HHS Public Access

Author manuscript

*Clin Chest Med*. Author manuscript; available in PMC 2023 March 16.

Published in final edited form as:

*Clin Chest Med*. 2022 June ; 43(2): e1–e14. doi:10.1016/j.ccm.2022.05.001.

# Sleep Deficiency and Opioid Use Disorder Trajectory, Mechanisms, and Interventions

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**Keywords**

Opioid use disorder; Sleep deficiency; Control of breathing

## INTRODUCTION: PRIMER ON OPIOID DOSE DISORDER

In Greek mythology, Hypnos is the God of Sleep, and he is often depicted floating through the air spreading poppies or opium elixir to induce sleep. His son, Morpheus, is the Greek God of Dreams and from whose name the word morphine is derived. These ancient mythological inferences suggest a strong relationship between sleep and opioids, but it is only recently in the context of the opioid use disorder (OUD) epidemic that this relationship has begun to receive significant scientific inquiry. Examining this relationship provides the opportunity to significantly improve symptoms among patients with OUD and potentially improve long-terms outcomes from this disorder.

The Diagnostic and Statistical Manual of Mental Disorders 5th Edition (DSM V) defines the presence and severity of substance use disorder based on several key criteria including tolerance, withdrawal, increasing use, loss of control over use, and craving in combination with social or functional impairment. OUD is a subset of substance use disorder and a chronic and relapsing brain disorder characterized by loss of control over opioid use and deficits in cognitive function, mood, pain perception, and autonomic activity. OUD affects more than 3 million US citizens, 16 million individuals worldwide, and causes one overdose death every 20 minutes.[1] In the 1990s, health care providers increased opioid prescribing in response to the "pain as fifth vital sign" campaign, a downplay of the abuse potential of opioids, and aggressive marketing of drugs such as oxycodone hydrochloride. However, opioids are indeed highly vulnerable to abuse and, due to their central nervous depressant effects, accidental death. Subsequently, there have been 3 “waves” contributing to the epidemic increase in opioid overdose death (Fig. 1): wave 1: increase in prescription

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opioid overdose deaths that started in 1990s; wave 2: increase in heroin overdose deaths that started in 2010; and wave 3: increase in synthetic opioid overdose deaths that started in 2013.[2] These progressive waves have in part been related to access (in the case of heroin) and the potency, speed, and intensity of the pleasure (in the case of synthetic opioids such as fentanyl). Most opioid-related deaths occur during sleep due to respiratory failure, where opioid-induced respiratory depression, sleep-related loss of respiratory drive, and loss of protective mechanisms that control breathing co-occur.

The endogenous opioid system is believed to significantly contribute to the development of OUD. The endogenous opioid system plays a central role in the regulation of mood and well-being consisting of 3 G protein–coupled receptors, mu, delta, and kappa, which are stimulated by a family of endogenous opioid peptides.[3] Opioid receptors can also be activated exogenously by alkaloid opiates, the prototype of which is morphine. The finding that morphine's analgesic and addictive properties are abolished in mice lacking the mu receptor[4] points to the mu-opioid receptor as a key molecular player in the therapeutic effects of opioids and in OUD.

Effective evidence-based frontline treatments exist in the form of Food and Drug Administration (FDA)-approved medications for OUD (MOUD). These include methadone (full mu-opioid receptor agonist), buprenorphine (partial mu-opioid agonist), and naltrexone (long-acting mu-opioid antagonist).[5] These treatments work by preventing withdrawal, relieving craving, and blocking or attenuating the euphoric effect of exogenous opioids; this has the effect of shifting the patient from "high" or "sick" functional states to a "straight" functional state. These treatments help decrease illicit drug use, treatment attrition, and disease transmission and improve social functioning. However, there is significant variability in treatment responses. Relapse rates are high (even in treatment) and are associated with lack of retention in treatment and a continued cycle of setbacks and return to use, risk for injection-related infectious complications, overdose, and death.[6,7]

## Basic Concepts of Sleep and the Construct of Sleep Deficiency

One of the basic concepts of sleep is termed the "2-process model." This model is a conceptual model of sleep regulation that posits that 2 constituent processes—(1) a sleep-wake–dependent homeostatic Process S (sleep drive) and (2) Process C (circadian drive)—generate the timing of sleep and wakefulness. The sleep drive is low on waking and continues to increase throughout wakefulness. Normally, this drive peaks just before habitual bedtime. In parallel, the circadian drive is low on wakening and also increases during the day in a manner that balances the sleep drive. However, just before habitual bedtime there is a sharp decrease in the circadian alerting signal, which creates maximal sleep pressure due to an unopposed, high level of sleep drive and potentiates the onset of sleep. The circadian system remains quiescent throughout the biological night, which is defined as the time from melatonin onset to offset. In fact, it is this lack of arousal from the circadian system that allows sleep to continue and be of the longest duration and highest quality during biological night.[8,9] Circadian entrainment (ie, alignment between biological time and solar day-night) is continuously adjusted by external cues of light, eating, physical activity, social

interactions, and so on such that, in the case of healthy sleep, biological night occurs during solar night.

