REVIEW ARTICLE OPEN

Found in translation: orexin receptor antagonism for the treatment of opioid use disorder

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Existing pharmacological treatment options for opioid use disorder (OUD) face challenges that limit their efficacy. Accumulating preclinical evidence implicates the orexin/hypocretin system in numerous aspects of OUD development and symptomology: opioid use, opioid-associated cue-driven drug seeking, and opioid withdrawal states that lead to relapse. Further, these studies indicate that selective and dual orexin receptor antagonists (SORAs and DORAs) could constitute promising treatments for OUD and other substance use disorders. Several DORAs have already been approved by the FDA for the treatment of insomnia, making their prospective repurposing potentially straightforward. To this end, recent clinical trials have demonstrated multifaceted efficacy of DORAs for ameliorating opioid craving, withdrawal, and related sleep disturbances in individuals with OUD. Consequently, warranted calls are mounting for the broader use of these agents in the treatment of OUD. This review adopts a translational approach to achieve several aims: (1) to outline the fundamental theories of orexin system function and relate orexinergic dysfunction to the disordered motivation and withdrawal states that characterize OUD; (2) to provide an up-to-date evaluation of preclinical and clinical evidence bases supporting the efficacy of orexin receptor antagonism for the treatment of OUD; (3) to discuss key clinical considerations of repurposing DORAs for OUD treatment, including safety and side effects (i.e., respiratory depression, anhedonia, and risk for abuse); and (4) to highlight the ongoing clinical efforts to determine therapeutic efficacy and safety profiles of DORAs for use in OUD populations.

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INTRODUCTION

Opioid use disorder (OUD) continues to pose a grave public health crisis in the United States and internationally. OUD is characterized by excessive motivation to obtain and use opioids, opioid tolerance, inability to cease opioid use, and withdrawal symptoms during opioid abstinence that often lead to relapse. Based on data from the National Institutes of Health, prevalence estimates suggest around 6.7–7.6 million US citizens were living with OUD in 2019 [1], and the 12-month incidence of overdose deaths involving opioids increased to over 80,000 in 2023 [2]. Current pharmacological treatments for OUD involve opioid agonist treatments, including buprenorphine and methadone. These treatments can be highly effective at reducing opioid use and represent an critical first-line treatment approach, but some issues challenge the utility of these interventions; for example, treatment is often chronic (months to years), and long-term use can lead to iatrogenic addiction and side effects that include impaired cognitive ability and respiratory depression [3]. Opioid antagonists, including naltrexone, represent an alternative treatment strategy; these medications are relatively safe, however patient adherence to medication is low, with patients often expressing a desire for non-opioid alternatives. Thus, existing medication options for OUD face challenges that limit their efficacy, necessitating the development of alternative non-opioid therapies that attenuate craving, promote abstinence, and prevent relapse without severe side effects.

Preclinical literature and emerging clinical studies indicate that the hypothalamic orexin (also known as 'hypocretin') system may be a viable target for novel medications to treat several substance use disorders (SUDs), including OUD [4]. Orexin levels are persistently elevated following opioid use in laboratory animals and humans, and this increase is causally linked with several core OUD symptoms, including drug craving elicited by environmental stimuli (e.g. drug-associated cues) [5–10]. Accordingly, orexin receptor antagonists are highly effective in preclinical models of OUD at decreasing a range of OUD-related behavioral outcomes [11–13]. Critically, the orexin system is also a known mediator of stress, anxiety, and sleep disturbances, and there is some evidence that orexin receptor antagonists ameliorate these outcomes during acute opioid withdrawal. Thus, orexin receptor antagonists may reduce return to use (i.e., relapse) in OUD patients via two interconnected mechanisms: (1) by reducing drug seeking and cravings that occur in response to drug-associated stimuli; and (2) alleviating aversive withdrawal symptoms that contribute to relapse via negative reinforcement processes [14]. Such treatments may have utility as standalone therapies or as adjuncts to existing opioid-based therapies [15].

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One of the largest impediments to rapid implementation of novel treatments for OUD in the USA is the elaborate Food and Drug Administration (FDA) approval process. In contrast to other potential OUD therapeutics currently in the drug development pipeline, several dual orexin receptor antagonists (DORAs) are already approved for clinical use in the United States (and many other countries) for the treatment of insomnia. Suvorexant, marketed as Belsomra® (Merck), was the first DORA to gain FDA approval (in 2014); two other DORAs—lemborexant (Dayvigo®, Eisai) and daridorexant (Quviviq®, Idorsia Pharmaceuticals)—were subsequently approved in 2019 and 2022, respectively. Extensive clinical trial and post-marketing data indicate that DORAs have low risk for dependence, tolerance, misuse, and withdrawal [16], which is significant as conventional sleep medications can worsen withdrawal symptoms or lead to new dependence on the sleep medication in individuals with substance use disorders (SUDs) [17]. Considering these characteristics, there has been recent mounting interest in the potential repurposing of DORAs as novel pharmacological treatments for OUD. In fact, orexin receptor antagonists and negative allosteric modulators were listed in the National Institute on Drug Abuse's top 10 medication development priorities for responding to the opioid crisis [18]. This recently culminated in the first-ever clinical studies testing DORAs in OUD patients; these preliminary studies indicated that in combination with a buprenorphine/naloxone taper, suvorexant improved several outcomes during initial abstinence, including sleep and drug craving [19, 20]. Here, we outline the major developments that have led to this point and provide an up-to-date overview of ongoing efforts to characterize the therapeutic utility of DORAs and alternative orexin receptor antagonists for OUD. While the role of orexin in OUD and substance use disorders (SUDs) more broadly have been discussed from various perspectives previously [21–24], here we highlight what we consider major priorities for ongoing work designed to optimize the safety and efficacy profile of these medications in OUD populations, particularly concerning respiratory depression, anhedonia, chronopharmacology, and risk for abuse.

THE OREXIN SYSTEM AND THEORIES OF OREXIN FUNCTION

Orexin peptides A and B (also called hypocretins 1 and 2) are produced by a small population of neurons in caudal hypothalamus. Initially identified as a mediator of feeding and arousal [25, 26], the orexin system has been subsequently implicated in a broad range of physiological and behavioral processes, including cardiovascular, respiratory, homeostatic and metabolic functions, as well as in reward and motivated behavior. This breadth of function reflects the widespread projections of orexin neurons throughout the brain [27–31], where they act at two G-protein coupled receptors, orexin receptor 1 (Ox1R) and orexin receptor 2 (Ox2R) [26, 32]. There is also some preclinical evidence that heterogeneity of orexin function is determined by the topography of cell bodies; under certain experimental conditions, the medial orexin field located in the dorsomedial (DMH) and perifornical (PF) regions of hypothalamus are preferentially engaged during periods of high arousal and anxiety, whereas those in the lateral hypothalamus proper (LH) are recruited during reward seeking, as reviewed by [33, 34]. This is rooted in evidence of anatomical specificity of projections; for example, DMH/PF orexin neurons preferentially innervate the amygdala, whereas those in the LH provide proportionately more dense input ventral tegmental area [35, 36]. Notably, while this medial/lateral dichotomy has been previously reported in other contexts (e.g., depressive behaviour [37]), the dichotomy is not generally reported in studies of reward and addiction in mice (discussed in [34]), and limited studies in humans make it difficult to determine the translational relevance of these anatomical effects in the context of OUD.

Motivational activation theory

A challenge for the field has been reconciling the apparent diversity of functions governed by the orexin system. Although best known for its role in regulating wakefulness and arousal, loss of orexin function (as in narcolepsy) does not result in loss of waking or produce changes in the total time spent awake relative to asleep, rather it is associated with unusual intrusions of sleep and wake in the active and rest periods, respectively [38, 39]. This complicates the role for orexin in wakefulness, as it is clear orexin is not acting as a simple 'on/off switch' but rather as a contributor to the stability and/or maintenance of wakefulness. In light of evidence that orexin neurons respond to several physiological need states (e.g., hunger, high CO_2 levels, glucose deficiency), Mahler, et al. [7] proposed a unified theory of orexin function: to translate motivational states associated with physiological need into coordinated and adaptive behaviors (a process termed '*motivational activation*'). Within this framework, increased signaling of orexin neurons would be considered a critical actuator of drug-directed behaviors following the presentation of stimuli that signal drug availability. Moreover, orexin neurons might also be expected to be activated during opioid withdrawal, in service of facilitating behavioral responses that alleviate this aversive state, including drug seeking and consumption (and thus, relapse).

