Crosstalk between Sleep Disturbance and Opioid Use Disorder: A Narrative Review

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Review Article

Abstract

Recent studies have revealed a growing number of patients affected by opioid use disorders (OUDs). Comorbid disorders are suspected to increase the risk of opioid-related adverse effects or treatment failure. The correlation of opioid use with sleep disturbances has been reported in many different studies and suggested to be linked to the brain regions involved in reward processing. This narrative review was intended to discuss the most recent developments in our understanding of the intricate interaction between sleep disturbance and OUD. In addition, in this study, the effects of sleep problems on the occurrence of unpleasant consequences in addiction management, such as craving and relapse in OCD patients, were highlighted. It has been shown that drug use may trigger the induction of sleep disturbances, and those suffering from difficulties in sleeping are prone to relapse to drug use, including opioids. Moreover, pharmaceutical sleep aids are likely to interfere with opiate use.

Keyword: Craving; Analgesics, Opioid; Sleep aids, Pharmaceutical; Recurrence; Sleep wake disorders

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Introduction

Substance use, irrespective of the type of drug, exclusively accounted for 42 million years of healthy life lost [Disability-Adjusted Life Years (DALYs)] across the globe in 2017.[1] Notably, 70% of the global burden of substance use disorder (SUD) arises from opioids.[2] Addiction to opioids and opiates has been considered as a major global health problem since the 2000s.[3] Australia and Canada have observed recent opioid epidemics,[4,5] and the use of opioid drugs has been on a sharp rise in the US with two primary health consequences, addiction and overdose-related deaths. The number of deaths due to drug overdose exceeded 65000 in 2016, with almost 50000 of those resulting from opioids.[6] The use of non-prescribed opioids is also on the rise in Asia.[7] Many countries in the Near East and Middle East/South-West Asia, including Iran, Qatar, and the United Arab Emirates have reported an escalation in opioid usage in recent years.[8]

The deleterious effects of opioids on vulnerable populations have raised serious concerns and placed pressure on healthcare systems. Opioids have been used commonly for pain relief, recreational purposes, coping with negative emotional states, and aiding sleep, especially by non-treatment-seeking individuals.[9,10] Moreover, diversion of opioid analgesics users from the prescription is common, and leads to nonmedical use of prescription drugs, SUDs, and overdose-related deaths.[11]

Sleep disorders among adolescents have become a significant health concern worldwide.[12] Long-term sleep problems can have extreme adverse outcomes in terms of the quality of life (QOL) and health that lead to death.[13,14] Indeed, sleep disturbances are anticipated to decrease QOL, regardless of comorbid medical conditions. Some studies have demonstrated the adverse effects of sleep disorders on QOL. A study on middle-aged and elderly adults, reported that the contribution of sleep problems to the QOL was considerable, and subjects reported lower QOL scores when the prevalence of sleep problems elevated.[15] Lee et al. reported that participants affected by both sleep problems and daytime impairment presented poorer QOL scores.[16]

Both sleep disturbances and poor QOL can lead to substance abuse.[17] In reference to normative samples, patients with clinical SUD gained considerably lower scores on physical and mental components than the general population.[18-20] In observational studies, it has been shown that SUD is correlated with significantly lower social and role functioning and that participants without a partner score lower on QOL.[19,21,22] The undesirable impact on the QOL increases with increased SUD severity.[21] Outpatients, in most cases, appear to have less severe SUD problems, whereas those under clinical detoxification therapies are likely to develop the most significant impairment in QOL.[18] In a study on a large sample of adult substance abusers in Massachusetts, USA, patients from detoxification centers had unexpectedly low scores in the physical health domain.[20] Indeed, they were comparable to patients with chronic somatic diseases (e.g., arthritis and lung diseases).[20] Moreover, their scores in the mental health domain were typically lower than those of patients with chronic somatic diseases and were similar to those of clinically depressed subjects.[20,23] Among patients with chronic obstructive pulmonary disease (COPD), alcohol abuse is one of the main factors strongly predicting poor QOL.[24]

In general, substance use is highly associated with disturbances in circadian rhythms and sleep.[17,25] The abuse of illicit and prescription drugs has acute harmful effects on sleep that probably persist or intensify as a result of long-term use, and worsen throughout withdrawal. Moreover, recent evidence has suggested that sleep problems and alertness are associated with the onset as well as the continuation of substance use, and are a risk factor for relapse.[26,27]

In addition to opioids' potential for addiction, respiratory depression and sleep disruption effects have been recognized as the adverse consequences of opioid use. Indeed, they intrude on sleep architecture and block access to rapid eye movement (REM) sleep and the deeper stages of non-REM (NREM) sleep.[28] On a molecular level, several types of opioid receptors have been reported in the same nuclei involved in sleep regulation,[29] and it has been proposed that opioid peptides are responsible for the induction and maintenance of sleep.[30]

The existing literature illustrates the association of sleep disturbance with analgesic opioid use,[31,32] opioid misuse,[33] and methadone maintenance treatment (MMT).[34-38] Despite this association, management of sleep disturbances in the treatment of substance abuse is often ignored. The interaction of sleep quality with treatment

outcome in the context of opioids is an emerging area of research with relatively few studies to date. In this narrative review, sleep problems and the contribution of pharmaceutical sleep aids to opioid use disorder (OUD) are discussed. Moreover, the associations of sleep disturbance with adverse event (craving) and treatment failure (relapse) were addressed along with sleep-related approaches to overcoming such issues. It is worthy of mention that the main topics described in the following sections chiefly deal with dependence on opioid and, if no pertinent or contradictory evidence exists, other substances.