There are several key functions of sleep and circadian rhythmicity including hormone secretion and metabolic regulation, supporting immune function, energy conservation (particularly in the brain), replenishment of brain macromolecules, removal of neurotoxic waste via the glymphatic system, cognitive function and memory consolidation, mood regulation, brain plasticity, performance, and recovery.[10]

The American Academy of Sleep Medicine recommends at least 7 hours of sleep daily for adults, based on evidence linking sleep duration to health outcomes.[11] In contrast to a focus on individual sleep disorders (eg, sleep apnea), sleep deficiency, as defined by the National Institutes of Health (NIH), is a broader construct that includes insufficient sleep duration (sleep deprivation), sleep out of sync with the body's circadian rhythm (noncircadian sleep), not getting all the different types of sleep that the body needs (impaired sleep architecture), and poor sleep quality. Common symptoms of sleep deficiency include insomnia (difficulty initiating or maintaining sleep), hypersomnia (excessive daytime sleepiness), or even parasomnia (abnormal behaviors during sleep).

## Sleep Deficiency Across the Opiod Use Disorder Trajectory

To achieve better outcomes for individuals who are maintained on MOUD, there is a critical need to identify novel strategies and new approaches to complement or even enhance MOUD programs and foster skills necessary for long-term recovery. One promising strategy is to identify and target a neurobiological system that may be linked to OUD relapse, namely the sleep and circadian system. Sleep deficiency is an important correlate of OUD. It is associated with overlapping cognitive deficits in executive function and reward processing.[12,13] Sleep is increasingly being recognized as a key determinant of brain health, as it is an important factor in several physical and mental health disorders.[14,15] A growing scientific consensus has identified sleep deficiency as a critical component of OUD, both during the active disease state and during recovery. A 2018 FDA public meeting that included patients with OUD identified sleep disturbance as a primary contributor to relapse and treatment attrition.[16] More recently, NIH committed 25 million to fund a research program entitled "Sleep dysfunction as a core feature of opioid use disorder and recovery" as part of the Helping End Addiction Long-term (HEAL) initiative.[17] Sleep deficiency accompanies OUD across the *trajectory* of this disorder from initial medical or recreational use through misuse, addiction, recovery, setbacks, return to use, overdose, and death (Fig. 2). Data have also emerged that disrupted circadian rhythms are linked to increasing susceptibility to addiction. For example, there is an association between delayed sleep phase chronotype and addiction vulnerability.[13,18] Delayed sleep-phase syndrome is a delay in the major sleep period accompanied by alertness in the evening, sleep-onset insomnia, morning sleepiness, and difficulty awakening from sleep. A form of noncircadian sleep termed "social jet lag" has been coined to describe the circadian desynchrony resulting from large time differences in social (weekend) and academic/work schedules (week-days). Social jet leg is the difference between the average midpoint of sleep on workdays versus the

average midpoint of sleep on free days, and this form of circadian desynchrony is associated with increased addiction among adolescents.[19]

Sleep disturbance is common and often severe during opioid withdrawal. Withdrawal occurs because taking opioids over a long period can lead to *tolerance and dependence*. A person who depends on opioids will experience symptoms of withdrawal should they reduce or suddenly stop taking opioids. Signs of withdrawal are similar for all opioids and can include nausea, vomiting, diarrhea, insomnia, anxiety, tachycardia, hypertension, muscle and bone pain, hyperthermia, sweating, and chills.[20] Persons with OUD undergoing supervised withdrawal report significant sleep disturbances including increased sleep-onset latency, reduced total sleep time, and poor sleep quality.[21] This reduced sleep quality often persists into the postwithdrawal period and has been linked to increased drug craving.[22]

Sleep disturbance remains a major concern for persons on MOUD.[23] Many patients report significant sleep disturbance on entering MOUD recovery programs[24] and continue to report poor sleep quality during treatment.[25] As with withdrawal, persons in early stages of abstinence who are craving opiates have increased sleep disturbance.[26] In one study of patients undergoing MOUD, 90% of patients experienced poor sleep quality defined as a Pittsburgh Sleep Quality Index greater than or equal to 5, nearly half had excessive daytime sleepiness defined as and Epworth Sleepiness Score greater than or equal to 10,[25] and 41% were found to be at high risk for sleep apnea.