Orexin reserve hypothesis

Extending on the motivational activation framework [7], we recently proposed that orexin's adaptive role in the regulation of motivation involves the ability of orexin neurons to actively modulate levels of orexin *peptide* production via the recruitment of a reserve pool of orexin neurons [8]. Evidence of reserve orexin neurons comes from studies showing that under baseline conditions, the number of orexin-immunoreactive neurons fluctuates by ~24% across the day-night cycle, with peak levels during the active period when the need for adaptive behaviors is highest [40]. In the case of SUDs, including OUD, it is proposed that the orexin system loses its ability to adaptively regulate peptide production: the previously acute, situational upregulation of orexin peptide production shifts toward constant and situationally inappropriate high levels of orexin production by the orexin reserve neurons [8]. Consequently, this chronic upregulation of the orexin reserve may contribute to hypermotivated drug seeking, particularly during opioid withdrawal (discussed in detail, below).

RECRUITMENT OF OREXIN NEURONS BY OPIOIDS AND ASSOCIATED STIMULI

Orexin neurons drive opioid-seeking behaviors

Opioids and stimuli associated with their use and reinforcing properties recruit the orexin system and modulate its activity. An early demonstration of this orexin-induced drive of opioid seeking was by Harris, et al. [41] who reported that orexin neurons exhibited markedly increased neuronal activiation (i.e., Fos expression) in rats exhibiting a conditioned place preference for morphine (as well as cocaine). Notably, the magnitude of orexin cell activity is proportional to the degree of morphine seeking behavior [41, 42]. The Harris study also indicated a causal relationship between elevated orexin activity and opioid seeking behavior: pharmacological stimulation of LH orexin neurons reinstated a previously extinguished morphine conditioned place preference. Recruitment of LH orexin neurons was later found to contribute to the acquisition of morphine conditioned place preference [43], and expression of morphine seeking behavior was shown to be dependent on Ox1R signaling [44]. Moreover, in mice with the gene coding for the orexin peptide removed, the expression of morphine-conditioned place preference was eliminated [45]. More recently, orexin signaling within specific nuclei [i.e., nucleus accumbens (NAc), ventral tegmental area (VTA), CA1

and dentate gyrus regions of the hippocampus] have been found to facilitate acquisition [46–48], expression [47, 49, 50], and reinstatement [51] of morphine conditioned place preference in rats. Extending beyond the focus on morphine, recent studies have also demonstrated a key role of orexin system activation in drug-seeking for the opioids fentanyl [5, 52] and remifentanil [6, 53, 54]. Taken together, opioids and their associated stimuli activate the orexin system, and exogenous stimulation of these neurons promotes opioid-seeking behavior.

Orexin neurons are activated by opioid withdrawal

Orexin neurons are also recruited during opioid withdrawal, implicating these cells in the aversive aspects of OUD. The first clear demonstration of this phenomenon was performed by Georgescu, et al. [9], who reported that opioid antagonist-precipitated morphine withdrawal in mice activated orexin neurons and induced orexin peptide gene expression in these neurons. Moreover, mice lacking the gene for the orexin peptide exhibited markedly blunted opioid withdrawal signs compared to wildtype mice [9]. Other studies reported that opioid withdrawal-like signs in rodents correlated with increased orexin neuron activity [55], and that orexin mRNA expression in the LH was elevated during spontaneous withdrawal from chronic morphine administration [56]. Several studies have also identified orexin-mediated mechanisms of morphine withdrawal specifically within the locus coeruleus (LC) [57]; for example, intra-LC administration of orexin-A produced morphine withdrawal-like signs in both morphine-dependent and morphine-naïve rats via activation of Ox1Rs [58]. Thus, increased orexinergic tone may underlie opioid withdrawal symptoms, and the orexinergic system's wide range of functional targets may be responsible for this manifestation of numerous and diverse symptoms of withdrawal syndrome.

Chronic opioid exposure recruits the 'orexin reserve'

As noted above, orexin neuron numbers are highly dynamic, fluctuating in accordance with behavioral state in service of adaptive behaviors. This plasticity of peptide production is lost following repeated drug use, as persistently higher numbers of orexin-immunoreactive neurons are observed in rats with a history of intermittent self-administration of fentanyl [52] and in mice following experimenter-administered morphine [59–61]. The extent to which additional orexin neurons are engaged appears to be associated with drug seeking, as the number of LH orexin neurons positively correlates with behavioral economics metrics of motivation for fentanyl and heroin [11, 52] (similar effects are reported for cocaine [62]). These findings in laboratory animals align closely with clinical research studies, which show that orexin peptide levels are elevated in the cerebrospinal fluid (CSF) of opioid users, and higher numbers of orexin neurons in the hypothalamus of postmortem heroin users [59, 63]. Increased numbers of orexin cells following opioid use is not due to neurogenesis [59], lending further support to the notion of a 'reserve' orexin neurons capable of adjusting orexin peptide levels according to behavioral state, as reviewed by [8]. This recruitment of the orexin reserve is also observed in response to other drugs of misuse [64–66], highlighting a general role for these neurons in the hypermotivation for drugs in SUDs.

Collectively, this evidence of elevated orexin reserve activity in humans and animals following opioid exposure likely reflects a loss of plasticity in the orexin reserve pool [8]. This constant engagement of the orexin reserve neuronal population—and, consequently, persistent upregulation of orexin system activity—plausibly contributes to (1) hypersensitivity to opioid-associated contextual cues and greater motivation to seek opioids, and (2) more intensely aversive opioid withdrawal states that mediate a heightened risk of relapse. Thus, the use of orexin receptor antagonists to pharmacologically attenuate orexin signaling represents a potential avenue to treat both of these aspects of OUD.

PRECLINICAL EVIDENCE SUPPORTING OREXIN RECEPTOR ANTAGONISTS AS TREATMENTS FOR OUD

As orexin signaling occurs via the activation of two receptor subtypes, Ox1Rs and Ox2Rs, pharmacological antagonism of orexin signaling can involve the selective inhibition of either orexin receptor subtype using selective orexin receptor antagonists (Ox1R or Ox2R SORAs) or inhibition of both receptor subtypes using dual orexin receptor antagonists (DORAs) [67]. Most experimental research investigating the therapeutic potential of orexin receptor antagonists for OUD-relevant outcomes has been conducted in preclinical rodent models, which are advantageous for characterizing the functional neural circuits that drive opioid motivation, opioid-seeking behavior, and withdrawal-like outcomes. While we have partly addressed orexin receptor antagonism in preclinical models above, here we comprehensively detail important aspects of preclinical orexin antagonist-based modulation as treatments for OUD-relevant behaviors.

Opioid motivation and intake

Opioid self-administration models represent preclinical assays of opioid motivation that align with volitional drug use in humans with OUD. These procedures typically require an operant response, such as a lever press or nose poke, to yield an intravenous infusion of heroin, fentanyl, oxycodone, or another opioid. When the effort required to obtain opioid infusions is low (e.g., fixed ratio-1 [FR1], where one lever press results in one infusion), evidence indicates that orexin receptor antagonism can reduce opioid intake. For example, systemic administration of an Ox1R SORA reduced FR1 intake of heroin [68] and oxycodone [69], and systemic administration of the DORA suvorexant also acutely (i.e., for the first hour post-administration) reduced FR1 oxycodone intake [70]. Further, systemic administration of an Ox2R SORA (NBI-80713) was sufficient to reduce heroin intake, but only in rats receiving extended access (i.e., 12 h) to heroin self-administration [71]. However, Ox1R antagonism did not impact remifentanil intake under low effort conditions [53], and Ox2R antagonism using the SORA TCSOX229 had no effect on oxycodone intake [69]. Thus, Ox1R SORAs and DORAs are generally effective at reducing low-effort opioid intake, although this may vary across opioids, potentially due to differences in their pharmacokinetic properties (e.g., half-life). In contrast, the efficacy of Ox2R SORAs might be limited to rats with a history of extended opioid exposure.