Sleep problems

There is a conclusive reciprocal relationship between substance use and sleep disturbances.[39] For instance, Teplin et al. reported that patients with sleep complaints might suffer from issues related to drug and/or alcohol use.[40] Sleep disturbances, particularly insomnia, are ascribed to many comorbid situations, including SUDs.[41] This section deals with current sleep issues associated with substance use, including opioids.

Initiation and continuation of opioid use

Early childhood sleep problems positively contribute to substance use.[42] The acute influences of substance use on period and quality of sleep to a great extent rely on the type of substance used. The use of stimulants, namely cocaine and amphetamine, results in light, restless, and interrupted sleep.[43] Other drugs, including depressants (e.g., alcohol and benzodiazepines) and opiates (e.g., heroin) are primarily associated with hypnotic effects, elevating daytime sleepiness, and decreasing sleep latency, but inducing sleep disruptions afterward in the night (e.g., augmented night awakenings) because of acute withdrawal effects.[39,43,44]

Sedation and daytime drowsiness are the outcomes of short-term use of opioids.[45-48] Dizziness and sleepiness are also reported as common adverse effects of opioid pain medications.[27,49] At a constant concentration, tolerance to the subjective, sedative influences of opioids is achieved within 2-3 days.[50,51] However, some studies have found that undesirable sedative effects and reduced alertness persist among some patients on a constant concentration of narcotic medication.[52-55] Such disparity may arise from inconsistencies in the definition of sedative effects.[48]

Acute administration of opioids to healthy adults has been known to make a difference in sleep architecture.[45,56-59] Kay et al. found that acute intoxication with heroin, morphine, or methadone produced dose-dependent increases in arousal during sleep-wake periods.[58] Opioids like morphine can induce both sedation and wakefulness,[60] and therefore, have site-dependent, receptor-dependent, and dose-dependent effects on sleep.[28] These effects were stronger in heroin use, especially on the decline of theta waves and REM sleep.[37,58] Morphine and methadone diminish slow-wave sleep (SWS) and promote stage 2 sleep.[56] Some studies have shown that acute use of opioids increases REM latency,[46,61] decreases REM sleep time,[45,46,58,59,61-64] enhances stage 1[45,56,59] and stage 2 sleep,[56] and reduces SWS.[46,58,61-64] Acute effects of opioids can also include increased sleep latency,[45,58] increased wakefulness after sleep onset (WASO),[38,45,46,58,61-64] and concomitant reduction in the total sleep time (TST)[38,58] and sleep efficiency.[38,46,58]

Acute dosing of opioids can be associated with different effects on REM sleep.[45,56,59] Wang and Teichtahl indicated that the initiation and continuation of opioid use led to a reduction of REM sleep.[37] Shaw et al. found that the acute use of morphine in healthy, pain-free, young adults yielded a moderate reduction in the REM period and failed to enhance correlates of arousal, such as awakenings, electroencephalogram arousals, and WASO.[59] Furthermore, chronic pain patients who were subjected to opioids had more sleep impairment compared with patients with chronic pain who were not prescribed opioid medications and patients who had no chronic pain. Significant differences were reported among these 3 groups in terms of 4 subscales of the Pittsburgh Sleep Quality Index (PSQI) (subjective reports of sleep quality, sleep latency, sleep disturbance, and use of sleeping medications), and the global score. Following adjustment for demographic and clinical covariates, prescription opioid status was considerably correlated with impairment in sleep latency.[32] Moreover, patients with prescribed opioids presented more nocturnal awakenings and central sleep apnea awakenings than patients without opioids.[65] Morasco et al. also reported a significant relationship between prescribed opioid dose and self-reported impairment in sleep.[32] In addition, opioid dose was significantly linked to global PSQI score and sleep latency, even following

adjustment for demographic and clinical factors.[32]

Partial tolerance to the influence of opioids due to its acute use has been found to elevate REM sleep time,[45,62,63] but less pronounced alterations in SWS, wakefulness, and arousal are reported upon the chronic use of opioids. Vocalization during REM sleep, delta bursts, and augmented daytime sleepiness can be seen in REM phase.[37] In spite of the formation of tolerance, abnormal polysomnography (PSG) results are very often observed in chronic opioid users; for example, they experience greater sleep latency,[66,67] higher number of awakenings,[62,66-68] and reduced TST[66,67] and sleep efficiency.[66,68] SWS time[62,63,67,68] and REM sleep are on the rise as compared to baseline,[37,62,67,68] while the duration of stage 2 sleep is in decline in chronic opioid users similar to acute users.[37,68] Further investigations using actigraphy data obtained from patients with prescription OUDs demonstrated poor sleep in terms of TST, sleep efficiency, sleep latency, total time awake, and time spent moving.[66]