## MECHANISMS OF SLEEP DEFICIENCY LEADING TO OPIOD USE DISORDER

Whether sleep deficiency contributes to OUD relapse is the focus of several ongoing mechanistic studies, observational cohorts, and mechanistic clinical trials studies funded by the NIH Helping to End Addiction Long-term (HEAL) initiative. Importantly, there are several plausible mechanisms whereby sleep deficiency may lead to worse OUD outcomes. Here, the “bio-psycho-social” model of cause holds very well for how sleep deficiency may affect and contribute to OUD. Fig. 3 illustrates that sleep deficiency may contribute to OUD outcomes through its influence on a range of *neurobiological* mechanisms linked to addiction, such as chronic stress, involvement of the orexin/hypocretin neurotransmitter system, and pain. On the other hand, sleep deficiency among patients with OUD may lead to *neuropsychiatric* mechanisms such as cognitive control, reward dysregulation, negative affect, as well as the influence other substance use (eg, nicotine, stimulants, alcohol) that may increase the likelihood of illicit opioid use. Finally, *social-ecologic* factors (at the individual, home-environment, and community level) that often accompany OUD may predispose to the development of sleep deficiency and subsequently influence outcomes. These mechanistic pathways are described later in further detail.

### Neurobiologic Mechanisms: Stress, the Orexin System, and Pain

Sleep deficiency activates both immediate short-term stress pathways that lead to the generation of catecholamines as well as prolonged stress pathways, leading to the generation of mineralocorticoids and glucocorticoids. Periods of sleep deficiency lead to heightened

blood pressure[27] and elevated cortisol[28] and promote sympathetic activation.[29] Both acute and chronic stress are associated with the onset and progression[30] of OUD, and chronic stress and stress reactivity contributes to setbacks and return to use in patients with addiction,[31] particularly early in recovery.[32] Thus, evidence points toward a bidirectional (and mutually enforcing) relationship between sleep deficiency and chronic stress among patients with OUD.

Orexin (a.k.a., hypocretin)-producing neurons, which are primarily located in the lateral hypothalamus, project to several subcortical and brainstem regions. Deficiency of orexin causes type I narcolepsy. Sleep and circadian rhythmicity provide inputs to the orexin system. Increased orexin signaling causes arousal, sleep disturbances, and stress activation. Orexin neurons also project to reward-associated brain regions. Orexin neurons are responsible for regulating wakefulness/ arousal, diurnal neuroendocrine stress signaling, food, drink, sexual behavior, and even drug consumption.[33-36] Evidence from preclinical models of OUD indicates that increased orexin signaling contributes to arousal and stress reactivity (one of the neurobiological hallmarks of OUD) and orexin receptor antagonists (commonly prescribed for insomnia) attenuate opioid withdrawal symptoms.[35-37] Thus, this system may be an important target in OUD. In 2018, the National Institute of Drug Abuse listed the orexin system as part of its “Ten Most Wanted” medication development priorities in response to the opioid crisis.

Pain disrupts sleep. Furthermore, sleep deficiency produces “hyperalgesia” (increased pain sensitivity to noxious stimuli) in healthy subjects and clinical samples.[38] Relatedly, acute and chronic opioid use impairs sleep (Table 1), and this may lead to a vicious cycle of opioid dose escalation, whereby opioids impair sleep, which lowers the pain threshold and leads to greater opioid use and worsened pain (Fig. 4).[38] Importantly, there may be important sex differences in these relationships. Experimental research indicates that women experience pain differently from men.[39] Women may be more likely to take prescription opioids without a prescription to cope with pain and are more likely to misuse prescription opioids to self-treat other problems such as anxiety.[40] Women have an earlier age of initiation of substance use and a more rapid progression to drug involvement and dependence than men.[41]

## Neuropsychiatric Mechanisms: Cognitive Mechanisms, Mood, and Other Substances

Repeated drug exposure can affect circuits in the prefrontal cortex (regulates executive function), extended amygdala (regulates reward/antireward), and basal ganglia (responsible for incentive salience).[42] These 3 brain regions and circuits correspond to a 3-stage cycle of addiction of binge intoxication, withdrawal, and preoccupation anticipation (craving). Importantly, these cognitive domains are impaired in addictive disorders and are also affected by sleep deficiency forming, a feed-forward allostatic framework.[43]

Among adults with mood disorders, sleep deficiency compromises health and may contribute to substance use comorbidity and suicidality.[44] Certain psychological states have been associated with increased opiate craving, including low positive affect and high negative affect. Increases in negative emotional responses to various stimuli and overall self-reported dysphoria are common in individuals with addictive disorders, and the reduction in negative affect (eg, self-medication) has long been held up as a primary driver for the

consumption of addictive substances mapping to the extended amygdala.[12,42] In addition, anhedonia is thought to partially mediate the relationship between sleep quality and opiate craving postwithdrawal.[22] This evidence has triggered a shift away from viewing sleep deficiency as an epiphenomenon to an important but underrecognized mechanism in the multifactorial cause and maintenance of the various mood disorders. In contrast to the current rates of depressive and anxiety disorders in the general population (2%–5% and 6%–10%),[45] between 4% and 24% of treatment-seeking individuals with OUD meet current criteria for a depressive disorder and between 5% and 17% meet criteria for an anxiety disorder.[46-49] Ongoing mood disorders are important to monitor, as they are associated with continued substance use, poorer retention, lower quality of life, and suicidality.[50-54]