Orexin receptor antagonists are also generally effective at reducing responding on behavioral models that assess motivation for opioids (i.e., involving higher effort for each drug infusion). One such procedure is progressive ratio breakpoint: the effort required to earn an opioid infusion progressively increases following every infusion and the 'breakpoint' is an animal's highest effort-to-reward ratio reached during the test [72]. Only one study has tested the effects of blocking orexin signaling on PR responding for an opioid: systemic administration of the Ox1R SORA, SB-334867, dose-dependently reduced breakpoints for heroin [68]. More recently, behavioral economics has emerged as a powerful approach for assessing opioid motivation, whereby consumer demand theory is used to represent experimentally derived opioid consumption data as a function of price [73]. Exponential demand equations are then used to compute multiple variables indicative of distinct behavioral constructs [74]. Primary among these variables is alpha, which reflects demand elasticity, or the rate at which drug consumption decreases with increases in 'price' (price is often manipulated by decreasing the duration of drug infusions throughout a session, thus increasing the number of responses required to earn a steady unit dose of drug). Alpha is thus often interpreted as a measure of drug motivation, which is dissociable from drug intake (defined in behavioral economics as Q_0, or intake at null cost). Notably, despite the capacity to suppress low effort responding for opioid rewards (i.e., FR1), the influence of orexin

receptor antagonism on Q_0 in behavioral economic procedures—which is conceptually similar to FR1 responding—does not fully recapitulate these results. For example, whereas systemic OxR1 antagonism reduced Q_0 for remifentanil [6, 54], similar outcomes are not observed for fentanyl [52]. This discordance appears to be specific to opioids, as Ox1R antagonists have no effect on FR1 responding or Q_0 levels for cocaine [64, 75–77] (although see [78]). Why Ox1R antagonists reduce FR1 intake for opioids (but not other drugs) and lower Q_0 levels for some (but not all) opioids is currently unclear and worthy of further investigation. Studies utilizing the behavioral economics approach generally indicate that inhibiting orexin receptor signaling increases demand elasticity (i.e., reduces motivation) for opioids. Indeed, pretreatment with the Ox1R SORA SB33486 increased demand elasticity for both fentanyl and remifentanil [52, 53]. In the case of remifentanil, these effects are partly mediated by actions at ventral pallidum, as local administration of an Ox1R SORA largely recapitulated the effects of systemic administration [6]. Similarly, systemic treatment with the DORA suvorexant increase demand elasticity for fentanyl [12].

Recently, there has been a shift toward using models of drug self-administration that better approximate human drug use patterns. Notable in this regard is the increasing utilization of intermittent access self-administration models, where brief drug-available periods are separated by longer periods of drug non-availability [79–82, 64]. When applying behavioral economics analyses to intermittent access models, intermittent access to fentanyl and heroin promotes lower demand elasticity for these drugs, indicating that this procedure is effective at shifting baseline motivation for these drugs [83]. These changes in demand are reversed by treatment with either an Ox1R SORA (SB334867) or a DORA (suvorexant) [12, 52], indicating that orexin signaling is necessary for the expression of higher motivation states for opioids. Interestingly, in these studies, lower doses of SORA and DORA were sufficient to reduce drug motivation following intermittent access, whereas ~3-fold higher doses were needed to produce similar effects prior to intermittent access [12, 52]. Similar effects have been observed for other drugs of abuse, including cocaine [84, 64]. Thus, intermittent schedules of opioid self-administration are effective at promoting enhanced drug motivation, and this shift occurs in an orexin-dependent manner.

Opioid-associated cue reactivity and reinstatement

Return to opioid use during abstinence represents a major problem for individuals with OUD and is often triggered by stress, re-exposure to the drug itself, or exposure to opioid-associated cues and contexts. Preclinical models of "relapse" typically involve an assessment of reinstatement of opioid seeking behavior, elicted by opioid priming, stress, or opioid-associated cues [85]. However, the translational homology of promoting non-reinforced drug-seeking behaviors due to environmental or internal cues (e.g., stress, stimuli, or drug-primed) is poor compared to what comprises relapse in the clinical condition (i.e., a direct return to substance use), which has likely contributed to the poor prospective predictive validity and translation of these models [86]. Thus, while these reinstatement models still provide valuable insight for evaluating cue reactivity and the role of opioid-associated cues in opioid-seeking behavior, interpretation as clear-cut translatable models of relapse should be avoided.

Early evidence of a role for orexin signaling in reinstatement behavior came from studies utilizing conditioned place preference assays: systemic treatment with the Ox1R antagonist SB334867 blocked reinstatement of an extinguished place preference for morphine elicited by chemical activation of orexin neurons [41]. Subsequent studies demonstrated that orexin acts at various central sites to mediate this type of reinstatement behavior: infusions of Ox1R SORAs into the NAc shell and DG attenuated stress-induced and drug-primed reinstatement of morphine seeking, respectively [51, 87, 88]. Similarly, localized Ox2R antagonism suppressed stress-induced reinstatement (intra-NAc shell) [87], stress- and morphine-primed reinstatement (intra-VTA) [89], and morphine-primed reinstatement (intra-DG) [51]. Collectively, this evidence suggests that orexin receptor antagonism of Ox1Rs and Ox2Rs can reduce the influence of opioid-associated contextual cues on drug-seeking behavior.

In self-administration models, volitional actions (i.e., lever presses) that earn opioid infusions can be paired with discrete cues such as lights and tones, which can then be used to reinstate extinguished opioid-seeking and investigate the influence of these associated cues on responding for opioids. Consistent with orexin neurons 'translating' environmental information into motivated, drug-directed behavior, orexin receptor antagonists are particularly effective at reducing drug seeking elicited by external stimuli. Systemic Ox1R SORA administration reduced cue-induced reinstatement to remifentanil [6, 53], fentanyl, oxycodone, and heroin [5, 52, 68, 69]. In the case of remifentanil, these effects are recapitulated in part by intra-ventral pallidal infusions of Ox1R SORAs [6]. Interestingly, although one study found no effect of an Ox2R SORA on oxycodone reinstatement [69], other studies using DORAs have demonstrated efficacy on reinstatement outcomes. Chronic DORA-12 treatment during opioid abstinence attenuated discriminative stimulus-induced reinstatement of oxycodone seeking [90], and acute administration of suvorexant reduced cue-induced reinstatement of fentanyl seeking in rats with a history of intermittent fentanyl self-administration [12]. Moreover, treatment with DORA-12 (which has similar properties to suvorexant) decreased cued reinstatement of heroin seeking even in the presence of competing food cues [11]. Ox1R SORAs and DORAs also potently reduce cue-elicited seeking of other drugs, including cocaine and alcohol [12, 34, 91], underscoring a general role for the orexin system in facilitating motivated behavior in response to relevant environmental stimuli.

Opioid withdrawal

Preclinical models are useful for studying withdrawal, as rodents exhibit readily observable withdrawal-like symptoms such as chewing, jumping, wet-dog shakes, and diarrhea, as well as heightened stress, anxiety, and sleep disturbances [92–94]. A withdrawal state following chronic opioid use in rodents is typically induced by either spontaneous forced abstinence from opioid or by administration of an opioid receptor antagonist (e.g., naloxone). Acute and chronic systemic administration of an Ox1R SORA (SB334867) can attenuate naloxone-precipitated withdrawal-like signs [10, 55, 95] and reduce anxious behaviour during spontaneous morphine withdrawal [96] in rodents. Furthermore, localized acute administration of an Ox1R SORA in the LC [97], lateral paragigantocellularis [98], and dorsal hippocampus [99] also ameliorated naloxone-precipitated withdrawal-like signs. Additionally, intra-LC administration of Ox1R SORA blocked orexin-induced and glutamate-induced morphine withdrawal-like signs [58, 100], and intra-VTA Ox1R SORA administration decreased anxious behavior during spontaneous morphine withdrawal in male mice [96]. Although the efficacy of Ox2R SORAs and DORAs in attenuating opioid withdrawal-like signs has yet to be fully explored in preclinical models, their efficacy at promoting sleep indicates that these agents would be expected to normalize sleep disturbances that emerge in animals during withdrawal [101–105].

CLINICAL EVIDENCE FOR THE EFFICACY OF OREXIN RECEPTOR ANTAGONISTS IN TREATING OUD

Based on these promising effects of orexin receptor antagonists in preclinical studies, there has been recent mounting clinical interest in testing the utility of DORAs in clinical populations

[14, 106]. Furthermore, given parallels in the orexin neurobiology of chronic opioid exposure in humans and animals, such as increased numbers of orexin-producing neurons [59] and increased serum orexin [107], a strong rationale exists for the potential translational capacity of orexin receptor antagonism for the clinical treatment of OUD. Accordingly, the past 5 years has seen a surge in studies designed to evaluate the efficacy and safety of these pharmacotherapeutics in OUD (and other SUD) populations, with outcomes so far largely aligning with those of foundational preclinical studies.

