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At the intersection of sleep deficiency and opioid use: mechanisms and therapeutic opportunities

Mark K. Greenwald

Tabitha E.H. Moses

Timothy A. Roehrs
Henry Ford Health, troehrs1@hfhs.org

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MARK K. GREENWALD, TABITHA E.H. MOSES, and TIMOTHY A. ROEHRS

DETROIT, MICHIGAN

Due to the ongoing opioid epidemic, innovative scientific perspectives and approaches are urgently needed to reduce the unprecedented personal and societal burdens of nonmedical and recreational opioid use. One promising opportunity is to focus on the relationship between sleep deficiency and opioid use. In this review, we examine empirical evidence: (1) at the interface of sleep deficiency and opioid use, including hypothesized bidirectional associations between sleep efficiency and opioid abstinence; (2) as to whether normalization of sleep deficiency might directly or indirectly improve opioid abstinence (and vice versa); and (3) regarding mechanisms that could link improvements in sleep to opioid abstinence. Based on available data, we identify candidate sleep-restorative therapeutic approaches that should be examined in rigorous clinical trials. (Translational Research 2021; 000:1–16)

Abbreviations: 5HT = serotonin; CB = cannabinoid; CBD = cannabidiol; CBTi = cognitive behavioral treatment for insomnia; D_2 = dopamine receptor 2 subtype; DSM-IV = Diagnostic and Statistical Manual version 4; eCB = endocannabinoid; EEG = electroencephalogram; FDA = Food and Drug Administration; GABA = gamma-amino-butyric acid; HEAL = Helping to End Addiction Long Term; IR = immediate release; HPA = hypothalamic-pituitary-adrenal; MBTi = mindfulness based treatment for insomnia; MOUD = medications for treating opioid use disorder; NIH = National Institutes of Health; NMDA = N-methyl-D-aspartate; NREM = non-rapid eye movement; OUD = opioid use disorder; OX = orexin; PSQI = Pittsburgh Sleep Quality Index; REM = rapid eye movement; rTMS = repetitive transcranial magnetic stimulation; SNS = sympathetic nervous system; SR = sustained release; SUDs = substance use disorders; tACS = transcranial alternating current stimulation; tDCS = transcranial direct current stimulation; THC = delta-9-tetrahydrocannabinol

RESPONDING TO THE OPIOID EPIDEMIC

Opioid overdoses, emergency department visits, and deaths related to opioid use have risen precipitously over the past 2 decades. These and other adverse consequences of opioid use (eg, unemployment, social and legal problems) are a major ongoing burden for individuals, families and society,[1,2] leading to aggressive federal, state and local policies and funding to combat this crisis including the NIH Helping to End Addiction Long-term (HEAL) Initiative (https://heal.nih.gov). It has been estimated that opioid misuse cost the US more than $2.5 trillion from 2015 through 2018.[3]

Substantial scientific evidence supports the effectiveness of medications for treating opioid use disorder (MOUD): methadone or buprenorphine are gold-

From the Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Detroit, Michigan; Sleep Disorders Center, Henry Ford Health System, Detroit, Michigan.

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Reprint requests: Mark K. Greenwald, Department of Psychiatry and Behavioral Neurosciences, School of Medicine, Wayne State University, Tolan Park Medical Building, 3901 Chrysler Service Drive Suite 2A, Detroit, MI 48201 e-mail: mgreen@med.wayne.edu.

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standard agonist options for maintenance treatment and naltrexone is an antagonist option for relapse prevention. Despite the availability of these MOUD alternatives, the rate of treatment engagement for OUD in the US remains unacceptably low: only about 20% of patients with OUD are receiving any form of treatment,[4-6] and few in the US receive MOUD.[7-9] It is also well established that longer retention in OUD treatment is associated with improved outcomes including higher rates of opioid abstinence, less mortality risk, and lower healthcare utilization/costs.[10-13] Nonetheless, an unacceptably high proportion of patients with OUD in treatment drop out; this can be driven by several factors including patient's non-preference for existing treatments, side effects, or lack of efficacy.[14] Patients who receive prompt follow-up care after opioid detoxification are at lower risk of subsequent mortality.[15] Long-acting naltrexone is effective for preventing relapse after detoxification, but is presently used less often than opioid agonist therapies.[16]

The US Food and Drug Administration (FDA) recently emphasized the importance of expanding OUD treatment alternatives, especially non-opioid options that may have less misuse potential.[17] Furthermore, the FDA has advocated for a holistic scientific approach to OUD, encouraging researchers to study and validate alternative, clinically meaningful endpoints besides drug abstinence. Among these phenotypes, remediation of sleep deficiency has tremendous potential to improve overall behavioral health and could partly mediate the successful outcome of drug abstinence.