Other substance use is common in OUD and may also contribute to sleep deficiency.[55-57] For example, the rate of cigarette smoking among individuals with OUD far exceeds that of the general population.[58] Nicotine lengthens sleep-onset latency and decreases total sleep duration, particularly during deeper sleep stages.[57] Likewise, alcohol and cocaine use disorders are highly comorbid in OUD[59] and are associated with poorer OUD treatment outcomes.[60] Alcohol, a depressant, may promote the initiation of sleep and maintenance of sleep during the first half of the sleep period (eg, decreased sleep onset latency), but it can be disruptive during the second half of sleep (eg, increased wake time after sleep onset, decreased slow wave sleep)[61,62] and contribute to sleep-disordered breathing (SDB).[63]

## Social-Ecologic Mechanisms Contributing to Sleep Deficiency: the Role of Individual-Level, Home/Family Environment, and Community Factors

Social-ecologic factors often accompany OUD and may predispose to the development of sleep deficiency and subsequently influence OUD outcomes. Individual psychosocial experiences and perceptions contribute to sleep deficiency. Stressful life events are powerful risk factors for both sleep deficiency[64] and drug use.[65] For example, adverse childhood experiences (ACEs), stressful traumatic life events that occur during the first 18 years of life (emotional, physical, or sexual abuse; emotional or physical neglect; or other forms of family dysfunction), are pervasive and significant public health problems that consistently contribute to drug use later in life.[65] Furthermore, ACEs contribute to many attributes of sleep deficiency[66] and specific sleep disorders, including sleep apnea, nightmare distress, and psychiatric sleep disorders.[67] ACEs and other stressful experiences also contribute to posttraumatic stress disorder (PTSD), a condition experienced by about 33% of people with OUD that may have a negative effect on adherence to MOUD.[68] Sleep deficiency is also a common risk factor and perpetuating factor for PTSD, with as many as 80% to 90% experiencing insomnia and nightmares; SDB, periodic limb movement disorder, and parasomnias are also common.[69]

OUD and its treatment and sleep deficiency occur within the context of the family. Social support from family and others contributes to successful MOUD[70] and good sleep quality. Sleep also occurs within the context of the family, with each member of the family influencing the sleep of the other.[71] For example, being married and having a close family relationship were associated with lower levels of drug use and successful treatment,[72] whereas married couples had better sleep than others in the United States[73] and single

marital status had a negative impact on sleep quality.[74] In one study, women who reported marital happiness had better sleep than others,[75] whereas marital conflict was a risk factor for poor sleep. Notably, the quality of attachment and family support[76] were associated with better sleep quality. In contrast, family conflict during childhood contributed to the development of insomnia in adults,[67] and household chaos and disturbing behaviors of family members also predicted poor sleep.[71]

Physical characteristics of the home environment are well-known proximal contributors to poor sleep. Factors such as bright light and noisy environments, the presence of other people in the bedroom, and comfortable bedding are traditional factors that are often the focus of behavioral sleep "hygiene" intervention. Exposure to electronic "screen time" near bedtime is increasingly a focus of concern because of the contributions of blue light to wakefulness and hyperarousal.[77] In addition, housing instability (ie, recent, past, or potential for homelessness) and housing type (eg, house, apartment, trailer) will be addressed because housing type is a risk factor for poorer sleep that is also often associated with economic adversity.[78]

Community-level factors can be either risk factors or protective factors for sleep. Both social and physical characteristics of the neighborhood in which one lives contribute to sleep deficiency.[79] Social factors including social ties and social cohesion in the community seem to be protective factors that are closely tied with sleep.[80] On the other hand, social fragmentation and neighborhood disadvantage (a factor that is often associated with racial disparities in sleep), contributed to wake after sleep onset.[81] Adverse neighborhood environments were associated with shorter sleep duration,[82] whereas neighborhoods characterized by more social disorder, low social cohesion, and lower safety were associated with shorter sleep duration after controlling for socioeconomic status and the physical environment.[83] Positive aspects of the physical neighborhood environment, such as those associated with good health (eg, walkability and green space, lower population density, lower noise levels), are associated with improved sleep.[84] A recent review indicated the promise of addressing environmental characteristics, such as walkability and green space on sleep.[79] Taken together, these findings suggest the critical importance of understanding the individual, family, and social context for sleep deficiency.

## Mechanisms of Opioid Use Disorder Leading to Sleep Deficiency

**Direct effects of opioids on sleep—**Information on the differential effects of opioid use on key sleep parameters in different populations including potential acute versus chronic differences is covered in detail elsewhere[85-87] and is summarized in Table 1.