Long-term use of substances can impact the quantitative and qualitative aspects of sleep. While the effects of acute use on the mood are more likely to be defined based on the class of substances used, the effects of chronic substance use on the mood as well as other psychiatric symptoms are similar in various substances.[69] Sleep alterations caused by chronic substance use are also similar irrespective of substance types.[43,70] Additionally, substance abuse has been documented to have troublesome effects on sleep, particularly on sleep onset, maintaining sleep, and changing the cycle of sleep stages, these impacts will have negative outcomes in terms of functioning during the day, such as daytime sleepiness and decreased alertness. The interruption of sleep and daytime sleepiness is also reported during active use.[71,72] A common consequence of the initiation of opioid use is somnolence.[73] Turk and Cohen reported a greater improvement in diverse sleep outcomes in patients with chronic osteoarthritis who were prescribed opioid medications than those receiving placebo.[74] Nevertheless, the available intervention studies evaluating the relationship between opioid prescriptions and sleep have some limitations, including short duration (usually 4-12 weeks), fixed dosing pattern, and high attrition rates.[74]

Abstinence from opioid use disorder

Withdrawal condition is associated with its specific effect on sleep parameters, which may depend on the duration of discontinuation. Acute substance withdrawal is often accompanied by sleep disturbance in the form of prolonged sleep onset latency, decreased TST, and declined SWS.[43,44] Moreover, it has been shown that REM sleep frequently displays a rebound impact throughout alcohol abstinence.[44] As the duration of withdrawal increases, sleep patterns are likely to return to baseline. Some studies, however, have indicated that some sleep properties (e.g., REM sleep disturbances) continue well into abstinence.[43,44] Notably, persistent sleep problems during abstinence can act as a risk factor for substance use relapse.[27,44,75,76] Although a body of literature corroborates the presence of a connection between SUDs and sleep problems, few longitudinal or prospective studies have been conducted to elucidate the unique causal relationship(s) between them. Initial studies have proposed that there is bidirectional connection between the 2 variables; SUD can directly lead to sleep problems, and sleep disturbance appears to be a risk factor for disruption of abstinence from substance use.[39] There are many studies addressing alterations in the patterns of sleep with continuous abstinence from opiates. At around 5-7 days of acute withdrawal in chronic heroin users, Howe et al. observed reduced TST, SWS, REM, and stage 2 sleep, as well as elevated sleep latency, WASO, and REM latency compared to healthy sleepers.[77] In another study, within the first 21 days of withdrawal, extended sleep latency, reduced sleep efficiency, declined TST, augmented arousal index, elevated stages 1 and 2 sleep, and reduced SWS were notable in comparison to healthy sleepers.[33] Following 6 weeks and up to 6 months of abstinence from methadone, a rebound elevation is observed in SWS and REM time compared to baseline.[62,63,78] Predictive factors for abstinence of more than 4 weeks following detoxification with naltrexone may be sleeping issues upon discharge as well as any alterations in sleeping problems.[79] The very few studies on sleep problems during abstinence from opioids confirm the changes in sleep architecture. None of the available investigations have addressed the effects on sleep quality, which calls for further research in this regard.

Treatment of opioid use disorder

Elucidating sleep disturbance in MMT patients is of utmost importance since it has the potential of

damaging their health status and QOL, which can subsequently put them at risk of relapse.[80,81] According to the existing studies, subjective sleep disturbance can be found in 70-84% of MMT patients.[82-85] The results obtained concerning the impact of opioids on sleep has been inconsistent, with one study showing enhancement in sleep quality and efficiency and some others reporting prevention of REM and NREM phases of sleep.[59,86] The observed impacts of long-term use of opioids on sleep in a non-pain population are mainly obtained from patients in MMT programs among whom daytime sleepiness and sleep complaints are prevailing.[85,87] Long-term use of methadone has been associated with decreased TST;[88] however, the results have been contradictory.[89] Xiao et al. investigated the quality of sleep in individuals affected by heroin use disorder following a median of 5.4 days of MMT.[38] Patients without pre-existing long-term sleep disturbances had a lower rating of sleep (PSQI) and daytime sleepiness [Epworth Sleepiness Scale (ESS)] versus healthy sleepers.[38] Oyefeso et al. reported insufficient sleep time and quality, and somatic difficulty starting and retaining sleep in patients with OUDs in the early stages of methadone detoxification.[36] Similar evidence has exhibited elevated daytime drowsiness and below normal sleep measures in this group of patients.[37,62,63,78] Upon longer duration of MMT, however, some extent of tolerance to these effects has been found[87] and sleep difficulty has been observed to exist only within the first 6-12 months of MMT.[90,91] Tolerance to sleep issues is more considerable in MMT,[37,46,62,78] with evidence showing that patients in treatment for at least 1 year have better recovery sleep after sleep deprivation than those in treatment for a shorter duration.[91] Peles et al., employing a logistic regression model, reported that a greater methadone dose (i.e., higher than 120 mg/day) contributed to poor sleep quality, higher frequency of sleep disturbance, more prevailing use of sleeping medications, and greater rate of daytime dysfunction.[84] Nevertheless, in further studying the topic, they observed no direct relationship between methadone dose, and worse objective and perceived sleep parameter (such as REM indexes and deep stages of sleep period). They proposed that duration and intensity of opioid abuse before admission to MMT were directly associated with sleep abnormalities.[92]

