. Sleep 2011;34:1–6.

42). Roehrs TA, Randall S, Harris E, Maan R, Roth T. Twelve months of nightly zolpidem does not lead to dose escalation: A prospective placebo controlled study. Sleep 2011;34:207–212. [PubMed: 21286241]

43). Randall S, Roehrs TA, Roth T. Efficacy of eight months of nightly zolpidem: A placebo controlled study. Sleep 2012;35:1551–1557. [PubMed: 23115404]

44). Roehrs T, Bonahoom A, Pedrosi B, Rosenthal L, Roth T. Disturbed sleep predicts hypnotic self-administration. Sleep Med 202:3:61–66.

45). Roehrs TA, Roth T. Hyperarousal in insomnia and hypnotic dose escalation. Sleep Medicine 2016;23:16–20. [PubMed: 27692272]

46). Vigneau-Victorri C, Dailly E, Veyrac G, Jolliet P. Evidence of zolpidem abuse and dependence: results of the French Centre for Evaluation and Information on Pharmacodependence (CEIP) network survey. Brit J Clin Pharm. 2007; 64:198–209.

47). Roehrs T, Roth T. Sleep and pain. In: Babson KA, Felder MT (eds), Sleep and Affect: Assessment, Theory, and Clinical Implications. New York: Elsevier, pp 377–399, 2015.

48). Roehrs T, Hyde N. Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. Sleep 2006;29:145–151. [PubMed: 16494081]

49). Roehrs TA, Harris E, Randall S, Roth T.Pain sensitivity and recovery from mild chronic sleep loss. Sleep 2012;35:1667–1672. [PubMed: 23204609]

50). Roehrs TA, Roth T. Increasing presurgery sleep reduces postsurgery pain and analgesic use following joint replacement: a feasibility study. Sleep Med 2017;33:109–113. [PubMed: 28449888]

51). Potter J, Hennessy G, Borrow JA, et al. Substance use histories in patients seeking treatment for controlled-release oxycodone dependence. Drug Alcohol Depend 2004;76:213–215. [PubMed: 15488345]

52). Causes Sinatra R. and consequences of inadequate management of acute pain. Pain Med 2010;11:1859–1871. [PubMed: 21040438]

53). Hartwell EE, Pfeifer JG, McCauley JL, Moran-Santa Maria M, Back SE. Sleep disturbances and pain among individuals with prescription opioid dependence. Adict Behav 2014:39:1537–1542.

54). Back SE, Payne RL, Simpson AN, Brady KT. Gender and prescription opioids: Findings from the National Survey on Drug Use and Health. Addict Behav 2010;35:1001–1007. [PubMed: 20598809]

55). Boyd CJ, McCabe SE, Cranford JA, Young A. Adolescents' motivations to abuse prescription medications. Pediatrics 2006;118:2472–2480. [PubMed: 17142533]

56). Rigg KK, Ibanez GE. Motivations for non-medical prescription drug use: A mixed methods analysis. Journal of Substance Abuse Treatment, 2010;39, 236–247. [PubMed: 20667680]

57). Roehrs T, Papineau K, Rosenthal L, Roth T. Sleepiness and the reinforcing and subjective effects of methylphenidate. Exp Clin Psychopharm. 1999; 7:145–150.

58). Kirkpatrick Haney M, Vosburg Comer SD, Foltin RW, Hart CL. Methamphetamine self-administration by humans subjected to abrupt shift and sleep schedule changes. Psychopharm 2009;203:771–780.

59). Griffiths RR, Mumford GF. Caffeine - A drug of abuse? In: Bloom FE, Kupfer DJ (eds). Psychopharmacology: The Fourth Generation of Progress. New York: Raven Press, 1995, pp. 1699–1713.

60). Nicholson AN, Stone BM. Heterocyclic amphetamine derivatives and caffeine on sleep. Br J Clin Pharmacol 1980;9:195–203. [PubMed: 6101960]

61). Rieder A, Kunze U, Groman E, Kiefer I, Schoberberger R. Nocturnal sleep-disturbing nicotine craving: a newly described symptom of extreme nicotine dependence. Acta Med Austriaca 2001;28:21–22. [PubMed: 11253627]

62). Wetter DW, Young TB. The relation between cigarette smoking and sleep disturbance. Prev Med 1994;23:328–334. [PubMed: 8078854]

63). Jaehne A, Loessl B, Barkai Z, Riemann D, Hornyak M. Effects of nicotine on sleep during consumption, withdrawal and replacement therapy. Sleep Med Rev 2009;13:363–377. [PubMed: 19345124]

64). Fillo J, Alfano CA, Paulus DJ, Smits JAJ, Davis ML, Rosenfield D, Marcus BH, Church TS, Powers MB, Otto MW, Baird SO, Zvolensky MJ. Emotion dysregulation explains relations between sleep disturbance and smoking quit-related cognition and behavior. Addict Behav 2016;57:6–12. [PubMed: 26827153]

65). Brower KJ, Perron BE. Sleep disturbance as a universal risk factor for relapse in addictions to psychoactive substances. Med Hypotheses. 2010; 74:928–933. [PubMed: 19910125]

66). Skoloda TE, Alterman AI, Gottheil E. Sleep quality reported by drinking and non-drinking alcoholics. In: Gottheil EL, Elmsford NY, eds. Addiction Research and Treatment. New York, NY: Pergamon Press;1979:102–112.