Sleep deficiency affects most patients in methadone treatment programs.[25] Importantly, in one prospective cohort study, receiving methadone, MOUD treatment had no significant effect on sleep disturbance. In the final multivariate model, younger age, pain, high nicotine dependence, and suicide risk were all associated with sleep disturbance.[88]

In this context, it is important to note that improvements in sleep architecture may occur with chronic opioid use[89]; opioids can improve sleep quality and increase sleep time in people with chronic nonmalignant pain.[87,90] Given the evidence for a bidirectional

relationship between sleep and pain, whereby poor sleep worsens pain perception and vice versa (see Fig. 4),[38,91] opioids may improve sleep, at least in part, via reductions in pain. Given that strategies to improve sleep can reduce pain,[92] evaluation of the effects of opioids on sleep may be an important consideration in the clinical management of pain in people taking opioids.

## Effects of Opioids on Sleep-Disordered Breathing: Ataxic Breathing, Central Apnea, and Obstructive Sleep Apnea

There are 3 basic components to the ventilatory control system: the controller (cerebral cortex, pons, medulla), the sensors (carotid, aortic bodies), and effectors (diaphragm, accessory muscles of respiration). Most opioid-related deaths occur during sleep; this is, in part, mediated by the sleep-related loss of wakefulness respiratory drive, decreased $O_2$ and $CO_2$ chemosensitivity, and decreased tone in the muscles of the upper airway pharyngeal dilator muscles and ventilatory pump effector muscles. Respiratory depression is further amplified by the addition of opioids, which results in the suppression of protective mechanisms that control breathing, leading to respiratory failure and death.

The combined effects of sleep and opioids on the ventilatory control system also contribute to several different forms of sleep apnea, including ataxic breathing (termed Biot respiration), central sleep apnea, and obstructive sleep apnea (OSA), which may further impair sleep quality.[93] Similar to high-altitude exposure, whereby everyone will eventually develop SDB if they go high enough,[93] the same is likely true for SDB and opioids.

Breathing can slow and become irregular, leading to hypercapnia and hypoxia with high doses of opioids.[93,94] An ataxic breathing pattern, termed Biot respiration after Dr Camille Biot (Fig. 5), with irregular variation tidal volumes and rhythm, bradypnea, oxygen desaturations, and arousals has been described in association with both acute neurologic disease as well as opioid use.[95,96]

The presence and severity and opioid-induced central sleep apnea vary due to multiple factors including the dose of opioid, wakefulness-to-sleep transitions, and sleep stage. Opioids cause central respiratory depression and central sleep apnea in a dose-dependent manner.[97,98] Loss of the wakefulness drive to breathe, which itself can predispose to central apnea at sleep onset,[93,99] may become magnified when combined with opioid-induced central respiratory depression via activation of mu-opioid receptors.[100]

On polysomnography, central apneic events are distinguished from obstructive apneic events by absent airflow in the context of no respiratory effort. However, there is overlap in the pathophysiology of obstructive and central sleep apnea. For example, centrally mediated loss of respiratory drive not only causes central apnea but it also contributes to upper airway closure due to concurrent central reductions in the neural drive to the pharyngeal dilators muscles.[101] Thus, unstable control of breathing is not only a contributor to central apnea but is also a feature of OSA for at least 30% of patients.[102] There are several key physiologic traits that contribute to OSA pathophysiology.[102-105] Impaired pharyngeal anatomy, or a collapsible upper airway, is the pathophysiological trait common to all patients with OSA. Stable upper airways require a more negative critical closing pressure (Pcrit),

whereas highly collapsible upper airways have a more positive Pcrit. Thus, the magnitude of anatomic impairment varies markedly between individuals.[102,103] Importantly, almost 60% of people with OSA also have one or more nonanatomical physiologic traits that contribute to their OSA.[102,103] These traits include (1) inadequate upper-airway dilator muscle activity during sleep, (2) unstable control of breathing/excessive sensitivity to minor changes in $CO_2$ (high loop gain), and (3) a low respiratory arousal threshold (waking up too easily to minor airway narrowing), which prevents deeper more stable sleep.[102,103] Limited data exist regarding the impact of escalating doses of opioids on these nonanatomic physiologic traits of OSA. Overall, the spectrum of variables that likely affect the effects of opioids on breathing stability during sleep include the dose of opioids, pharyngeal anatomy, nonanatomic physiologic traits of sleep apnea, pharmacokinetics of opioids, baseline sleep deficiency, comorbidities, and body habitus and position.