Among MMT patients, psychiatric disorders,

higher use of nicotine and benzodiazepine, somatic pain, and loss of job correlate with poor sleep quality.[84,85] Applying PSG, Peles et al. examined patients with heroin use disorder who received treatment with a high and low concentration of methadone.[92] Among the objective sleep indices, the percentage of NREM deep sleep (that is, SWS) had an inverse association with the duration of opioid abuse in years. They also reported that a lower percentage of SWS and more years of opioid abuse were seen in the group of patients treated using a greater concentration of methadone during MMT. Moreover, sensible use of opioid medications can ameliorate pain-induced sleep disorders.[93,94] Subjective findings regarding enhanced sleep following pain control with extended-release morphine sulfate for the treatment of chronic hip or knee arthritis are supported by objective evidence based on PSG revealing improved sleep quality.[95] Additionally, opioids have been administered for the treatment of a sleep disorder known as periodic limb movement, which is commonly accompanied with restless legs syndrome.[96]

Despite the greater tolerance to the adverse effects on sleep quality due to the long-term use of methadone compared to other opioids,[37,46,62,78] more than 75% of MMT patients still have sleep complaints.[36,84,85] These sleep complaints eventually become complicated because around half of MMT patients use both illicit drugs and prescribed medications to overcome sleep-related problems.[84,85] Methadone, along with electrostimulation (ES), has been applied for the treatment of insomnia in the first 4 weeks of opioid abstinence.[97] During the first 2 weeks of withdrawal, patients receiving ES had shorter sleep time and more awakenings than those treated with methadone. Moreover, participants in the ES group still undergoing treatment reported more sleep problems than those who failed to continue the study. In general, methadone and ES are not efficient in treating insomnia induced by withdrawal.[97] Stein et al. utilized trazodone (50 mg/night), one of the most widely prescribed medications for the treatment of insomnia, for the amelioration of sleep in MMT individuals with a PSQI score of 6 or above.[98] They indicated that trazodone could not enhance subjective or objective sleep issues in these patients.[98]

Since 2002, buprenorphine has been approved for the treatment of OUDs. Maremmani et al. found that buprenorphine is similar to methadone in promoting sleep quality in patients undergoing

long-term treatment.[99] In another study by Pjrek et al., patients with opiate use disorder were subjected to either methadone or buprenorphine and slowly tapered down for 14-21 days.[100] Buprenorphine-treated patients showed 2.5% lower sleep efficiency and 9% shorter actual sleep time than those receiving methadone. Such marked differences between the groups became more evident at the lowest concentrations toward the late withdrawal phase.[100] It is noteworthy that the duration of buprenorphine tapering throughout detoxification also affected the quantity of sleep. A randomized controlled trial utilized buprenorphine for prescription opioid detoxification and assessed sleep time in patients selected to receive 7, 14, and 28-day buprenorphine tapers. The third group with a 4-week taper demonstrated remarkably lower loss of sleep as compared to the other 2 groups.[101]

In a prospective and longitudinal study by Nordmann et al., it was shown that despite the intra-individual variability of sleep disturbance severity over follow-up, MMT initiation had no effect on sleep disturbance, suggesting that sleep disturbance is not an obstacle to MMT initiation or continuation.[83] Furthermore, MMT patients with severe sleep disturbance were younger, had a high suicidal risk and bodily pain, and a significant level of nicotine dependence.[83] Other similar studies have explored factors ascribed to sleep disorders in MMT patients via a multivariate model;[84,85] however, no study has been performed based on a longitudinal design. Stein et al. reported that depressive symptoms, anxiety symptoms, higher nicotine dependence, somatic pain, and unemployment were considered as a correlate of poor sleep quality.[85] Peles et al. demonstrated that the presence of a sleeping disorder significantly contributed to the development of a psychiatric comorbidity and benzodiazepine abuse, daily methadone prescriptions, and duration of opioid abuse prior to MMT initiation.[84]

Effective pain management in this group is multifactorial, affected by greater pain sensitivity, high opioid tolerance, illicit substance use, and varying cross-tolerance to opioid pain medications.[102] It has been suggested that cognitive-behavioral therapies for pain or insomnia hold promise for the mitigation of pain severity and amelioration of sleep quality.[102,103] Indeed, the relation between sleep problems and pain is most likely to be circular and reciprocal, disturbed sleep leading to increased pain sensitivity and intense pain causing sleep disturbance.[103,104] Pain seems to be correlated with an elevated likelihood of persistent drug abuse during and following opioid addiction treatment,[105] as well as reduced treatment retention.[106] As for nicotine dependence, it is well-accepted that opioid abusers tend to smoke during MMT programs.[107-109] Smoking at least 1 cigarette within an hour of bedtime probably causes a delay in the onset of sleep.[58] Later in the night, nicotine withdrawal exerts mixed effects, through generating cortical arousal, it causes smokers to undergo withdrawal, awaken during the night, and get up to satisfy their craving.[83] Furthermore, smoking can enhance snoring, obstructive sleep apnoeic episodes, and coughing that disrupts sleep.[110-112]