SLEEP DEFICIENCY AND OPIOID USE

Nomenclature. Throughout this review, we will use the broad term "sleep deficiency" to encompass non-restorative patterns of sleep including delayed sleep-onset, sleep-maintenance problems (eg, difficulty returning to sleep after awakening and/or early awakenings), disruption of regular cycling between non-rapid eye movement (NREM) and rapid eye movement (REM) phases, and diagnoses of insomnia and other sleep disorders (eg, apnea, periodic leg movements). Adopting this broader terminology can help to account for large differences in methodology across studies. However, when describing individual studies, we will refer to the specific characteristics of the sleep deficiency. Also, consistent with the literature and clinical practice, we define the metric "sleep efficiency" as (total sleep time ÷ time in bed); we will refer to improvements in sleep efficiency using this metric, and normalization as reaching 85% or higher during an 8-hr sleep opportunity.[18,19]

Likewise, we will broadly refer to "opioid use" to encompass the non-medical and recreational use of opioids (ie, this review will generally not refer to appropriate FDA-indicated use of prescription opioid analgesics, because such behavior would not meet diagnostic criteria for OUD[19]). Again, when describing individual studies, we will use study-specific language.

Sleep deficiency and substance use disorders. Across studies of individuals with varying substance use disorders (SUDs), it has been reported or experimentally demonstrated that sleep deficiency is related to increased pain sensitivity,[20-24] emotion dysregulation,[25-27] and impaired frontal-executive control and decision making.[28-33] Furthermore, sleep deficiency is associated with increased propensity for lapse/relapse to substances[34] including alcohol,[35-38] tobacco/nicotine,[26,39-41] cannabis,[42-44] and methamphetamine,[45] and has been hypothesized to impair extinction of drug-environment conditioning.[46] However (as will be discussed in ''Alleviating sleep deficiency as a pathway to improving opioid abstinence''), few clinical studies have explicitly addressed the role of sleep deficiency in opioid craving and relapse risk.

Fig 1 presents an overarching conceptual framework, which is intentionally broader in scope than this focused review, to situate our discussion in a more comprehensive context. There are hypothesized bidirectional relationships between sleep deficiency and opioid craving, opioid use, and severity of OUD,[47-51] and between sleep deficiency and nociceptive behaviors[52-56]; although there are obvious relationships between pain and opioid use, this is not our emphasis here. These clinical problem areas — sleep deficiency, pain, and opioid use — are closely linked via activation of stress-regulatory systems: sympathetic nervous system (SNS), hypothalamic-pituitary-adrenal (HPA) axis, and inflammatory processes.[57] We also represent negative mood states in this model, which are associated with these problem areas, but we touch only briefly on these issues.

Sleep-related effects of opioid use and discontinuation. Starting about 50 years ago, rodent studies of opioid physical dependence and discontinuation were conducted, in which morphine, methadone, or l-alpha-acetyl-methadol were self-administered intravenously while EEG sleep and wake periods were continuously recorded across the 24-hr day; all 3 opioids disrupted the timing and normal staging of sleep.[58] Specifically, sleep and wake episodes 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, the initial wake period was followed by solely NREM sleep, and then REM sleep intermixed with NREM and wake, and the next injection followed after a brief awakening.

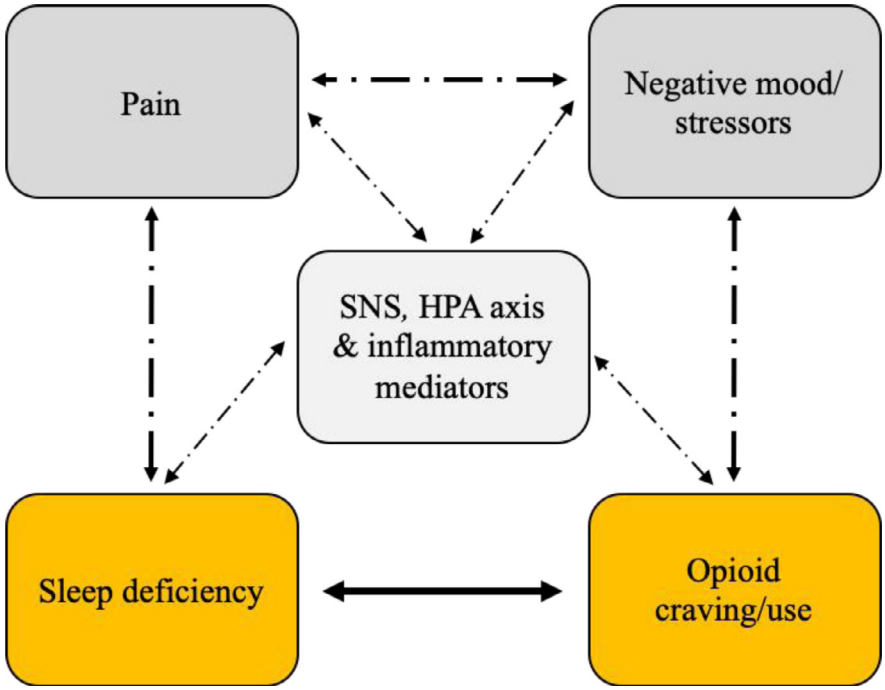

Fig 1. Conceptual model, illustrating hypothesized bidirectional relationships of sleep deficiency (focus of this review), and other salient factors (pain states, negative mood/stressors, physiological mediators), with opioid craving and/or use.