## Targeting Sleep Deficiency to Improve Opiod Use Disorder: Behavioral, Positive Airway Pressure, and Pharmacologic Interventions

**Behavioral—**Cognitive-behavioral therapy for insomnia (CBTi) is the first-line treatment of insomnia and can be delivered face-to-face, via telehealth, or web-based platforms. It involves (1) behavioral techniques (sleep restriction, stimulus control) designed to target excessive time in bed, irregular sleep schedules, sleep incompatible activities, and hyperarousal; (2) cognitive techniques (cognitive therapy, paradoxic intention) designed to target unrealistic sleep expectations, misconceptions about sleep, sleep-related worries, and poor coping skills; and (3) educational techniques (sleep hygiene education, sleep information) designed to target inadequate sleep hygiene. There is a real need to conduct intervention trials to determine whether CBTi helps to consolidate sleep among patients with OUD and sleep deficiency and explore its impact on key outcomes. Importantly, this therapy does not involve the use of prescription sedative-hypnotics that have abuse potential. Furthermore, CBTi may have overlapping benefits in other domains including the treatment of anxiety and pain.

**Positive airway pressure therapy—**Given the dose-response relationship between opioids and SDB,[97,98] dose reduction is highly effective in reducing SDB severity and, thus, should be prioritized.[93,106-108] Few studies have systematically investigated positive airway pressure (PAP) therapy for people with opioid-induced SDB. The existing data indicate variable success with PAP and adaptive servo-ventilation (ASV) approaches.[87,106,109-114] Variable responses likely reflect, at least in part, the different manifestations of opioid-induced SDB (ie, central vs obstructive). ASV may be effective in treating opioid-induced central sleep apea.[109,111] Effective treatment of SDB with PAP may improve health and well-being in this population.[115]

**Pharmacologic—**Given concerns for abuse with benzodiazepines, previous pharmacologic trials targeting sleep consolidation and insomnia among patients with OUD have largely focused on nonbenzodiazepine medications. To date, we are aware of only 3 published trials. The first was a randomized, double-blind, placebo-controlled trial that compared trazadone with placebo with 6 months of follow-up in 137 patients recruited from methadone maintenance programs. Trazadone did not improve subjective or objective

sleep nor did it significantly increase or decrease illicit drug use relative to placebo.[116] A more recent pilot trial of 10 methadone maintenance patients compared mirtazapine (30 mg) versus zolpidem sustained release (12.5 mg) versus mirtazapine (30 mg) + zolpidem (10 mg) versus placebo using a within-subject, cross-over design with a 1-week washout between drugs. The mirtazapine arm alone improved total sleep time (23 minutes), sleep latency (23 minutes), and sleep efficiency (3%), surpassing all the other regimens.[117] Finally, a randomized, double-blind, placebo-controlled trial of 54 patients receiving methadone maintenance comparing melatonin, 10 mg, with placebo for 3 months resulted in significant improvement in subjective sleep quality, depression symptoms, and anxiety symptoms versus placebo.[118]

Given the overlapping effects of modulating sleep and opioid withdrawal symptoms of the orexin (hypocretin) system described earlier (see discussion neurobiological mechanisms), there is considerable interest in examining the impact of antagonists or negative modulators of the orexin neuropeptides on sleep deficiency and other outcomes among patients with OUD. Currently, 2 FDA-approved dual orexin receptor antagonists (DORAs) already exist and are FDA approved for the treatment of insomnia: suvorexant (Belsomra) and another recent DORA, lemborexant. In addition to insomnia therapeutic benefits, there is preclinical evidence that DORAs reduce opioid withdrawal and drug seeking[35,36]; this may, in part, be mediated through normalizing sleep disturbances present in 75% of patients with OUD, as sleep disturbances can worsen OUD outcomes.[24] Given that these are schedule IV controlled substances, this drug needs to be rigorously tested in clinical trials, several of which are currently underway: NCT03412591, NCT03897062, NCT03789214, NCT03937986, NCT03789214, NCT03657355.

To date, the effects of the opioid receptor antagonist naloxone on sleep apnea have been mixed,[119,120] and respiratory drive suppression and depression of the hypoglossal nerve activity remains a critical problem. The use of ampakines, modulators of α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) glutamatergic receptors that mediate the excitatory transmission of respiratory centers and the cranial nerve XII (hypoglossal nerve), may counteract mu-opioid receptor–mediated depression; this offers the promise that it may be possible to maintain analgesia while preventing the unwanted respiratory depression that accompanies opioids.[121-125] Intranasal leptin can augment hypercapnic and hypoxic sensitivity, prevent opioid-induced SDB, and has been demonstrated to improve survival after overdose in mouse models. Thus, this therapy has the potential to be of benefit in opioid-induced SDB, particularly those with major hypoventilation.[126,127] However, this work has not yet been translated to humans. New emerging pharmacotherapies to treat OSA have recently reported both using metabolic modulation and targeting the nonanatomic physiologic traits.[128-131] However, these approaches may be beneficial for opioid-related SDB, but this requires further investigation in this target population.