Effect of sleep-related treatments on opioid use

Several lines of animal studies have revealed the probable consequences of sleep aid medications on some characteristics of SUDs. In an in vivo study, Gentile et al. showed that suvorexant, dual orexin antagonist, decreased cocaine-evoked premature responses to the 5-choice serial reaction time task (5CSRTT) when the ventral tegmental area (VTA) of rats was treated directly or systemically.[113] Hypothalamic hypocretin (orexin) peptides serve to intervene in arousal and reward mechanisms. Neither suvorexant nor SB334867, an orexin-1 receptor antagonist, or TCS-OX2-29, an orexin-2 receptor antagonist changed delay discounting. Though it does not impact Fos-immunoreactivity within the tyrosine hydroxylase-immunolabeled neurons of VTA, suvorexant mitigates cocaine-associated and orexin-associated elevation of calcium transient amplitude within VTA neurons. All these imply the potential therapeutic application of orexin antagonists in declining psychostimulant-induced motor impulsivity in SUDs.[113] More to the point, Shahzadi et al. found that propofol, a short-acting intravenous anesthetic drug, carried conditioned place preference effects in male Wistar albino rats through nitric oxide-based mechanisms, so propofol has rewarding effects.[114]

Moreover, this drug can interact with the brain's dopaminergic system, known to be responsible for the rewarding effects of drugs of addictive potential. Pain et al. reported that propofol produced an increase in dopamine levels in the nucleus accumbens (NAc).[115] Further studies by Lian et al.

highlighted that its self-administration enhanced reinforcement through dopamine D1 receptors.[116] Therefore, propofol is more likely to alter the activity of dopamine neurons in the mesolimbic system. An in vivo study on adult male Sprague Dawley rats has provided some conflicting evidence that initial treatment with chloral hydrate, a sedative-hypnotic drug that can induce sleep quickly, could interrupt the conditioned place preference effects of morphine from the opiate family possibly via interactions with the endogenous opioid system.[117] The midbrain dopamine neurons are modulated by chloral hydrate and opiates in opposite ways in the NAc. Indeed, the former prevented the firing of dopamine neurons projecting to the NAc in a dose-dependent manner;[118] by contrast, the latter led to the elevation of extracellular dopamine concentrations.[119]

Given the complex relationship between sleep and substance use, it is expected that sleep interventions also affect the use of drugs and its clinical outcome. To the best of our knowledge, there has been no published clinical study on the risk of SUDs across all stages of a complicated drug habit caused by sleep-aid medication in patients with sleep disorders. However, more recently, some clinical evaluations of suvorexant in the treatment of patients with SUD and insomnia have been undertaken.[120] Table 1 summarizes some studies on the effects of sleep-related medicines on substance abuse. More details are provided in the following sections.

Initiation and continuation of opioid use

Tricyclic antidepressants improve sleep through the antagonism of histamine, acetylcholine, and norepinephrine, all of which are responsible for the maintenance of arousal and wakefulness. It has been reported that the abuse potential of tricyclic antidepressants is insignificant. Thus, this class of drugs is effective in treating insomnia among patients with substance abuse.[130] Mirtazapine has been shown to possess sleep-promoting benefits resulted from its antagonism of serotoninergic (5HT2 and 5HT3), adrenergic (α1), and histaminergic (H1) receptors.[131] Akin to other antidepressants, mirtazapine has been reported to be beneficial for patients prone to SUD because of its low potential for inducing abuse.[130] Anticonvulsants, namely pregabalin, tiagabine, and gabapentin, may be applied in insomnia treatment. Gabapentin as well as

pregabalin bind to the alpha-2-delta subunit of N-type voltage-gated calcium channels to reduce the function of wake-promoting glutamate and norepinephrine systems. Tiagabine can enhance sleep via suppressing the reuptake of gamma-Aminobutyric acid (GABA).[132,133] Of these drugs, only pregabalin has been observed to have abuse potential, which should be considered in subjects prone to substance abuse.[122]

Many different pharmacological treatments are the cause of sleep problems.[134] The most commonly prescribed medications are benzodiazepines and other GABA$_A$ receptor agonists, namely zolpidem and clomethiazole.[135-137] However, those with SUD are liable to the misuse of benzodiazepines, that is, using higher or more frequent doses than prescribed, or even using them without the doctor's permission.[138-141] It has been exhibited that benzodiazepine overdose occurs in patients with alcohol use disorder (AUD), and such cases are prone to benzodiazepine withdrawal symptoms. Accordingly, these types of sleep medications should be prescribed with caution in such cases, and some reports call for complete avoidance.[138,142]

Rush et al. assessed the potential of abuse in 3 sleep aids, triazolam, zolpidem, and trazodone, among male drug and alcohol addicts.[143] Trazodone acts as a triazolopyridine antidepressant generally prescribed for sleep disorders; however, its exact behavioral, pharmacologic profile is unknown in comparison with benzodiazepine hypnotics. Zolpidem is an imidazopyridine hypnotic, often used due to its specific benzodiazepine-receptor binding profile. Triazolam, known as a triazolobenzodiazepine hypnotic, was the standard component in Rush et al. study, since its abuse potential had been partly identified in previous reports. The influences of trazodone on subject-rated items for the evaluation of abuse potential (e.g., subject ratings of Willingness to Take Again) were less than those of triazolam. Zolpidem and triazolam similarly affected these measures. Therefore, trazodone appears to have less abuse potential than triazolam and might be an appropriate alternative to hypnotics in people with a history of SUD.[143] Almost no study was found to deal with the effects of pharmaceutical sleep aids on the initiation or continuation of OUDs. Almost no study was found to deal with the effects of pharmaceutical sleep aids on the patterns of use among patients with an initial diagnosis of OUD.