To-date, the landmark randomized controlled trial (RCT) conducted by Huhn, et al. [19] represents the most convincing and ecologically valid evidence available supporting the efficacy of orexin receptor antagonists for the treatment of OUD-related withdrawal and craving. Individuals underwent a 4 d stepwise buprenorphine/naloxone taper as in-patient treatment for opioid withdrawal and received evening administration of the DORA suvorexant (20 and 40 mg) or placebo [19]. Relative to those that received buprenorphine/naloxone + placebo, suvorexant markedly increased sleep duration both during the taper (1.5 h/night increase, on average) and post-taper (~1 h/night increase, on average) periods—clinically relevant improvements according to American Academy of Sleep Medicine guidelines (i.e., ≥20 min/night increase) [108]. This is significant given the high prevalence and severity of sleep disturbances experienced during opioid withdrawal [109] and opioid agonist treatments [110], which likely contribute to high rates of relapse to opioid use [14, 15, 111, 112]. Concomitant to these sleep improvements, suvorexant attenuated subjective severity of withdrawal symptoms during the post-taper but not the taper period [19]. Follow-up analyses of sleep electroencephalography during this in-patient treatment revealed complex associations between spectral power and opioid withdrawal severity: overnight during the taper period, suvorexant dose-dependently increased sigma power compared to buprenorphine/naloxone + placebo—indicative of sleep stability—and increases in sigma power were linked to greater reductions in subjective withdrawal severity [20]. Additionally, suvorexant treatment exhibited promising effects on multiple domains of opioid craving, reducing desire for use and enhancing subjective control over use [19]. Given that patients received suvorexant concurrent with buprenorphine/naloxone during the taper period and were compared to a buprenorphine/naloxone + placebo control group, it is hard to discern whether suvorexant alone may alleviate withdrawal severity during the acute withdrawal period. Nevertheless, this clinical trial provides clear evidence that dual orexin receptor antagonism treatment exerts beneficial effects for individuals with OUD, likely via a dual-faceted process of diminishing opioid cravings and assuaging withdrawal severity and associated sleep disturbances that can contribute to relapse.

Evidence also exists demonstrating the clinical efficacy of orexin receptor antagonism for the treatment of other SUDs, including for cocaine. In a proof-of-principle study carried out in non-treatment seeking patients (n = 20) with cocaine use disorder (CUD), Suchting, et al. [113] found that evening administration of suvorexant for 2w (10 and 20 mg/night for weeks 1 and 2, respectively) improved several relapse-related outcomes. This included improved subjective sleep quality and objective sleep outcomes, reduced physiological and psychological stress, enhanced inhibitory control, and diminished cocaine craving [113]. Notably however, these positive effects of suvorexant for CUD outcomes are not consistent across all clinical studies. Both Strickland, et al. [114] and Stoops, et al. [115] found that suvorexant treatment for at least 3 d (i.e., 5–20 mg/day) enhanced motivation for cocaine-seeking in individuals with CUD. The reason(s) for the inconsistency in results between opioid vs. cocaine using populations are unclear but might reflect differences in motivation to discontinue use (OUD patients were enrolled in an inpatient treatment center, whereas CUD patients were *not* treatment seeking). In addition, differential processes are theorized to underpin continued drug use and relapse between opioids and psychostimulants [116]; alleviation of withdrawal states and negative affect (i.e., negative reinforcement) for opioids [117] and pleasure-seeking (i.e., positive reinforcement) for psychostimulants [118].

Another important clinical consideration of relevance to OUD and the efficacy of orexin receptor antagonism is pain [119], which is a known contributor to the initiation of opioid use and the subsequent development of OUD [120, 121]. Clinical evidence also supports a bidirectional interaction between sleep and pain [122]; sleep disturbance can contribute to hyperalgesia [123–125] and sleep disturbances are highly prevalent in individuals experiencing chronic pain [126, 127]. Thus, the efficacy of orexin receptor antagonism in the treatment and management of pain and pain-related sleep disturbances would likely result in beneficial outcomes for individuals with OUD and comorbid pain and/or sleep disturbances [128]. Most experimental studies investigating the role of orexin and orexin receptor antagonism in pain are preclinical [129], however some preliminary clinical studies have been conducted. The findings from these studies are mixed. Numerous regions of the central nervous system critical for pain modulation receive projections from orexinergic neurons, and activity within these connections can enhance or reduce nociception [130]. Most studies have demonstrated that orexin system agonism, via local injections of orexin-A into specific regions that regulate pain, produces analgesic effects and that Ox1R antagonism typically blocks or reverses this orexin-induced analgesia [24, 122, 129]. However, this influence of orexin receptor antagonism is complicated by evidence that the DORA suvorexant diminished chronic mild stress-induced hyperalgesia in mice [131] and nociceptive activity in trigeminal pain circuitry in rats [132]. These inconsistencies between orexin system agonism and antagonism for pain outcomes may be partially due to differences in the effects of orexin at distinct stages of acute vs chronic pain [24]. The clinical literature investigating orexin antagonism and pain syndromes is similarly mixed. For women experiencing fibromyalgia and comorbid insomnia, compared to placebo, treatment with suvorexant (20 mg/night for 9 nights) improved sleep (i.e., increased total sleep duration by 30 min and reduced sleep onset latency by 30 min) and reduced pain sensitivity in both the morning and evening [133]. Similarly, in their retrospective observational study of patients with chronic pain, Ueno, et al. [134] found that lemborexant (5 mg) reduced the severity of insomnia symptoms. However, no clear improvement in pain outcomes was observed [134]. This aligns with the RCT by Chabi, et al. [135], which found that administration of filorexant (10 mg/night for 3 months) in patients experiencing regular migraines (i.e., headaches) did not significantly reduce the frequency of migraines or headaches experienced. Given the heterogeneity of DORAs administered and pain syndrome populations sampled in these studies, it is difficult to draw conclusions of efficacy beyond the suggestion that—in cases of comorbid chronic pain, sleep disturbances, and OUD—orexin receptor antagonism may improve pain and/or sleep outcomes, which could facilitate concomitant improvements in OUD outcomes.

CLINICAL CONSIDERATIONS FOR USE

The therapeutic potential for orexin receptor antagonists in the treatment of OUD is clear, however since clinical investigation is still so preliminary in this space, numerous factors of implementation require thoughtful consideration.

Side effects, tolerability, and safety

Side effect profiles constitute a key factor influencing the decision to initiate and select a pharmacological treatment for individuals with OUD [136]. For methadone pharmacotherapy, a major side

effect of concern is drowsiness [136], which is also relevant to orexin receptor antagonists given their dampening of the wake-promoting arousal pathways [137]. For individuals with OUD undergoing buprenorphine/naloxone taper, Huhn, et al. [19] found no difference in the number of participants reporting daytime drowsiness as an adverse event following evening suvorexant (20 and 40 mg) and placebo administration. Similarly, no difference in the frequency of reported drowsiness/sedation was observed between evening placebo and suvorexant administration (10–20 mg) for individuals with CUD [113]. Hence, the limited evidence in SUDs populations indicate that suvorexant—at the doses and times administered—likely does not induce problematic levels of next-day drowsiness or sedation. Outside of individuals with SUDs, congruent evidence indicates a lack of substantial residual sedative consequences for next-day functioning in most individuals [137] following treatment with various orexin receptor antagonists, including suvorexant [138–140], the Ox1R SORA ACT-539313 [141] and the Ox2R SORA JNJ-4287922 [142]. However, contrary evidence exists demonstrating that orexin receptor antagonism can produce drowsiness in certain populations and circumstances [133, 143, 144].