Early clinical studies produced results that paralleled the animal studies above. In 3 separate double-blind placebo-controlled studies, morphine,[59] heroin,[60] or methadone[61] were administered acutely to recently-abstinent opioid-dependent research participants, who would have otherwise entered a period of opioid withdrawal. These opioid agonists dose-dependently decreased total sleep time, stage 3-4 sleep time, and REM sleep time. All 3 opioids also increased brief arousals and frequency of sleep-stage changes (ie, sleep fragmentation).

It is important to recognize that several factors may affect the generalizability of these conclusions. First, morphine, heroin and methadone are full *mu*-opioid agonists, but they differ in their duration of action and tendencies to produce receptor internalization; it is unknown whether pharmacokinetics or receptor signaling properties of different opioids may influence the degree of tolerance to opioid-related sleep outcomes. Second, we lack systematic data that would enable us to conclude whether misuse of other common opioids (eg, oxycodone, hydrocodone, tramadol, fentanyl) produce the same effects on objectively-measured sleep efficiency or subjective sleep quality. Third, population differences (eg, OUD, low back pain, cancer) complicate the interpretation of opioid agonist effects on sleep.

Opioid agonist-related sleep disruptions may also occur by disturbing respiratory mechanisms. Opioids cause hypoventilation, even controlling for cigarette use that is highly prevalent among those with OUD.[62] It should also be recognized that other drugs used via smoking/inhalation routes (eg, marijuana, cocaine) and through delivery vehicles (eg, vaping devices) that contain respiratory-tract irritants could cause pulmonary inflammation (with possible airway stenosis or coughing) leading to sleep deficiency. Sleep itself normally reduces respiratory drive and, combined with opioids, the risk of sleep-disordered breathing (ie, central sleep apnea) and the consequent disruption and fragmentation of sleep is heightened.[63] In contrast to obstructive sleep apnea, which predominates in obese men and is related to excessive daytime sleepiness, central apnea as a general rule (independent of opioid use) is most typically is associated with insomnia.[64] Central apnea is characterized by cessation of both respiratory effort and airflow and is related to awakening and not the brief EEG arousal of obstructed breathing.

Discontinuation of chronic opioid use is associated with protracted rebound of REM sleep, lasting 12 days in rodents[65] and with sleep deficiency and disturbed sleep staging that can last many weeks in humans.[66-68] Specifically, early-stage and protracted opioid withdrawal are associated with increased sleep latency, decreased total sleep time, decreased slow-wave sleep, and early-phase opioid withdrawal is associated with decreased REM sleep and increased REM latency.[69]

Notably, these outcomes are qualitatively similar to those produced by acutely administering *mu*-opioid agonists to recently-abstinent, opioid-dependent individuals (see above). In other words, objective sleep outcomes in states of opioid withdrawal and acute opioid administration (to physically-dependent individuals) are comparable and one pharmacological state is not inherently more deleterious than the other. As discussed in ''Does treatment of opioid use disorder improve sleep outcomes?'', evidence is mixed as to whether longer-term opioid agonist maintenance is associated with the development of tolerance to these objective measures of opioid-related sleep deficiency.

When people who were heroin-dependent and maintained on buprenorphine in an outpatient program were discontinued from their treatment both sleep latency and latency to REM sleep were prolonged and percent stage 3-4 sleep was reduced, compared to healthy controls.[70] In that study, after a week of buprenorphine 4 mg/day, sleep patterns normalized. The improvement in sleep may be dose-related as 4 mg improved sleep, but 8 mg/day did not.[71] In another study, methadone or buprenorphine dose-tapering led to changes in actigraphic recordings (a validated method of monitoring sleep and wake) indicative of disrupted sleep and circadian rhythm.[72] Finally, 2 case reports of patients with chronic pain using opioids and with sleep-related disordered breathing suggest that discontinuation of chronic opioid use may resolve the breathing disturbance.[73,74]

Notably, the opioid antagonist naltrexone is not expected to resolve opioid detoxification-associated sleep disturbance. Naltrexone treatment has been associated with sleep deficiency (all based on self-reported symptoms) in newly-abstinent patients with opioid dependence.[75-78] Therefore, use of naltrexone following opioid detoxification may not be addressing one hypothesized cause of relapse (ie, continued sleep deficiency). However, some comparative data suggest that individuals maintained on naltrexone may experience less insomnia than individuals maintained on methadone[79] or buprenorphine/naloxone.[80] The latter 2 studies used different sleep metrics, ie, polysomnogram[79] vs. symptom reporting,[80] which highlights the importance of using common objective sleep metrics in comparing OUD treatment effects on sleep.