Table 1. Summary of studies on the interaction between sleep-related medicines and substance use

Drug	Authors	Study	Effect on sleep	Effect on substance use
Mirtazapine	Afshar et al.[121]	The efficacy of mirtazapine in the treatment of cocaine dependence with comorbid depression	Improved sleep, Lower sleep latency	no more effective than placebo in reducing cocaine use
Pregabalin	Guay[122]	Pregabalin in neuropathic pain: a more "pharmaceutically elegant" gabapentin?	Treatment of insomnia	Abuse potential
	Feltner et al.[123]	Long-term efficacy of pregabalin in generalized anxiety disorder	Treatment of insomnia	Abuse potential
	Montgomery and Kasper[124]	Pharmacotherapy update: pregabalin in the treatment of generalized anxiety disorder	Treatment of insomnia	Abuse potential
Carbamazepine + Tiapride	Gartenmaier et al.[125]	Treatment of alcohol withdrawal syndrome with combined carbamazepine and tiapride in a patient with probable sleep apnoe syndrome	Ameliorated severe disturbances in sleep with awakening during the night	No alcohol withdrawal complications occurred
Lorazepam	Morgan and Malison[126]	Pilot study of lorazepam and tiagabine effects on sleep, motor learning, and impulsivity in cocaine abstinence	Increased total sleep time, Significantly enhanced light sleep	Worsened withdrawal symptoms, including next-day impulsivity and overnight, sleep-dependent motor learning
Quetiapine	Litten et al.[127]	A double-blind, placebo-controlled trial to assess the efficacy of quetiapine fumarate xr in very heavy-drinking alcohol-dependent patients	Improvement of poor sleep	No efficacy in reducing alcohol consumption
Trazodone	Friedmann et al.[128]	Trazodone for sleep disturbance after alcohol detoxification: A double-blind, placebo-controlled trial	Short-term benefit on sleep quality	No improvements in alcohol consumption in the post detoxification period, Increased drinking when stopped
Zolpidem	Bottlender et al.[129]	Zolpidem dependence in a patient with former polysubstance abuse	Treatment of persistent insomnia, Developed tolerance with an increasing dose and frequency of zolpidem intake	Led to dependence with withdrawal symptoms upon dose reduction

Abstinence from opioid use

Currently, some double-blind, placebo-controlled, and other trials have used gabapentin and found that this medicine may improve sleep outcomes as well as abstinence in those affected by AUDs during abstinence.[144-147] Indeed, gabapentin, especially a dosage of 1800 mg, could improve successful abstinence along with no heavy drinking,[147] and delay the onset of heavy drinking.[144] Moreover, it was found to significantly lower many measures of subjective craving for alcohol and affectively-evoked craving.[146] The prescription of trazodone as a sleep aid is on the rise among persons with addictions due to its lack of addictive potential. Friedmann et al. performed a randomized, double-blind, placebo-controlled trial of low dose

trazodone (50-150 mg) on alcohol detoxification patients.[128] They reported that the administration of trazodone after quitting alcohol, frustratingly way after the good effects on the first few days, would not only reduce the effective anstinence period but also could result in increase alcohol.consumption after discunuation.[128]

However, evidence on the influence of sleep medications in opioid users is rare. Srisurapanont and Jarusuraisin investigated the contribution of amitriptyline (57.7 ± 12.0/night) in comparison with lorazepam (2.1 ± 0.5/night) to insomnia treatment in 27 patients with opioid withdrawal in a randomized, double-blind trial.[148] The Sleep Evaluation Questionnaire and the 3 insomnia items of the Hamilton Rating Scale for Depression (HRSD) were employed as instruments in their study. All dimensions of sleep were comparable between the 2 groups. This finding implied that, in addition to the hangover effect, amitriptyline was as effective as lorazepam in treating opioid-withdrawal insomnia.[148]

Treatment of opioid use disorder

Various studies have dealt with the contribution of sleep-promoting medications to the treatment of people with AUD.[149] Stein et al. investigated if trazodone (50 mg/night), a common prescription for the treatment of insomnia, can enhance sleep in MMT patients who had a PSQI score of 6 or more. They reported that trazodone failed not only to ameliorate subjective or objective sleep problems, but also to notably increase or decrease illicit drug use, as compared with placebo.[98] There is only one study directly evaluating the effect of sleep aids on use patterns among MMT patients; thus, the lack of sufficient evidence and complexity of the subject suggests that the findings require confirmation.