67). Brower KJ, Hall JM. Effects of age and alcoholism on sleep: a controlled study. J Studies on Alcohol. 2001;62:335–343.

68). Chaydgary NS, Wong MM, Kolla BP, Kampman KM, Chakravorty S. The relationship between insomnia and intensity of drinking in treatment seeking individuals with alcohol dependence. Drug Alcohol Dep.2020;215:10.1016/j.drugalcdep.2020.108189

69). Thakkar MM, Sharma R, Sahota P. Alcohol disrupts sleep homeostasis. Alchol 2015;49:299–310.

70). Bolla KI, Lesage SR, Gamaldo CE, Neubauer DN, Funderburk FR, Cadet JL, David PM, Verdejo-Garcia A, Benbrook AR. Sleep disturbance in heavy marijuana users. Sleep. 2008;31:901–908.. [PubMed: 18548836]

71). Bonn-Miller MO, Babson KA, Vandrey R. Using cannabis to help you sleep: Heightened frequency of medical cannabis use among those with PTSD. Drug Alcohol Depend 2014:136:162–165. [PubMed: 24412475]

72). Copersino ML, Boyd SJ, Tashkin DP, Huestis MA, Heishman SJ, Dermand JC, Simmons MS, Gorelick DA. Cannabis withdrawal among non-treatment-seeking adult cannabis users. Amer J Addictions 2006;15:8–14.

73). Schierenbeck T, Riemann D, Berger M, Hornyak M. Effect of illicit recreational drugs upon sleep: cocaine, ecstasy and marijuana. Sleep Med Rev 2008;12:381–389. [PubMed: 18313952]

74). Moreton JE, Roehrs T, Khazan N. Drug self-administration & sleep-wake activity in rats dependent on morphine, methadone or 1-alpha-acetyl-methadol. Psychopharmacology 1976;47:237–241. [PubMed: 823559]

75). Khazan N, Colasanti B Protracted rebound in rapid eye movement sleep time and electro-encephalogram voltage output in morphine-dependent rats upon withdrawal. J Pharm Exp Ther 1972;183:23–30.

76). Kay DC, Eisenstein RB, Jasinski DR (1969) Morphine effects on human REM state, waking state, and NREM sleep. Psychopharmacologia 1969;14:404–416. [PubMed: 4310918]

77). Kay DC, Pickworth WB, Neidert GL Morphine-like insomnia from heroin in non-dependent human addicts. Br J Clin Pharmacol 1981;11:159–169. [PubMed: 7213520]

78). Pickworth WB, Neidert GL, Kay DC. Morphine-like arousal by methadone during sleep. Clin Pharmacol Ther 1981;30:796–804. [PubMed: 7307428]

79). Kay DC. Human sleep during chronic morphine intoxication. Psychopharmacologia 1975;44:117–124. [PubMed: 172930]

80). Farney RJ, McDonald AM, Boyle KM, Snow GL, Nuttall RT, Coudreaut MF, Wander TJ, Walker JM. Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone. Eur Respir J 2013;42:394–403. [PubMed: 23100497]

81). Wang D, Teichtahl H, Drummer O, Goodman C, Cherry G, Cunnington D, Kronborg I. Central sleep apnea in stable methadone maintenance treatment patients. Chest 2005;128:1348–1356. [PubMed: 16162728]

82). Farney RJ, McDonald AM, Boyle KM, Snow GL, Nuttall RT, Coudreaut MF, Wander TJ, Walker JM. Sleep disordered breathing in patients receiving therapy with buprenorphine/naloxone. Eur Respir J 2013;42:394–403. [PubMed: 23100497]

83). Wang D, Teichtahl H. Opioids, sleep architecture and sleep-disordered breathing. Sleep Med Rev. 2007;1;11:35–46.

84). Wilkerson AK, Sahlem GL, Bentzley BS, Lord J, Smith JP, Simmons RO, Uhde TW, Book SW. Insomnia severity during early abstinence is related to substance use treatment completion in adults enrolled in an intensive outpatient program. J Sub Abuse Treat 2019;104:97–103.

85). Drummond SPA, Gillin JC, Smith TL, Demondena A. The sleep of abstinent pure primary alcoholic patients: Natural course and relation to relapse. Alcohol Clin Exp Res. 1998; 22:1796–1802 [PubMed: 9835298]

86). Brower KJ. Insomnia, alcoholism and relapse. Sleep Med Rev. 2003; 7:523–539. [PubMed: 15018094]

87). Allen RP, Wagman AM, Funderburk FR, Well DT. Slow wave sleep: A predictor of individuals differences in response to drinking? Biol Psychiatry. 1980; 15:345–348. [PubMed: 7417622]

88). Gillin JC, Smith TL, Irwin M, et al. Increased pressure for rapid eye movement sleep at time of hospital admission predicts relapse in nondepressed patients with primary alcoholism at 3-month follow-up. Arch Gen Psychiatry. 1994; 51:189–197. [PubMed: 8122956]

89). Nair US, Haynes P, Collins BN. Baseline sleep quality is a significant predictor of quit-day smoking self-efficacy among low-income treatment-seeking smokers. J Health Psych 2019;24:1484–1493.