Sleep deficiency and stress. Insomnia disorder, and probably also comorbid insomnia that occurs in SUDs, is hypothesized to reflect a 24-hr state of hyperarousal.[81] Evidence suggests that this physiologic hyperarousal is associated with activation of the sympathetic nervous system (SNS) and hypothalamic-pituitary-adrenal (HPA) axis. People with insomnia show elevated levels of circulating catecholamines,[82] increased metabolic rates,[83] increased body temperature,[84] enhanced cardiovascular risk,[85] and smaller resting pupil diameters.[86] HPA axis activation in insomnia is indicated by elevated levels of night-time urinary free cortisol proportional to amount of wakefulness during the night.[82] An activated SNS and HPA axis suggests a central mechanism, possibly involving corticotropin releasing factor neurons.[87,88] Thus, when conducting studies that investigate links between sleep and OUD, it is important to measure biomarkers of HPA axis and SNS function including cortisol and catecholamines. Among patients with chronic insomnia, Vgontzas et al (1998) found that cortisol and catecholamine metabolites positively correlated with total wake time and stage 1 sleep.[82]

Chronic sleep deficiency may modulate stress-reactivity and its influence on craving and opioid use. In a recent experimental study of persons with OUD, average self-reported nightly sleep duration moderated the relationship between an acute laboratory stressor and opioid cue-induced craving response.[89] Likewise, in a prospective observational study with daily measurements, lower-than-usual self-reported sleep quality was associated with greater opioid craving, a relationship that was mediated by decreased positive affect.[50]

ALLEVIATING SLEEP DEFICIENCY AS A PATHWAY TO IMPROVING OPIOID ABSTINENCE

Research findings reviewed above positively connect sleep deficiency with opioid use. This evidence motivates the strategy of using novel sleep-restoration strategies to facilitate opioid abstinence (eg, in persons receiving opioid agonist treatment) and/or prevent relapse (eg, following detoxification or treatment with naltrexone). Although the approach of treating sleep deficiency to promote abstinence from substance use has been explored in persons with other SUDs including alcohol,[90-92] cocaine,[93-97] cannabis,[98,99] and tobacco,[100] this has not been systematically and thoroughly investigated in persons with OUD. The overall model shown in Fig 1 and the specific sleep−opioid research literature makes a compelling case for exploring, in patients with OUD, non-opioid treatments that may reverse opioid medication-induced sleep deficiency and thereby help patients maintain opioid abstinence.

Does treatment that normalizes sleep improve opioid use outcomes?. Behavioral approaches. Although there is substantive evidence that behavioral treatments can reduce sleep deficiency, data are lacking as to whether improved sleep mediates or moderates substance use.[101] For instance, cognitive-behavioral treatment for insomnia (CBTi) has been shown to improve sleep in

persons without SUDs[102,103] but, to our knowledge, only one CBTi interventional study has been conducted in people with OUD. In a small-scale randomized-group study of methadone-maintained patients (11 per group), the authors[104] found that, over the 8-week trial, CBTi significantly reduced sleep disturbance (measured with the Pittsburgh Sleep Quality Index [PSQI][105] compared to a behavioral placebo group (which focused on reducing conditioned arousal/frustration associated with not initiating or maintaining sleep). Similarly, mindfulness-based therapy for insomnia (MBTi) has been shown to be effective for improving sleep[106] but there are no such studies with OUD. In a small randomized trial, yoga added to buprenorphine/naloxone treatment did not significantly improve sleep over buprenorphine/naloxone alone, and drug use outcomes were not reported.[107] To our knowledge, there are no published studies of other behavioral treatments for sleep (eg, stimulus control, paradoxical intention) that have been used in persons with OUD. In short, we presently lack data from non-pharmacological approaches to test the sleep-efficiency → opioid abstinence hypothesis.

Neuromodulation. Previous studies have demonstrated that patients with insomnia exhibit heightened cortical excitability and hyperarousal, relative to healthy controls.[108-111] Thus, neuromodulation techniques that inhibit cortical excitability/arousal could be useful in treating sleep deficiencies. Guided by this hypothesis, Babiloni et al (2020) systematically reviewed studies that used repetitive transcranial magnetic stimulation (rTMS), transcranial direct current stimulation (tDCS), or transcranial alternating current stimulation (tACS) in sleep-deficient populations.[112] These authors concluded that multiple (10-14) sessions of inhibitory (1 Hz, 80-100% of resting motor threshold) rTMS over the dorsolateral prefrontal cortex or right posterior parietal cortex seem to improve subjective sleep quality and objective biomarkers (normalization of sleep efficiency and NREM/REM cycling) in patients with primary insomnia; however, studies reviewed typically had a high risk of bias (eg, no sham control), tDCS and tACS research is less technically advanced than rTMS, and more rigorous clinical research is needed. Similar conclusions were reached in 2 other recent reviews of studies of rTMS for treating primary insomnia and other sleep disorders.[113,114]

Medication approaches. Sleep deprivation has wide-ranging effects on the function of neurotransmitters and their receptors,[115,116] implying that neuropsychopharmacological interventions that reverse these changes could be therapeutic. In the general population, current prescribed medications for treating insomnia include benzodiazepines, 'z'-drugs (eg, eszopiclone, zaleplon, zolpidem), gabapentin, antidepressants, melatonin receptor agonists, and atypical antipsychotics.[117-123] Yet, these hypnotic agents have limited efficacy, can produce side effects (eg, cognitive impairment, dizziness), and some display misuse potential.