Sleep-related changes in craving or relapse of opioid use disorder

The quality of sleep among substance users, who are attempting to quit, constitutes an indispensable element of the treatment process that predicts its outcome, with poor sleep quality resulting in increased risk of relapse.[27,37] Insomnia is recognized as a psychopathological indicator of psychiatric relapse.[150,151] Additionally, it has been shown to increase the risk of relapse among patients with SUD.[27,152]

Most of the studies on sleep problems as a predictor of relapse have been carried out on alcoholism.[27] Sleep disturbance may continue for up to 3 years in alcoholism. Sleep remains reduced and REM sleep pressure augmented as seen in increased REM percentages, decreased REM latencies, and greater REM densities.[153] Subjective and objective measures of sleep following acute abstinence are predictive of the likelihood of relapse during chronic abstinence. Early evidence by Allen et al. exhibited that low levels of SWS could explain alcohol drinking relapse.[154] Gillin et al. proposed REM problems, either increased REM sleep percentage or decreased REM sleep latency, as predictors of relapse.[57] Intriguingly, sleep-associated relapse risk to drug use was higher than those correlated with other factors, namely employment, marital status, age, depression ratings, period and severity of alcoholism, and hepatic enzymes.[26] In the study by Brower and Perron, it was hypothesized that in the light of common neurobiological and psychosocial processes between sleep and addictive behaviors, the connection between sleep disturbance and relapse risk reported in alcohol addiction could be generalized to psychoactive substances.[27] Angarita et al. conducted a study on cocaine-dependent individuals receiving 12 days of residential treatment and 42 days of out-patient behavioral treatment and gathered PSGs on 1, 3, and 6 weeks of cocaine abstinence.[155] They observed that TST was positively correlated with days of cocaine discontinuation over the 6-week study, suggesting that it would be more likely to improve TST via extended abstinence.[155]

Recently, there have been some studies on patients with OUD. For instance, Dijkstra et al. performed a study on opioid-dependent patients who were followed for up to 30 days after detoxification.[79] They indicated that the general quality of health (SF-36) and sleeping problems Symptom Checklist-90 (SCL-90) could predict discharge;[79] in addition, change in sleeping problems (SCL-90) during detoxification acted as a predictor. Poor sleep during opioid detoxification was linked to abstinence. This study concluded that care providers seemed to have given additional attention to poor sleepers to accomplish better outcomes; however, the authors failed to support this with enough data.

Furthermore, PSG was not carried out.[79] More recently, 68 detoxified patients were assessed for the within-person association between craving and sleep quality.[156] The patients had prescription opioid dependence and were selected from a residential drug and alcohol treatment facility. Applying momentary ecological assessment, cravings were significantly higher on days of lower than usual sleep quality. As much as 31% of the overall association between craving and sleep quality was justified by positive affect so that lower sleep quality was correlated with lower positive affect, which, in turn, resulted in higher craving. There was no evidence supporting an indirect association between sleep quality and craving using negative affect.[156] Accordingly, clinicians should take into account a combination of symptoms, including low positive affect and sleep disturbance as risk factors for high levels of drug craving, and therefore, relapse. Opioid-dependent patients appear to be at higher risk of craving in the early stages of recovery, especially on days when there is sleep disturbance partly because of accompanied decreases in positive affect. From a clinical perspective, this necessitates a more personalized approach to treating patients, and therefore, attenuating the risk of relapse, in particular, if medical care is intended to target sleep disturbance.[156]

The correlation of sociodemographic and relapse factors in alcohol dependence and opioid dependence has been reviewed by Kadam et al.[157] They found a significant difference in the sociodemographic properties of the groups. An opioid addict generally was single and unemployed, belonged to a lower socioeconomic level, and had a criminal record. Sleep difficulties were experienced by 30.00% and 23.33% of alcohol and opioid groups, respectively. Among the parameters related to relapse, the opioid group rated considerably lower on self-efficacy and perceived criticism, and higher on craving. The most reported reasons for relapse in both groups included the desire for positive mood, followed by sleep difficulties and negative affect in alcoholics, and craving and sleep difficulties in opioid users.[157] Using 122 participants as poly-drug users (52.46% alcohol, 41.80% cocaine, 30.33% heroin, 28.69% prescription opiates, 7.38% methamphetamine, 22.95% cannabis, and 1.64% benzodiazepines and dextromethorphan), Freeman and Gottfredson

showed that the within- and between-person effects of maximum craving on quality of sleep were statistically significant, as were the between- and within-person effects of daily sleep quality on maximum cravings.[158] Employing the mediation analysis of the indirect effect of sleep quality on cravings through willpower, both the indirect effect for the between-person pathway and the indirect within-person pathway were statistically significant. These findings highlight a potentially cumulative effect of poor sleep on cravings.[158] Given the association of sleep quality with abstinence, craving, and relapse, the question is raised whether disturbed sleep architecture can affect these 3 factors in opioid users.

Sleep-related therapeutic approaches to reduce craving and relapse

From a clinical standpoint, both the pharmacological influences of drugs and the psychosocial stressors linked to addiction can lead to disrupted sleep. However, patients have reported that their natural sleep rhythms return to normal as a result of abstinence from substances and recovery from addiction. While this appears to truly happen for some patients, it is not the case for every individual. In fact, sleep disturbances can continue for months to even years after starting abstinence,[44] if they do not produce relapse before then. Previously, some studies have suggested different strategies for the management of sleep problems after avoiding drugs.[159,160] More importantly, however, that although insomnia can explain relapse or craving, it has not been proven that treatment of insomnia impedes relapse.