## SUMMARY

OUD is a chronic and relapsing brain disease characterized by loss of control over opioid use. Sleep deficiency is present in greater than 75% of patients with OUD. The focus of this

article is to highlight bidirectional mechanisms between OUD and sleep deficiency and point toward promising therapeutic targets. Behavioral, pharmacologic, and PAP interventions targeting sleep deficiency may ultimately help promote long-term, healthy recovery among patients with OUD.

## DISCLOSURE

Agency: NIH/NHLBII.D.#: U01 HL150596Title: The Collaboration Linking Opioid Use Disorder and Sleep (CLOUDS") Study.

H.K. Yaggi is supported by U01 HL150596, R01 NR018335, K24 HL132093.

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## CLINICS CARE POINTS

- OUD is a subset of substance use disorder and a chronic and relapsing brain disorder characterized by loss of control over opioid use and deficits in cognitive function, mood, pain perception, and autonomic activity.
- Relapse rates are high (even in treatment) and are associated with lack of retention in treatment and a continued cycle of setbacks and return to use, risk for injection-related infectious complications, overdose, and death. To achieve better outcomes for individuals who are maintained on MOUD, there is a critical need to identify novel strategies and new approaches to complement or even enhance MOUD programs and foster skills necessary for long-term recovery. One promising strategy is to identify and target a neurobiological system that may be linked to OUD relapse, namely the sleep and circadian system.
- Sleep deficiency accompanies OUD across the *trajectory* of this disorder from initial medical or recreational use through misuse, addiction, recovery, setbacks, return to use, overdose, and death.
- There are bidirectional (and mutually reinforcing) mechanisms between sleep deficiency and OUD.
- There are behavioral, PAP, and pharmacologic interventions targeting sleep deficiency that may help to improve symptoms and outcomes among patients with OUD; these include CBTi, ASV, mirtazapine, melatonin, and DORAs.
- Ampakines and intranasal leptin are experimental therapies that offer promise in reducing the unwanted respiratory depression associated with opioids.

**KEY POINTS**

- Opioid use disorder (OUD) is a chronic and relapsing brain disease characterized by loss of control over opioid use and impairments in cognitive function, mood, pain perception, and autonomic activity.
- Sleep deficiency, a term that encompasses insufficient or disrupted sleep due to multiple potential causes, including circadian disruption, and poor sleep quality, is present in greater than 75% of patients with OUD.
- This article focuses on existing bidirectional mechanisms between OUD and sleep deficiency and points toward promising therapeutic targets.
- Behavioral, pharmacologic, and positive airway pressure interventions targeting sleep deficiency may ultimately help promote long-term, healthy recovery among patients with OUD.

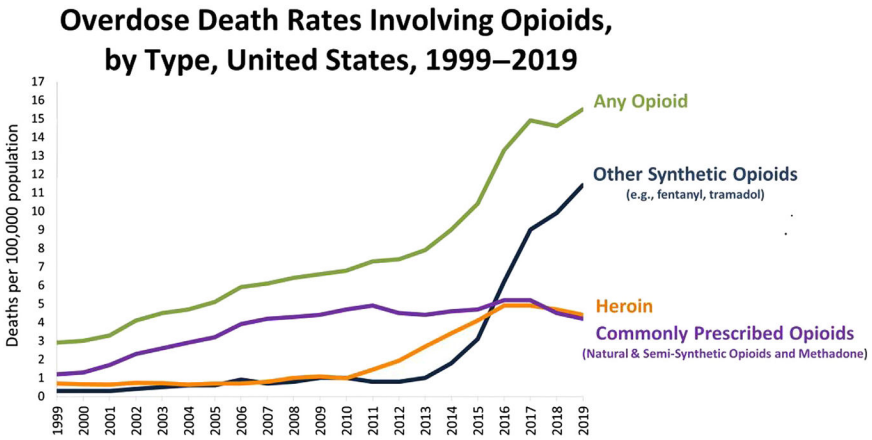


**Fig. 1.**

The 3 epidemiologic “waves” of overdose deaths involving opioids: prescribed opioids, heroin, and synthetic opioids. (*Data from* CDC/NCHS, National Vital Statistics System, Mortality. CDC WONDER, Atlanta, GA: US Department of Health and Human Services, CDC; 2020. https://wonder.cdc.gov/.)