In persons with OUD, physicians have increasingly eschewed prescribing benzodiazepines to treat sleep deficiency due to the significant added risk of respiratory depression, although some persons with OUD report using benzodiazepines without a prescription for sleep problems.[124] Notably, the FDA (2016) issued a boxed warning related to combining opioids and benzodiazepines.[125] These concerns of increased risk of respiratory depression or misuse when prescribing medications for insomnia to people with OUD lead to fewer insomnia treatment options available to this population. Misuse of gabapentin, a non-benzodiazepine with sedating and analgesic properties, appears to be greater in combination with opioids than gabapentin alone.[126]

Findings are mixed concerning the efficacy of medications other than benzodiazepines for improving sleep outcomes *during opioid discontinuation*. The α_2-adrenergic agonist lofexidine has demonstrated some positive effects; however, these findings are not consistent. For patients who had begun opioid detoxification, lofexidine was found to reduce self-reported sleep problems to a greater extent than methadone dose tapering, measured over the course of 23-27 days of inpatient opioid detoxification[66]; however, that study allowed patients to choose which medication they would receive and assessments were conducted at different times across groups (ie, 2 confounds), and other studies have not found this benefit (see review, Gish et al 2010).[127] Quetiapine (an atypical antipsychotic with actions at dopamine, serotonin, histamine, muscarinic, and adrenergic receptors) has also been examined for this purpose. In a retrospective analysis of an observational study, 20% of outpatients undergoing opioid discontinuation reported that quetiapine helped to reduce their insomnia.[128] Notably, in the same study, patients also reported that quetiapine reduced their opioid craving (74%), anxiety symptoms (48%), and somatic pain (22%), so it possible that quetiapine played an indirect role in reducing insomnia by attenuating these other symptoms.

Slightly more research has examined the efficacy of non-benzodiazepine medications for improving sleep outcomes *during opioid agonist treatment*. Melatonin may be effective in certain subsets of patients with OUD. Patients maintained on methadone seeking to stop their benzodiazepine misuse underwent 6 weeks of gradual clonazepam dose-tapering alongside either nightly melatonin treatment or placebo. The melatonin group demonstrated significantly improved subjective

sleep quality but only among patients who could not discontinue their benzodiazepine use. For patients who discontinued benzodiazepines (ie, only remained on methadone), the melatonin had no effect on sleep quality (measured with the PSQI); however, this group had a general improvement in sleep quality compared to those who did not discontinue benzodiazepine use.[129] Certain medications, included long-term benzodiazepine use, have been associated with decreased levels of endogenous melatonin.[130] These findings suggest that melatonin (which drives circadian rhythm) may improve sleep quality in patients receiving opioid agonist treatments, but only when they have concurrent dysfunction in the circadian system. Support for this hypothesis comes from a recent study, in which patients with OUD in methadone treatment received either 12 weeks of melatonin or placebo. Patients receiving melatonin had significant self-reported sleep improvements compared to placebo. Also, those receiving melatonin had reductions in depression and anxiety scores whereas the placebo group saw no change.[131] Notably, all participants entering the study scored in the moderate-to-severe range on the Beck. Depression Inventory. Depression can impair sleep outcomes and is associated with lower levels of melatonin and dysfunction of the melatonin system, further supporting a role for melatonin within a subset of patients with OUD.[132]

The atypical antipsychotic quetiapine has also been found to decrease sleep problems among patients with OUD maintained on methadone who also used methamphetamine; however, the study also demonstrated that patients in the quetiapine group (vs. placebo) showed improvements in depression and some cognitive functions. These findings, once again, suggest a role for quetiapine in improving sleep outcomes in patients with OUD, although these sleep-related effects may be indirectly related to improvements in other measures.[133] Trazodone (a triazolopyridine derivative with activity at serotonergic, histaminic, and adrenergic receptors), the second most commonly-prescribed medication for treating insomnia in the United States, has shown improvements in sleep latency, sleep efficiency, and sleep duration in patients with insomnia. Although commonly prescribed for insomnia in patients with OUD, a double-blind, placebo-controlled randomized trial with methadone-maintained patients found that one month of trazodone treatment failed to produce subjective or objective sleep-restorative effects when compared to placebo.[134] At present, there are no studies that demonstrate trazadone's efficacy in this population. Zolpidem is the most commonly prescribed sleep aid in the United States; however, it may also be ineffective in this population. A small pilot study examining the efficacy of zolpidem and mirtazapine on sleep outcomes in methadone-maintained patients found that zolpidem had the poorest sleep outcomes even when compared to placebo. This same study showed that mirtazapine (30 mg IR) improved total sleep time, onset latency and sleep efficiency (measured with actigraphy) relative to zolpidem (12.5 mg SR), mirtazapine + zolpidem, and placebo.[135] Notably, this study was insufficiently powered to fully compare between these groups, so the results should be considered preliminary. Nonetheless, the findings of this study and previous studies indicate that people with OUD should be considered a unique group when evaluating appropriate medications to improve sleep-related outcomes, and that the findings of studies in clinical groups without OUD may not translate to this population.