In a randomized controlled trial of trazodone (a sedating antidepressant) versus placebo, alcohol-dependent subjects treated with active medication demonstrated sleep amelioration but drank more often and in larger amounts during the study.[128] Kolla et al. used trazodone (50-300 mg) to treat sleep problems in patients with AUD in an open-label, non-controlled study.[149] The results of this study indicate that the use of Trazodone has positive effects on management of insomnia at this point in the study.[149] Drinking outcomes in trials using sleep-promoting drugs are mixed. Currently, a large placebo-controlled trial of gabapentin reported improved drinking outcomes and sleep measurements.[147]

A placebo-controlled trial of acamprosate [Food

and Drug Administration (FDA) approved treatment for AUD] over 15 days revealed that the treatment used could successfully enhance WASO and stage 3 sleep on the PSGs. Nevertheless, drinking outcomes and their association with sleep were not examined in this study.[149] The BzRAs are a class of drugs prescribed for the management of insomnia in patients without co-morbid alcoholism. They are influential on the immediate in-patient withdrawal syndrome since it has a common mechanism of action similar to alcohol itself, i.e., enhancement of GABA suppression.[149] A further word of caution concerning their out-patient use is that these drugs put the patients at high risk of toxicity and overdose if combined with alcohol,[150] and thus, are harmful to those with the potential for AUD relapse.

Cognitive-behavioral treatment for insomnia is another approach successfully fulfilled as an alternative to the current medications. In this regard, many trials have been conducted in patients with AUD and sleep disturbance. A randomized controlled trial applied a brief cognitive-behavioral treatment among 60 insomnia patients with AUD and no comorbid depression diagnosis.[161] This treatment compared to wait-list controls effectively enhanced sleep diary measures of sleep quality, awakenings, sleep efficiency, and time to fall asleep; no effect on drinking relapse rates was observed during the 6-month follow-up, however. Likewise, an open trial among patients with alcoholism indicated that sleep was improved; however, drinking outcomes remained without improvement.[162] Nevertheless, the justification of these findings is debatable at this time, and more research studies are required on this subject, notably OUD. Care providers should prescribe medication rationally, apply behavioral strategies whenever possible, and observe those patients with sleep disturbances closely.

A new emerging strategy for the treatment of sleep disturbances and addictive disorders can be neuromodulation interventions, ranging from invasive techniques such as deep brain stimulation to non-invasive techniques such as repetitive transcranial magnetic stimulation and transcranial direct current stimulation.[163-165] More

precisely, previous studies have shown the beneficial contribution of these techniques to the decline in craving.[166-168] However, some investigations have reported that such interventions cause sleepiness[169,170] or insomnia[171] in patients with addictive disorders. To our knowledge, there was no study in the literature of sleep disturbances that showed the effectiveness of brain stimulation techniques in controlling craving and relapse in SUD patients.

Conclusion

It is often the case that sleep and substance use seem to interrelate; in other words, substance use is capable of inducing sleep disturbances, and difficulty sleeping can act as a risk factor for substance use relapse. Patients with OUD are found to suffer from sleep disturbances evident from their sleep structure or quality before and after treatment. The existing experimental studies have emphasized that sleep medications, hypnotics, or sedatives might have interference with opiate use, with one evidence showing that chloral hydrate may reduce the rewarding effects of morphine. This may warrant further investigation in rigorous animal and human trials concerning the risk of OUD as a result of drugs prescribed in sleep problems. Almost no study addressed the risk of relapse and craving behaviors under the combined effect of sleep problems and OUD, which calls for future research.

Conflict of Interests

The authors have no conflict of interest.

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Authors' Contribution

HRF, AY, and ARA had designed the review structure. A literature search was performed by HRF, and the whole group had cooperated in manuscript writing by the supervision of AY.

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مروری بر ارتباط دوسویه اختلالات خواب و اختلال مصرف مواد شبه افیونی: مطالعه مروری نقلی

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مقاله مروری

چکیده

نتایج مطالعات اخیر، افزایش تعداد بیماران متأثر از مصرف مواد شبه افیونی را نشان می‌دهد. اختلالات همبود، احتمال خطر بروز عوارض ناشی از مصرف مواد افیونی و شکست درمان و عود اختلال را افزایش می‌دهد. همبستگی مصرف مواد افیونی و اختلالات خواب در تحقیقات متعددی گزارش شده است و آن را احتمالاً ناشی از نواحی مشترک با فرایندهای پاداش دانسته‌اند. در پژوهش مروری حاضر، سعی شد بر اساس یافته‌های جدید، ارتباط این دو به بحث گذاشته شود. همچنین، در یافته‌های جدید در تأثیر اختلالات خواب بر عوارض نامطلوبی مانند ولع مصرف، لغزش و شکست درمان در بیماران اختلال مصرف مواد مخدر، تمرکز بیشتری گردید. بر این اساس، مصرف مواد می‌تواند منجر به اختلال خواب شود و کسانی که اختلال خواب دارند، بیشتر در معرض بروز عود مصرف مواد از جمله مواد شبه افیونی قرار دارند. علاوه بر این، داروهای خواب‌آور ممکن است در مصرف مواد مخدر تداخل ایجاد کنند.

واژگان کلیدی: ولع مصرف؛ داروهای ضد درد، مواد افیونی؛ خواب‌آورها، دارویی؛ عود؛ اختلالات خواب و بیداری

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