90). Short NA, Mathes BM, Gibby B, Oglesby ME, Zvolensky MJ, Schmidt NB. Insomnia symptons as a risk factor for cessation failure following smoking cessation treatment. Addic Res & Theory 2017;25:17–23.

91). Johanson CE, Roehrs T, Schuh K, Warbasse L, The effects of cocaine on mood and sleep in cocaine-dependent males. Exp Clin Psychopharm 1999;7:338–346.

92). Matuskey D, Pittman B, Forselius E, Malison RT, Morgan PT. A multistudy analysis of the effects of early cocaine abstinence on sleep. Drug Alcohol Dep 2011;115:62–66.

93). Dolsen MR, Harvey AG. Lifetime history of insomnia and hypersomnia symptoms as correlates of alcohol, cocaine and heroin use and relapse among adults seeking substance use treatment in the United States from 1991 to 1994. Addiction 2017;112:1104–1111. [PubMed: 28127809]

94). Angarita GA, Canavan SV, Forselius E, Bessette A. Abstinence-related changes in sleep during treatment for cocaine dependence. Drug Alcohol Dep. 2014; 134:343–347.

95). Babson KA, Boden MT, Harris AHS, Stickle TR, Bonn-Miller MO. Poor sleep quality as a risk factor for lapse following a cannabis quit attempt. J Subst Abuse Treat. 2013;44:438–443. [PubMed: 23098380]

96). Haney M, Hart C, Vosburg S, Comer S, Reed S, Cooper Z, et al. Effects of baclofen and mirtazapine on a laboratory model of marijuana withdrawal and relapse. Psychopharmacology 2010;211:233–244. [PubMed: 20521030]

97). Vandrey R, Smith M, McCann U, Budney A, Curran E. Sleep disturbance and the effects of extended release zolpidem during cannabis withdrawal. Drug Alcohol Depend. 2011;117:38–44. [PubMed: 21296508]

98). Haney M, Hart C, Vosburg S, Comer S, Reed S, Foltin R. Effects of THC and lofexidine in a human laboratory model of marijuana withdrawal and relapse. Psychopharmacology. 2008;197:157–68. [PubMed: 18161012]

99). Cohen-Zion M, Drummond SPA, Padula CB, Winward J, Kanady J, Medina KL, Tapert SF. Sleep architecture in adolescent marijuana and alcohol users during acute and extended abstinence. Addict Behav 2009;34:976–979. [PubMed: 19505769]

100). Conroy DA, Arnedt JT. Sleep and substance use disorders: An update. Curr Psychiatry Rep 2014;16:487–496. [PubMed: 25135784]

101). Babson KA, Boon-Miller MO. Sleep disturbances: Implication for cannabis use cessation and cannabis use treatment. Curr Addict Rep 2014;1:109–114.

102). Miller MB, Donahue ML, Carey KB, Scott-Sheldon LAJ. Insomnia treatment in the context of alcohol use disorder: A systematic review and meta-analysis. Drug Alcohol Dep 2017:181:200–207.

103). Morgan PT, Angarita GA, Canavan S, Pittman B, Oberleitner L, Malison RT, Mohsensin V, Hodges S, Easton C, McKee S, Bessette A, Forselius E. Modafinil and sleep architecture in an inpatient-outpatient treatment study of cocaine dependence. Drug Alcohol Dep 2016:160:49–56.

Highlights

- This article argues that sleep/alertness disturbance and substance use disorder are bi-directionally related
- The article reviews evidence showing that sleep/alertness disturbance affects all phases of the addiction cycle
- The article shows that the bi-directional relation exists for a variety of substances with abuse liability
- Considering this bi-directional relation will lead to a better understanding of substance use disorder and its treatment

Table 1

Neurotransmitters of Sleep and Wake

Neurotransmitter	**Origin**	**Firing Rate**		
		Awake	**NREM**	**REM**
Serotonin (5-HT)	Raphe	Hi	Lo	Off
Norepinephrine (NE)	Locus Coeruleus	Hi	Lo	Off
Histamine (HA)	TMN	Hi	Lo	Off
Dopamine (DA)	VTA/NC SNr	Mod	Mod	Increased
Acetylcholine (Ach)	LDT&PPT BF	Hi	Lo	Hi
Orexin (OX)	LHA	Hi	Off	Off
gamma aminobutyric acid (GABA)	VLPO	Off	Hi	Hi
Adenosine	VLPO, Striatum	Not Relevant	Not Relevant	Not Relevant

TMN – tuberommillary nucleus; VTA/NC – ventral tegmental area-nucleus accubens: SNr – substantia nigra; LDT – lateral dorsal tegmentum; PPT – pedunculopontine tegmental nuclei; BF – basal forebrain; VLPO – ventral lateral preoptic nucleus