Does treatment of opioid use disorder improve sleep outcomes?. Literature is mixed as to whether sleep problems resolve with extended opioid agonist treatment and, if so, through what mechanisms. Some early studies found tolerance can develop to opioid agonist-induced sleep disruption[61,136]: in those studies, sleep fragmentation and REM sleep suppressive effects diminished within weeks. However, more recent studies in methadone- or buprenorphine-treated patients suggest that REM sleep remains suppressed[70,137] and there can be excessive daytime sleepiness.[138,139] Importantly, ongoing sleep disturbance during OUD treatment is often related to comorbid conditions,[140,141] which are common in this population. For instance, one uncontrolled study found that self-reported sleep problems improved over 90 days of buprenorphine treatment; however, this could have been secondary to observed reduction in depression symptoms.[142] A recent experimental study found that manipulating an exogenous factor, opioid agonist treatment clinic attendance schedule (earlier vs. later daytime hours), can modulate sleep deficiency (measured with electronic diary and actigraphy), with an earlier daily clinic attendance requirement leading to greater sleep disruption.[143] Importantly, that study also found ongoing illicit opioid use was related to greater sleep disruption, suggesting that opioid maintenance dosing requirements and 'on-top' illicit opioid exposures may independently determine persistence of sleep deficiency (see "Sleep-related effects of opioid use and discontinuation''). Taken together, findings point to the clinical importance of monitoring sleep problems using multiple methods during opioid agonist treatment,[144] while accounting for substance use and co-occurring psychiatric (eg, depression) and medical (eg, respiratory) conditions. Given the current state of research evidence, it is not possible to make clear recommendations

Table 1. Treatment-combination matrix: testing candidate treatments for sleep deficiency in persons with opioid use disorder (OUD)

	Primary medications for treating OUD		
Sleep intervention	**Buprenorphine**	**Methadone**	**Naltrexone**
Cognitive-behavioral			
CBTi		(104)	
MBTi			
Yoga	(107)		
Neuromodulation			
rTMS			
tDCS or tACS			
Medications		(133, 135)	
5-$HT_{2,3}$ receptor antagonists		(129, 131)	
$Melatonin_{1,2}$ receptor agonists			
Endocannabinoid modulators		NCT04287062	NCT04287062,
Orexin $_{1,2}$ receptor antagonists			NCT04262193

Abbreviations: CBTi, cognitive behavioral treatment for insomnia; *MBTi,* mindfulness-based therapy for insomnia; *rTMS,* repetitive transcranial magnetic stimulation; *tDCS,* transcranial direct current stimulation; *tACS,* transcranial alternating current stimulation.
Examples in the table refer to the few relevant published or ongoing clinical studies (see text for discussion).

regarding the timing and/or efficacy of using medications for the treatment of OUD to resolve nonmedical or recreational opioid use-related sleep disturbances.

MECHANISM-DRIVEN APPROACHES FOR FUTURE INVESTIGATION

Table 1 summarizes promising therapeutic candidates for future rigorous testing at the intersection of sleep deficiency and OUD. When experimental data are available, we highlight examples below of sleep-restorative interventions (cognitive-behavioral, neuromodulation, medication) in people with OUD who are receiving standard medication treatments (buprenorphine, methadone or naltrexone). In essence, this table identifies potential treatment-combination studies that could be designed for efficacy evaluations.

Evidence reviewed above ("Does treatment that normalizes sleep improve opioid use outcomes?") suggests that medications with primary GABAergic agonist actions are unlikely to be promising (ie, not first-tier) candidates for managing sleep deficiency in opioid agonist-maintained patients with OUD, due to added risks of respiratory depression and misuse potential, as well as cognitive impairment, accidents, tolerance and rebound insomnia upon discontinuation.[145] However, results from one small-scale study suggest a possible benefit of the benzodiazepine prazepam in opioid-detoxified, naltrexone-maintained patients.[77] It is noteworthy that persons with OUD who use sedatives only as prescribed appear to experience fewer opioid-related consequences,[146] so there is a subset of individuals with OUD for whom carefully-monitored, short-term hypnotic use could be acceptable. Clinical use of sleep-promoting gabapentinoids, which act through voltage-gated calcium channels and NMDA receptors (unlike benzodiazepines), requires careful assessment and risk stratification in the context of chronic opioid use but is not universally contraindicated.[147]