Another key safety consideration for orexin antagonism-based treatment of OUD pertains to potential risks for outcomes of respiratory depression [145]. The primary mechanism involved in opioid overdose-related fatalities is respiratory depression; that is, hypoventilation leading to protracted apnea, and consequent cardiopulmonary arrest [146]. Critically, the concurrent use of benzodiazepine sedative medications often used to counter sleep disturbances alongside opioids—including those used as opioid agonist treatments for OUD such as methadone and buprenorphine—can produce synergistic increases in the rate of onset, magnitude, and duration of respiratory depression over and above use of either substance alone [147]. Activity of the orexin system also influences respiratory function, primarily via innervation of the pre-Bötzinger region of the rostral ventrolateral medulla that regulates rhythmic breathing and phrenic motoneurons that innervate the diaphragm. The pre-Bötzinger region and phrenic motoneurons express Ox1Rs and Ox2Rs and respond in a dose-dependent manner to orexin administration by increasing diaphragmatic muscle activity [148, 149]. Thus, it is possible that administration of SORAs or DORAs for dampening orexinergic activity to improve OUD symptoms and related sleep disturbances could exacerbate the respiratory depressive consequences of opioids. Despite this, scant clinical and preclinical research has investigated the influence of co-administration of opioids and orexin receptor antagonists on outcomes of respiratory depression. In their RCT, Huhn, et al. [19] found no evidence of exacerbated respiratory depression during suvorexant treatment (20 and 40 mg/day) in OUD patients undergoing the buprenorphine/naloxone taper. However, it is worth noting that buprenorphine/naloxone was administered in the morning, whereas suvorexant was administered in the evening, and thus peaks in bioavailability of the two agents did not overlap. To this end, one preclinical study examined the co-administration of 60 mg/kg suvorexant and 150 mg/kg oxycodone in rats; despite a trend towards the combination increasing arterial pCO_2 levels at later time points (2 and 3 h), this interaction was not statistically significant [150]. In contrast, a more recent preclinical study identified respiratory depression using whole-body plethysmography in rats when suvorexant (18 mg/kg) and oxycodone (3 mg/kg) were co-administered, but not when a lower dose of suvorexant (10 mg/kg) was co-administered nor when suvorexant (10 and 18 mg/kg) was administered alone [151]. Inconsistencies in these outcomes may derive from differences in methodology (i.e., blood gas analysis vs ventilation), dose, and route of administration; it is possible that the high oxycodone dose in the former study may have produced a ceiling effect obscuring a further depressive effect of suvorexant [151]. In isolation, the frequency of reported respiratory depression during orexin receptor antagonist treatment is rare compared to benzodiazepine and non-benzodiazepine sleep medications [152]. Evidence from placebo-controlled RCTs also supports a safe profile of DORAs for sleep-related respiratory outcomes, including in patients with mild-to-moderate chronic obstructive pulmonary disorder [153], mild-to-moderate obstructive sleep apnea [154–157], and in healthy individuals [158]. Although these studies involved relatively small samples and short durations of DORA treatment (i.e., 1–8 days), this evidence indicates that DORAs administered alone at approved clinical doses pose little risk for nighttime respiratory depression. Taken together, there is currently no clinical evidence and no consensus of preclinical evidence definitively linking DORAs with exacerbation of opioid-induced respiratory depression, however there is a clear need (based on recent data) to characterize these outcomes more extensively, particularly in the potential case that an individual undergoing DORA treatment relapses on potent opioids. As it is also likely that the risk of respiratory depression following opioid-DORA co-administration would increase with higher doses of opiates, the dose-dependency of this drug-drug interaction warrants critical future study.

Another potential side effect of concern for orexin receptor antagonism-based clinical treatment is anhedonia (i.e., the loss of motivation) towards natural rewards (e.g., food, social interaction, sexual activity, etc.). While the clinical evidence assessing the effects of orexin receptor antagonism on anhedonia is limited, some insight can be gained from consideration of these effects in clinical trials for major depressive disorder, of which anhedonia is a cardinal symptom [159]. Savitz, et al. [160] found that the Ox2R antagonist seltorexant administered at night (20 mg for 6w) reduced depressive symptomology compared to placebo, although because this drug also improves sleep, it is difficult to ascribe mood improvements to direct or indirect (i.e., sleep-mediated) mechanisms. The majority of clinical studies testing the DORAs filorexant or seltorexant have found no change in mood [161–163]. The lack of significant increases in depressive symptomology suggests that orexin receptor antagonism likely does not exacerbate existing anhedonia, and consequently, may not induce a loss of motivated behavior in non-depressed individuals. Although not assessing motivation for natural rewards, this is congruent with the clinical studies by Strickland, et al. [114] and Stoops, et al. [115], which demonstrate increased—not reduced—motivation for cocaine.

It is also promising that in several of the aforementioned clinical studies, treatment with orexin receptor antagonists was reported as "well tolerated" [115, 137, 141, 142, 164] and high compliance was observed in a SUD population (96%) [113]. Additionally, most of these studies report an absence of major adverse events [137, 141], including in the OUD RCT by Huhn, et al. [19], and even in the case of toxicity or overdose, no major effects were observed [165], and intensive treatment was not required [166]. Taken together, this evidence supports the tolerability and safety of employing orexin receptor antagonist-based treatments for individuals with OUD.

Chronopharmacology

Consideration of chronopharmacology [167]—how orexin receptor antagonism might interact with circadian processes relating to sleep and opioid use—requires further experimentation and might guide the optimal timing of administration. Prescribing guidelines for clinically available DORAs mandate evening dosing (i.e., at bedtime) [168]; this aligns with relatively short Tmax values of these compounds (for sleep induction) and is intended to avoid next day somnolence [137]. However, because of the relatively long elimination half-lives of these drugs (~6-55 h), next-day effects of DORAs on drug craving/seeking [19, 113] might reflect indirect consequences of improved sleep, combined with more

minor direct effects of residual bioavailable orexin receptor antagonism during the day. Although further research is required to validate this above assertion, if accurate, it might be the case that nighttime dosing could be augmented by daytime administration of a non-sedating dose, thus targeting both indirect and direct processes [15]. Alternatively, based on evidence that Ox1R SORAs have markedly reduced effects on arousal compared to DORAs [141], optimal treatment may involve 1) daytime SORA administration to reduce craving and opioid-associated cue reactivity (i.e., when opportunity for drug use is high) with minimal sedation, and 2) nighttime DORA administration to additively alleviate withdrawal severity and related sleep disturbances.

Consideration should also be given to appropriate dose ranges for SORAs and DORAs, and potential challenges associated with their chronic use. Both Huhn, et al. [19] and Suchting, et al. [113] observed positive effects of suvorexant at a dose of 20 mg/night—the maximum daily FDA-approved dose for insomnia treatment [169]. Notably, for individuals with OUD undergoing a buprenorphine/naloxone taper, a higher nightly dose of 40 mg was associated with slightly poorer outcomes relating to adverse events, particularly sedation, without improving efficacy [19]. Thus, 20 mg/night may represent the appropriate dose for treatment of opioid withdrawal and craving. Notably, these two studies administered suvorexant for relatively short periods (8 days [19] and 2 weeks [113]), so little is known about the optimal length of treatment required to offer long-term protection against return to use. Moreover, although there is evidence that patients do not develop tolerance to the sleep-promoting effects of DORAs following chronic treatment [170, 171], it is currently not clear if the same is in the context of OUD.

Risk for abuse

A concern with any drug designed to promote sedation is risk of misuse or diversion. The DORA class are currently categorized as Schedule IV controlled substances in the US according to the DEA, based on studies suggesting similar yet comparatively lower risk of abuse potential than current sedative medications such as zolpidem [172, 173]. Since individuals with OUD are at elevated risk of sedative hypnotic medication use [174], this scheduling currently limits the use of orexin receptor antagonists in OUD patient populations. However, as noted by Schoedel, et al. [172], while these experimental studies suggest *potential* abuse liability, retrospective post-marketing data should be used to assess *actual* abuse rates—a more accurate evaluation of abuse liability. Correspondingly, in recent years, petitions have been made for the DEA to de-schedule DORAs based on retrospective internet surveillance and data from FAERS (FDA Adverse Event Reporting System) demonstrating negligible risk liability profile in the community—exceptionally low incidence of rates of reported abuse and dependence, serious adverse events, and those events requiring hospitalization [16]. Additionally, there is an absence of known recreational (i.e., non-medical) use in communities [16] and no known 'black market' exists for suvorexant despite its approval for insomnia disorder treatment almost 10 years ago [19]. Consistent with this, in individuals with OUD, Huhn, et al. [19] demonstrated that the DORA suvorexant did not exhibit elevated risk for abuse compared to placebo: no differences in self-reported liking or 'experience of a high' and were observed, and these measures were both rated as low. Additionally, individuals assigned low monetary value to both doses of suvorexant (i.e., US$2.80–5.33) and this was not different from placebo, further indicating low abuse liability of orexin receptor antagonism within a clinical in-patient OUD treatment modality [19]. Thus, arguably, the revision of this scheduling may be appropriate to facilitate improved capacity for treatment of individuals with OUD, but prior to this decision, future clinical trials should assess abuse liability in OUD populations in long-term outpatient samples [19].