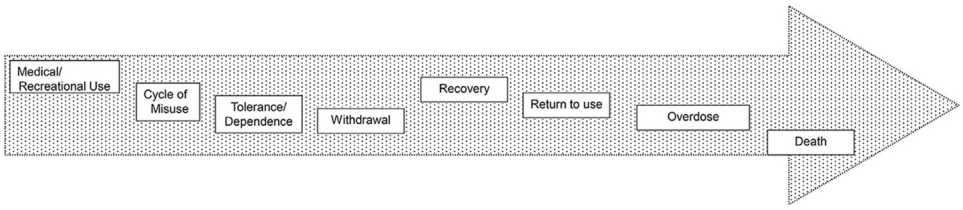


**Fig. 2.**
Opioid use disorder trajectory.

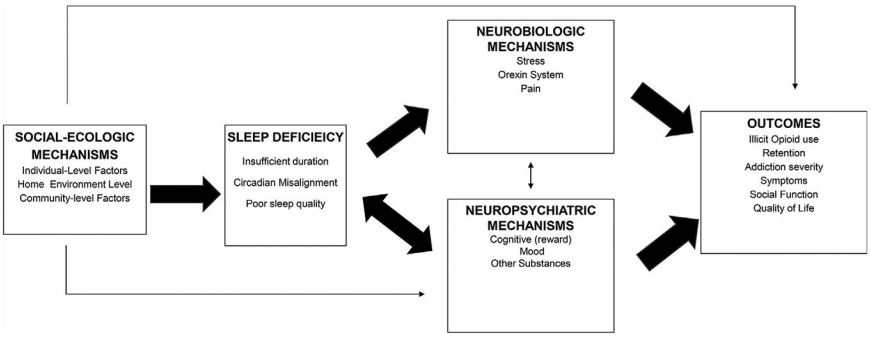


**Fig. 3.**

An organizing framework for the neurobiologic, neuropsychiatric, and social-ecologic mechanisms for sleep deficiency influencing outcomes along the trajectory of opioid use disorder.

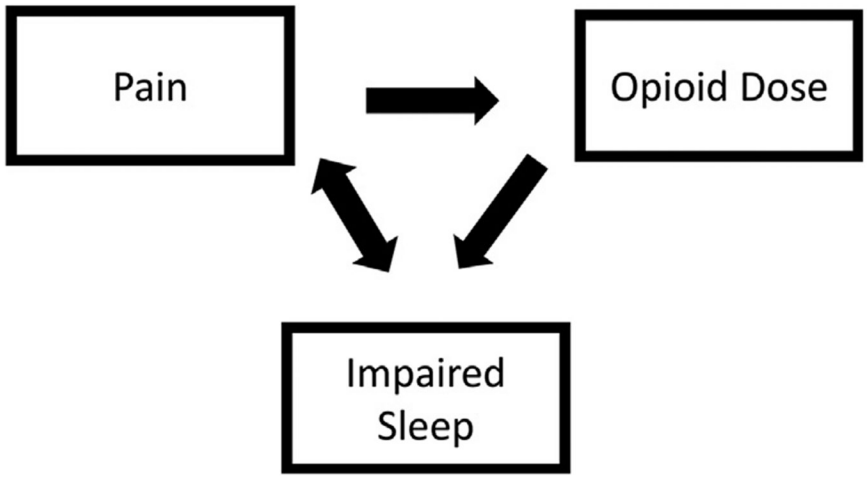


**Fig. 4.**
Pain, opioid, sleep-deficiency cycle.

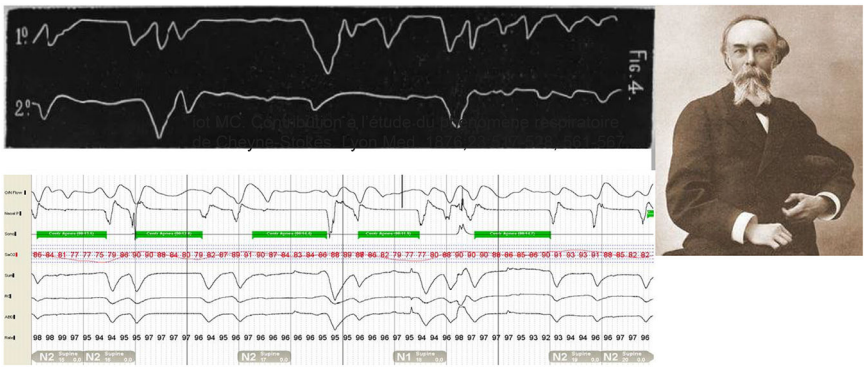


**Fig. 5.**

A current tracing compared with an original tracing from Biot's Respiration: Ataxic Breathing with Opioid Use. (*From* Camille Biot. Contribution a l'étude du phénomène respiratoire de Cheyne-Stokes. Lyon Med. 1876;23:517-528.)

**Table 1**

Acute and chronic effects of opioids on sleep

| | Acute Use | Chronic Use |
|---|---|---|
| REM latency | ← | ← |
| % REM sleep | ← | ← |
| % Light (N1/N2) sleep | ← | ← |
| % Deep (N3) | ← | ← |
| Total sleep time | Unchanged | Unchanged |
| Number of arousals/sleep disturbances | ← | ← |

*Abbreviation:* REM, rapid eye movement.