Monoaminergic drugs. Medications with mixed monoaminergic effects are extensively used to treat neuropsychiatric conditions with affective features, and may alter sleep deficiency (which is correlated with those emotional disturbances). Extant data suggest it may be worthwhile to conduct studies to further investigate preliminary efficacy of the mixed-action D_2/5-HT_{2A} antagonist, $5HT_{1A}$ partial agonist, and $alpha_1$/$histamine_1$ receptor antagonist quetiapine[128] and the mixed-action, $5HT_{2/3}$ antagonist and $alpha_2$ antagonist, mirtazapine[135] in patients with uncomplicated OUD. Quetiapine may also be effective in reducing sleep problems among OUD patients with co-occurring psychostimulant use.[133] Common receptor mechanisms linking quetiapine and mirtazapine are the $5HT_2$ antagonist and $5HT_{1A}$ agonist actions; the $5HT_{2/3}$ receptor antagonism of mirtazapine may restore $5HT_{1A}$ function that becomes desensitized during chronic sleep deprivation.[148]

Melatonin receptor agonists. Melatonin is a hormone synthesized by the pineal gland, and functions in the suprachiasmatic nucleus to synchronize circadian cycling of central and peripheral biological functions including sleep/wake rhythm.[149] Melatonin has promising effects on treating sleep deficiency and

pain[54,150,151] but, to our knowledge, only 2 clinical studies of melatonin have been conducted in relationship to sleep and opioid use. In one double-blind placebo-controlled, within-subject crossover trial, melatonin (5 mg/day prior to bedtime) improved self-reported sleep quality in methadone-maintained outpatients with co-occurring benzodiazepine use; however, melatonin had equivocal effects on benzodiazepine discontinuation.[129] A double-blind, placebo-controlled, parallel-group study found melatonin (10mg/day prior to bedtime) supplementation during methadone maintenance improved subjective sleep, as well as depression and anxiety scores.[131] The melatonin$_{1/2}$ agonist ramelteon would also be a reasonable candidate for evaluation in this drug class, although there are no studies to date.

Endocannabinoid modulators. Therapeutically-motivated use of cannabinoid (CB) drugs has been increasing in the general population, often in the absence of clear scientific evidence. It is therefore timely to consider whether drugs that modulate endocannabinoid (eCB) function could be useful in treating sleep deficiency. Δ^9-tetrahydrocannabinol (THC), a CB_1 receptor-preferring agonist, when administered acutely can decrease sleep onset latency, decrease waking after sleep onset, increase slow-wave sleep and decrease REM sleep time; however, repeated THC exposure can lead to tolerance to these effects, and THC discontinuation can produce rebound insomnia (review by Kesner & Lovinger 2020).[152] Thus, orthosteric CB_1 receptor-preferring agonists seem unlikely to be promising medications for treating sleep deficiency.

Cannabidiol (CBD) acts via multiple eCB mechanisms including CB_1 negative allosteric modulation,[153,154] and inhibition of anandamide reuptake,[155] thereby increasing eCB signaling. CBD also has non-eCB pharmacological actions including inhibition of adenosine reuptake[156] and $5HT_{1A}$ partial agonism,[157] each of which can promote sleep. At higher doses, CBD is sedating.[158,159] Thus, although CBD has a complex pharmacology, its synergistic actions (reviews by Campos et al 2012; Izzo et al 2009; Mechoulam et al 2007) are likely to exert multiple sleep-promoting actions.[160-162]

Literature reviews related to cannabinoid impact on sleep efficiency as a primary outcome identified some initial supportive (but often mixed) evidence; authors have concluded that available studies were not of high quality, but that data offer an adequate 'signal' for designing well-controlled studies.[163-165] There are virtually no published clinical trials testing cannabinoid impact on sleep efficiency in people with OUD. One interview study found that patients with concurrent DSM-IV cannabis and opioid dependence reported more sleep disturbance than patients with only cannabis dependence[166]; thus, consistent with evidence noted above regarding chronic THC exposure, excessive use of cannabis may worsen sleep deficiency. A randomized, placebo-controlled trial found – in *post hoc* analysis – that, among opioid-detoxification patients who received oral THC (dronabinol) in addition to extended-release naltrexone, individuals who smoked marijuana regularly (outpatient) reported less insomnia and anxiety, and were more likely to complete the trial, than those who did not smoke marijuana; dronabinol itself did not improve sleep over placebo.[167]

Orexin receptor antagonists. Two research groups simultaneously discovered a cluster of 50,000-80,000 neurons located in the lateral hypothalamus that project widely throughout the brain to regulate sleep-wake, feeding, stress-reactivity, and drug-motivated behavior.[168-170] These cells express 2 neuropeptides, named hypocretin by the sleep research group and orexin (OX) by the feeding research group. Lateral hypothalamic OX neurons project to cholinergic and monoaminergic systems, stimulating arousal and motivation. Orexin comes in 2 isoforms, orexin-A and orexin-B, with ≈50% sequence homology, derived from the same precursor protein, prepro-orexin; these isoforms bind to 2 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 significance and specificity of OX receptors is not clearly defined.[170] Pre-clinical models suggest that OX_2 receptors are primarily involved in maintaining wakefulness and arousal.[171-175] Clinically, OX receptor antagonists are being developed; the dual $OX_{1/2}$ antagonist, suvorexant, is the first-in-class FDA-approved hypnotic.[176-178] Experiments have not directly parsed whether suvorexant's OX_2 or OX_1 antagonism mediates its hypnotic effects; however, the OX_2 selective antagonist seltorexant (an investigational drug) improves sleep in people with insomnia, which suggests OX_2 antagonism is necessary for suvorexant's hypnotic effects, as does pre-clinical literature.[170,179-181]