PRIORITIES FOR FUTURE STUDIES AND CONCLUDING REMARKS

Future directions

The preclinical evidence supporting the use of orexin antagonists as OUD therapeutics far outweighs the clinical evidence to date, and thus considerably more clinical research is needed before these treatments can be broadly adopted. The recent clinical trial in individuals with OUD undergoing a buprenorphine/naloxone taper by Huhn, et al. [19] showcases promise and enhances enthusiasm for the therapeutic potential of DORAs like suvorexant for the treatment of OUD symptoms. Longer-term, larger-scale clinical studies with greater sample sizes, including multi-center trials with greater sex/gender representation, are needed to fully evaluate orexin antagonists as OUD therapeutics. Since not all patients seeking treatment for OUD will be treated through in-patient programs, clinical trials are needed to assess the efficacy, safety, and abuse liability of orexin antagonists in populations from outpatient treatment programs, with a particular priority in the assessment of respiratory depression that may occur with opioid agonist treatment or a return to use (relapse) episode. Further research is needed to determine optimal doses of FDA-approved DORA medications and timing of administration to optimize treatment for different patient populations, including those with OUD and other comorbid conditions, such as mood disorders, chronic pain syndromes, and sleep disorders such as insomnia and obstructive sleep apnea. The investigation of circadian-informed combination therapies (e.g., DORA at nighttime and Ox1R antagonism during daytime) is also a priority, dependent on the approval of an Ox1R SORA for clinical use. Of the clinical trials currently investigating the therapeutic potential of orexin receptor antagonists for the treatment of OUD (see Table 1), it is promising that many trials address several of these issues by including outpatient components, a range of OUD severity and stages of OUD recovery, comorbid disorders with OUD (e.g., stimulant and opioid co-use), and other antagonists beyond only suvorexant (e.g., lemborexant [DORA], AZD4041 and INDV-2000 [Ox1R SORAs]).

On the preclinical side, studies are lacking that mimic the type of dosing regimen used in clinical studies. Since early evidence suggests that suvorexant taken nightly by mouth at bedtime is efficacious at reducing opioid craving and withdrawal symptoms [19], preclinical studies in animal models of OUD are needed that administer the DORA prior to the animal's sleep phase, repeatedly over days or weeks. Though many preclinical studies have controlled for potential acute sedative effects, studies employing such a dose regimen would shed new light on the ability of orexin antagonists to have therapeutic effects on OUD behaviors beyond the window of acute activity. Both preclinical and clinical studies are needed with repeated administration of orexin antagonists (both alone and in combination with opioid replacement therapies) to begin to assess the potential for tolerance to develop to the therapeutic and/or synergistic sedative or depressive respiratory effects of these agents. Further, studies that assess the efficacy of normalizing OUD-related sleep disturbances on opioid use and seeking behaviors (as has been shown previously for preclinical models of cocaine use and seeking behaviors [175, 176]), using orexin receptor antagonists and other sleep-promoting medications, would help determine whether sleep disturbances are a primary contributor to the maintenance of OUD. This would also serve to determine if neglecting sleep during OUD treatment may limit the efficacy of other interventions. Consideration should also be given to the potential effects of orexin medications on cognition and associated processes [177]. Finally, given the critical role of pain in the initiation and maintenance of opioid use, as well as its contribution to sleep disturbances, preclinical research investigating a variety of pain models concomitant with models of OUD are warranted.

Table 1. Current clinical trials investigating the therapeutic potential of orexin receptor antagonists for the treatment of opioid use disorder.

Orexin receptor antagonist	Dose information	Population	Study primary purpose	Phase(s)	Clinical trial number
Dual orexin receptor antagonists (DORAs)					
Lemborexant	5 and 10 mg; First and second visit, respectively	OUD; at least moderate severity	Adjunctive treatment alongside buprenorphine/naloxone	1 and 2	NCT04818086
Suvorexant	Dose not disclosed; Nightly dosing	OUD; recent fentanyl use	Adjunctive treatment alongside buprenorphine/naloxone (Includes outpatient component)	2	NCT05145764
Suvorexant	20 mg/day; Duration: ~14–16 days	OUD; at least moderate severity	Acute drug demand and subjective drug liking	1 (early)	NCT05829655
Suvorexant	20 mg/day; Nightly dosing (30 min prior to bedtime)	OUD; any severity	Improving sleep efficiency and opioid abstinence (Includes outpatient component)	2	NCT04262193
Suvorexant	20 mg/night; Patients can self-titrate to 10 mg/night	OUD; receiving outpatient opioid maintenance therapy (methadone, buprenorphine, or naltrexone)	Improving sleep and stress-related outcomes during early recovery from OUD (Includes outpatient component)	2	NCT04287062
Suvorexant	20 mg/day Duration: up to 30 days	Stimulant use disorder and OUD; receiving outpatient opioid maintenance therapy (methadone or buprenorphine)	Reducing co-occurring opioid and stimulant use (Includes outpatient component)	2	NCT05546515
Selective orexin receptor antagonists (SORAs)					
AZD4041 (Ox1R antagonist)	Dose not disclosed; Daily dosing for 7 days Days 1–3 treatment alongside hydromorphone; Days 4–7 treatment alongside buprenorphine or buprenorphine + naloxone	OUD; at least moderate severity Receiving buprenorphine or buprenorphine and naltrexone as treatment for opioid withdrawal	Evaluating efficacy and safety of AZD4041 to reduce opioid withdrawal symptoms	2	NCT06406400
INDV-2000 (Ox1R antagonist)	100–400 mg/day Days 1–7 treatment alongside buprenorphine; Day 8 onwards treatment alone	OUD; at least moderate severity New to treatment/recently initiated or completed short-term transmucosal buprenorphine/interested in transitioning to non-opioid treatment	Evaluating efficacy and safety of INDV-2000 to promote opioid abstinence (Includes outpatient component)	2	NCT06384157

All information was obtained from ClinicalTrials.gov.

Concluding remarks

We perhaps stand on the precipice of orexin receptor antagonists being broadly adopted for use in OUD populations [15]. This approach is supported by extensive preclinical studies as well as preliminary clinical evidence. Thus, DORAs and SORAs may soon become the first non-opioid-based FDA-approved treatments for OUD that address both drug seeking and cravings derived from opioid-associated stimuli, and the aversive withdrawal state that drives relapse. Moreover, orexin receptor antagonism is increasingly being explored as a viable treatment approach across other SUDs, including cocaine and alcohol use disorders, highlighting its potential as a broad treatment strategy for addictions and polysubstance use [4, 78]. We hope that as more clinical studies are conducted and further supporting evidence is gathered, these orexin-based agents will prove valuable tools for mitigating the opioid epidemic and substance use disorders in the near future.