Suvorexant is effective for treating primary sleep-onset and/or sleep-maintenance insomnia in healthy persons.[182,183] Notably, suvorexant improves sleep maintenance via sustained reduction of wake across the 8-hr sleep period, measured electrophysiologically as sleep efficiency (sleep time ÷ time-in-bed) or waking after sleep onset. That effect, in turn, likely will stabilize the ultradian rhythm of NREM-REM sleep, which is disrupted in SUDs (ie, stage 3-4 and REM disturbance). Efficacy of suvorexant for promoting drug

abstinence or preventing drug relapse directly, or indirectly by improving sleep efficiency, has not yet been evaluated among individuals with SUDs. As noted above, evidence indicates OX_2 (more so than OX_1) receptor antagonism mediates improvements in sleep maintenance. In contrast, OX_1 (more so than OX_2) antagonism attenuates stress-, cue-, and priming-induced reinstatement of drug seeking.[184,185] Few animal studies have tested whether OX_2 antagonists block drug reinstatement/ seeking, but some studies demonstrate a positive effect.[186-188] Thus, it is possible that both OX_1 and OX_2 receptors modulate drug relapse-like behaviors, independent of sleep-wake function.

Accordingly, dual OX antagonism could be a unique strategy to target both insomnia and drug relapse. To date, clinical studies on the efficacy of suvorexant have focused solely on treating insomnia disorder; none have addressed the utility of suvorexant to improve sleep as an indirect means of reducing the risk of substance relapse, although this approach has recently been suggested for alcohol use disorder,[189] comorbid cocaine and alcohol use disorders,[190] and OUD.[191,192] Our research team is presently conducting a randomized, placebo-controlled, mechanistic clinical trial to assess whether suvorexant (10 mg and 20 mg at bedtime) dose-dependently modulates sleep efficiency (following opioid detoxification, allowing for extended-release naltrexone maintenance) and subsequent opioid abstinence (across 3 months of weekly outpatient follow-up visits) in people with OUD (NCT04262193). We hypothesize that treatment aimed at improving sleep efficiency (ie, reducing disruptive effects of wake intrusions on normal sleep staging) is a key mechanism for reducing the risk of drug relapse. Two other ongoing placebo-controlled randomized trials are examining whether suvorexant can increase total sleep time among patients with OUD undergoing supervised withdrawal (NCT03789214), and prevent relapse in recently-abstinent patients who are maintained on extended-release naltrexone or methadone (NCT04287062).

In the alcohol use disorder literature, 2 predictors of relapse are deficient NREM sleep (ie, reduced age-corrected NREM stage 3-4 sleep) and shortened REM onset[69,193]; again, this has not studied with opioids. Both these effects directly relate to sleep maintenance and the normal NREM-REM ultradian rhythm. Normalization of ultradian rhythm by suvorexant (relative to placebo) should be reflected in REM latency of 80-120 min and REM percent of 18-24%.[18] Notably, chronic opioid use and discontinuation both disturb sleep and its rhythms in 2 ways: (1) disruption of circadian timing of sleep such that sleep is tied to the user's opioid intake irrespective of light-dark cycle; and (2) disruption of ultradian rhythm within sleep, the normal NREM-REM cycling. Thus, in our ongoing project (NCT04262193), we are anchoring sleep to the dark cycle with suvorexant and a fixed light-dark cycle with no daytime sleep, to increase likelihood of normal ultradian rhythmicity by suppressing wake intrusion throughout the 8-hr sleep period. We predict one or both suvorexant doses will produce more rapid resolution of this ultradian disturbance than placebo, ie, sleep will normalize across assessment nights on the inpatient unit. We will test whether normalization of sleep efficiency predicts weekly opioid abstinence over a 3-month outpatient period.

CONCLUSIONS

Consistent with our conceptual model (Fig 1), the evidence reviewed here indicates that sleep deficiency and opioid use are likely bidirectionally linked, with additional bidirectional contributions (outside the scope of this review) of pain and affective distress. Although research findings suggest that sustained opioid abstinence can ultimately improve sleep efficiency, opioid agonist or naltrexone treatment for OUD may itself prevent full resolution of sleep deficiency. Thus, it is essential to develop and test non-opioid (including behavioral and neuromodulation) approaches in this clinical population. Presently, there are a few promising medication options including suvorexant, mirtazapine and quetiapine, and other possible targets (eg, melatonin receptor agonists, eCB modulators) although all require rigorous testing. Furthermore, systematic investigations are needed to establish whether normalization of sleep efficiency is necessary for, or simply contributes to, opioid abstinence and recovery of global function. Such studies will need to account for the influence of demographic factors (eg, sex, race, age), psychiatric conditions (eg, depression, anxiety) and medical conditions (particularly, but not limited to, pulmonary disorders). In this way, we will be able to translate findings from mechanism to clinical application.

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