REFERENCES

1. Keyes KM, Rutherford C, Hamilton A, Barocas JA, Gelberg KH, Mueller PP, et al. What is the prevalence of and trend in opioid use disorder in the United States from 2010 to 2019? Using multiplier approaches to estimate prevalence for an unknown population size. Drug Alcohol Depend Rep. 2022;3:100052.
2. Ahmad FB, Anderson RN, Cisewski JA, Rossen LM, Sutton P. County-level provisional drug overdose death counts. National Centerfor Health Statistics. 2025. https://doi.org/10.15620/cdc/20250305009..
3. Noble F, Marie N. Management of opioid addiction with opioid substitution treatments: beyond methadone and buprenorphine. Front Psychiatry. 2018;9:742. https://doi.org/10.3389/fpsyt.2018.00742
4. Mehr JB, Bilotti MM, James MH. Orexin (hypocretin) and addiction. Trends Neurosci. 2021;44:852–5. https://doi.org/10.1016/j.tins.2021.09.002
5. Fragale JE, Pantazis CB, James MH, Aston-Jones G. The role of orexin-1 receptor signaling in demand for the opioid fentanyl. Neuropsychopharmacology. 2019;44:1690–7. https://doi.org/10.1038/s41386-019-0420-x
6. Mohammadkhani A, Fragale JE, Pantazis CB, Bowrey HE, James MH, Aston-Jones G. Orexin-1 receptor signaling in ventral pallidum regulates motivation for the opioid remifentanil. J Neurosci. 2019;39:9831–40. https://doi.org/10.1523/jneurosci.0255-19.2019
7. Mahler SV, Moorman DE, Smith RJ, James MH, Aston-Jones G. Motivational activation: a unifying hypothesis of orexin/hypocretin function. Nat Neurosci. 2014;17:1298–303. https://doi.org/10.1038/nn.3810
8. James MH, Aston-Jones G. Orexin reserve: a mechanistic framework for the role of orexins (Hypocretins) in addiction. Biol Psychiatry. 2022;92:836–44. https://doi.org/10.1016/j.biopsych.2022.06.027
9. Georgescu D, Zachariou V, Barrot M, Mieda M, Willie JT, Eisch AJ, et al. Involvement of the lateral hypothalamic peptide orexin in morphine dependence and withdrawal. J Neurosci. 2003;23:3106–11.
10. Sharf R, Sarhan M, Dileone RJ. Orexin mediates the expression of precipitated morphine withdrawal and concurrent activation of the nucleus accumbens shell. Biol Psychiatry. 2008;64:175–83. https://doi.org/10.1016/j.biopsych.2008.03.006
11. Giannotti G, Mottarlini F, Heinsbroek JA, Mandel MR, James MH, Peters J. Oxytocin and orexin systems bidirectionally regulate the ability of opioid cues to bias reward seeking. Transl Psychiatry. 2022;12:432. https://doi.org/10.1038/s41398-022-02161-z
12. O'Connor, SL, Fragale, JE, James, MH, Aston-Jones, G The dual orexin/hypocretin receptor antagonist suvorexant reduces addiction-like behaviors for the opioid fentanyl. 2020. bioRxiv: 2020.2004.2025.061887.
13. Khoo SY, Brown RM. Orexin/Hypocretin based pharmacotherapies for the treatment of addiction: DORA or SORA? CNS Drugs. 2014;28:713–30. https://doi.org/10.1007/s40263-014-0179-x
14. Gyawali U, James MH. Sleep disturbance in substance use disorders: the orexin (hypocretin) system as an emerging pharmacological target. Neuropsychopharmacology. 2023;48:228–9. https://doi.org/10.1038/s41386-022-01404-3
15. James MH, Fragale JE, Aurora RN, Cooperman NA, Langleben DD, Aston-Jones G. Repurposing the dual orexin receptor antagonist suvorexant for the treatment of opioid use disorder: why sleep on this any longer? Neuropsychopharmacology. 2020;45:717–9. https://doi.org/10.1038/s41386-020-0619-x
16. Moline M, Asakura S, Beuckman C, Landry I, Setnik B, Ashworth J, et al. The abuse potential of lemborexant, a dual orexin receptor antagonist, according to the 8 factors of the Controlled Substances Act. Psychopharmacology. 2023;240:699–711. https://doi.org/10.1007/s00213-023-06320-y
17. Fathi HR, Yoonessi A, Khatibi A, Rezaeitalab F, Rezaei-Ardani A. Crosstalk between sleep disturbance and opioid use disorder: a narrative review. Addict Health. 2020;12:140.
18. Rasmussen K, White DA, Acri JB. NIDA's medication development priorities in response to the opioid crisis: ten most wanted. Neuropsychopharmacology. 2019;44:657–9. https://doi.org/10.1038/s41386-018-0292-5
19. Huhn AS, Finan PH, Gamaldo CE, Hammond AS, Umbricht A, Bergeria CL, et al. Suvorexant ameliorated sleep disturbance, opioid withdrawal, and craving during a buprenorphine taper. Sci Transl Med. 2022;14:eabn8238. https://doi.org/10.1126/scitranslmed.abn8238
20. Reid MJ, Dunn KE, Abraham L, Ellis J, Hunt C, Gamaldo CE, et al. Suvorexant alters dynamics of the sleep-electroencephalography-power spectrum and depressive-symptom trajectories during inpatient opioid withdrawal. Sleep. 2024;47:zsae025.
21. Kukkonen JP, Jacobson LH, Hoyer D, Rinne MK, Borgland SL, Ohlstein E. International union of basic and clinical pharmacology CXIV: orexin receptor function, nomenclature and pharmacology. Pharmacol Rev. 2024;76:625–88.
22. Matzeu A, Martin-Fardon R. Targeting the orexin system for prescription opioid use disorder. Brain Sci. 2020;10:226.
23. Baimel C, Bartlett SE, Chiou LC, Lawrence AJ, Muschamp JW, Patkar O, et al. Orexin/hypocretin role in reward: implications for opioid and other addictions. Br J Pharmacol. 2015;172:334–48.
24. Mun CJ, Reid MJ, Sarandos S, Elam KK, Li CM, Strickland JC. Improving sleep to address Co-Occurring substance use disorder and chronic pain: exploring the potential of the orexin (Hypocretin) system as a clinical target. Curr Addict Rep. 2024;11:1–13.
25. Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, Tanaka H, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior. Cell. 1998;92:573–85. https://doi.org/10.1016/s0092-8674(00)80949-6
26. de Lecea L, Kilduff TS, Peyron C, Gao X, Foye PE, Danielson PE, et al. The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. Proc Natl Acad Sci USA. 1998;95:322–7. https://doi.org/10.1073/pnas.95.1.322
27. Peyron C, Tighe DK, van den Pol AN, de Lecea L, Heller HC, Sutcliffe JG, et al. Neurons containing hypocretin (orexin) project to multiple neuronal systems. J Neurosci. 1998;18:9996–10015.
28. Hagan JJ, Leslie RA, Patel S, Evans ML, Wattam TA, Holmes S, et al. Orexin A activates locus coeruleus cell firing and increases arousal in the rat. Proc Natl Acad Sci USA. 1999;96:10911–6. https://doi.org/10.1073/pnas.96.19.10911
29. Bourgin P, Huitron-Resendiz S, Spier AD, Fabre V, Morte B, Criado JR, et al. Hypocretin-1 modulates rapid eye movement sleep through activation of locus coeruleus neurons. J Neurosci. 2000;20:7760–5. https://doi.org/10.1523/JNEUROSCI.20-20-07760.2000
30. Liu RJ, van den Pol AN, Aghajanian GK. Hypocretins (orexins) regulate serotonin neurons in the dorsal raphe nucleus by excitatory direct and inhibitory indirect actions. J Neurosci. 2002;22:9453–64.
31. Arrigoni E, Mochizuki T, Scammell TE. Activation of the basal forebrain by the orexin/hypocretin neurones. Acta Physiol. 2010;198:223–35. https://doi.org/10.1111/j.1748-1716.2009.02036.x
32. Marcus JN, Aschkenasi CJ, Lee CE, Chemelli RM, Saper CB, Yanagisawa M, et al. Differential expression of orexin receptors 1 and 2 in the rat brain. J Comp Neurol. 2001;435:6–25.
33. Harris GC, Aston-Jones G. Arousal and reward: a dichotomy in orexin function. Trends Neurosci. 2006;29:571–7. https://doi.org/10.1016/j.tins.2006.08.002
34. James MH, Mahler SV, Moorman DE, Aston-Jones G. A decade of Orexin/Hypocretin and addiction: where are we now? Curr Top Behav Neurosci. 2017;33:247–81. https://doi.org/10.1007/7854_2016_57
35. Pantazis CB, James MH, O'Connor S, Shin N, Aston-Jones G. Orexin-1 receptor signaling in ventral tegmental area mediates cue-driven demand for cocaine. Neuropsychopharmacology. 2022;47:741–51.
36. Schmitt O, Usunoff KG, Lazarov NE, Itzev DE, Eipert P, Rolfs A, et al. Orexinergic innervation of the extended amygdala and basal ganglia in the rat. Brain Struct Funct. 2012;217:233–56.
37. Arendt DH, Ronan PJ, Oliver KD, Callahan LB, Summers TR, Summers CH. Depressive behavior and activation of the orexin/hypocretin system. Behav Neurosci. 2013;127:86.
38. Maski K, Mignot E, Plazzi G, Dauvilliers Y. Disrupted nighttime sleep and sleep instability in narcolepsy. J Clin Sleep Med. 2022;18:289–304.
39. Mochizuki T, Crocker A, McCormack S, Yanagisawa M, Sakurai T, Scammell TE. Behavioral state instability in orexin knock-out mice. J Neurosci. 2004;24:6291–6300.
40. McGregor R, Shan L, Wu M-F, Siegel JM. Diurnal fluctuation in the number of hypocretin/orexin and histamine producing: implication for understanding and treating neuronal loss. PLoS One. 2017;12:e0178573.

41. Harris GC, Wimmer M, Aston-Jones G. A role for lateral hypothalamic orexin neurons in reward seeking. Nature. 2005;437:556–9. https://doi.org/10.1038/nature04071
42. Richardson KA, Aston-Jones G. Lateral hypothalamic orexin/hypocretin neurons that project to ventral tegmental area are differentially activated with morphine preference. J Neurosci. 2012;32:3809–17. https://doi.org/10.1523/JNEUROSCI.3917-11.2012
43. Harris GC, Wimmer M, Randall-Thompson JF, Aston-Jones G. Lateral hypothalamic orexin neurons are critically involved in learning to associate an environment with morphine reward. Behav Brain Res. 2007;183:43–51. https://doi.org/10.1016/j.bbr.2007.05.025
44. Sharf R, Guarnieri DJ, Taylor JR, DiLeone RJ. Orexin mediates morphine place preference, but not morphine-induced hyperactivity or sensitization. Brain Res. 2010;1317:24–32.
45. Narita M, Nagumo Y, Hashimoto S, Narita M, Khotib J, Miyatake M, et al. Direct involvement of orexinergic systems in the activation of the mesolimbic dopamine pathway and related behaviors induced by morphine. J Neurosci. 2006;26:398–405.
46. Alizamini MM, Farzinpour Z, Ezzatpanah S, Haghparast A. Role of intra-accumbal orexin receptors in the acquisition of morphine-induced conditioned place preference in the rats. Neurosci Lett. 2017;660:1–5.
47. Farahimanesh S, Zarrabian S, Haghparast A. Role of orexin receptors in the ventral tegmental area on acquisition and expression of morphine-induced conditioned place preference in the rats. Neuropeptides. 2017;66:45–51.
48. Sadeghi B, Ezzatpanah S, Haghparast A. Effects of dorsal hippocampal orexin-2 receptor antagonism on the acquisition, expression, and extinction of morphine-induced place preference in rats. Psychopharmacology. 2016;233:2329–41.
49. Sadeghzadeh F, Namvar P, Naghavi FS, Haghparast A. Differential effects of intra-accumbal orexin-1 and-2 receptor antagonists on the expression and extinction of morphine-induced conditioned place preference in rats. Pharmacol Biochem Behav. 2016;142:8–14.
50. Farahimanesh S, Karimi S, Haghparast A. Role of orexin-1 receptors in the dorsal hippocampus (CA1 region) in expression and extinction of the morphine-induced conditioned place preference in the rats. Peptides. 2018;101:25–31.
51. Ebrahimian F, Naghavi FS, Yazdi F, Sadeghzadeh F, Taslimi Z, Haghparast A. Differential roles of orexin receptors within the dentate gyrus in stress-and drug priming-induced reinstatement of conditioned place preference in rats. Behav Neurosci. 2016;130:91.
52. Fragale JE, James MH, Aston-Jones G. Intermittent self-administration of fentanyl induces a multifaceted addiction state associated with persistent changes in the orexin system. Addict Biol. 2021;26:e12946. https://doi.org/10.1111/adb.12946
53. Porter-Stransky KA, Bentzley BS, Aston-Jones G. Individual differences in orexin-I receptor modulation of motivation for the opioid remifentanil. Addiction Biol. 2017;22:303–17. https://doi.org/10.1111/adb.12323
54. Mohammadkhani A, James MH, Pantazis CB, Aston-Jones G. Persistent effects of the orexin-1 receptor antagonist SB-334867 on motivation for the fast acting opioid remifentanil. Brain Res. 2020;1731:146461.
55. Laorden ML, Ferenczi S, Pintér-Kübler B, González-Martín LL, Lasheras MC, Kovács KJ, et al. Hypothalamic orexin–a neurons are involved in the response of the brain stress system to morphine withdrawal. PLoS One. 2012;7:e36871. https://doi.org/10.1371/journal.pone.0036871
56. Zhou Y, Bendor J, Hofmann L, Randesi M, Ho A, Kreek MJ. Mu opioid receptor and orexin/hypocretin mRNA levels in the lateral hypothalamus and striatum are enhanced by morphine withdrawal. J Endocrinol. 2006;191:137–45.
57. Mousavi Y, Azizi H, Mirnajafi-Zadeh J, Javan M, Semnanian S. Blockade of orexin type-1 receptors in locus coeruleus nucleus attenuates the development of morphine dependency in rats. Neurosci Lett. 2014;578:90–94.
58. Ghaemi-Jandabi M, Azizi H, Ahmadi-Soleimani SM, Semnanian S. Intracoerulear microinjection of orexin-A induces morphine withdrawal-like signs in rats. Brain Res Bull. 2017;130:107–11.
59. Thannickal TC, John J, Shan L, Swaab DF, Wu MF, Ramanathan L, et al. Opiates increase the number of hypocretin-producing cells in human and mouse brain and reverse cataplexy in a mouse model of narcolepsy. Sci Transl Med. 2018;10:eaao4953. https://doi.org/10.1126/scitranslmed.aao4953
60. McGregor R, Wu M-F, Holmes B, Lam HA, Maidment NT, Gera J, et al. Hypocretin/orexin interactions with norepinephrine contribute to the opiate withdrawal syndrome. J Neurosci. 2022;42:255–63.
61. McGregor R, Wu M-F, Thannickal TC, Li S, Siegel JM. Opioid-induced neuroanatomical, microglial and behavioral changes are blocked by suvorexant without diminishing opioid analgesia. Nat Ment Health. 2024;2:1018–31.
62. Pantazis CB, James MH, Bentzley BS, Aston-Jones G. The number of lateral hypothalamus orexin/hypocretin neurons contributes to individual differences in cocaine demand. Addict Biol. 2020;25:e12795. https://doi.org/10.1111/adb.12795
63. Sadat-Shirazi MS, Soltani H, Nikpour N, Haghshenas M, Khalifeh S, Mokri A, et al. Alteration of orexin-A and PKCα in the postmortem brain of pure-opioid and multi-drug abusers. Neuropeptides. 2020;83:102074. https://doi.org/10.1016/j.npep.2020.102074
64. James MH, Stopper CM, Zimmer BA, Koll NE, Bowrey HE, Aston-Jones G. Increased number and activity of a lateral subpopulation of hypothalamic orexin/hypocretin neurons underlies the expression of an addicted state in rats. Biol Psychiatry. 2019;85:925–35.
65. Collier AD, Yasmin N, Chang GQ, Karatayev O, Khalizova N, Fam M, et al. Embryonic ethanol exposure induces ectopic Hcrt and MCH neurons outside hypothalamus in rats and zebrafish: role in ethanol-induced behavioural disturbances. Addict Biol. 2022;27:e13238.
66. Matzeu A, Martin-Fardon R. Cocaine-seeking behavior induced by orexin A administration in the posterior paraventricular nucleus of the thalamus is not long-lasting: neuroadaptation of the orexin system during cocaine abstinence. Front Behav Neurosci. 2021;15:620868.
67. Han Y, Yuan K, Zheng Y, Lu L. Orexin receptor antagonists as emerging treatments for psychiatric disorders. Neurosci Bull. 2020;36:432–48.
68. Smith RJ, Aston-Jones G. Orexin / hypocretin 1 receptor antagonist reduces heroin self-administration and cue-induced heroin seeking. Eur J Neurosci. 2012;35:798–804. https://doi.org/10.1111/j.1460-9568.2012.08013.x
69. Matzeu A, Martin-Fardon R. Targeting the orexin system for prescription opioid use disorder: orexin-1 receptor blockade prevents oxycodone taking and seeking in rats. Neuropharmacology. 2020;164:107906. https://doi.org/10.1016/j.neuropharm.2019.107906
70. Illenberger JM, Flores-Ramirez FJ, Matzeu A, Mason BJ, Martin-Fardon R. Suvorexant, an FDA-approved dual orexin receptor antagonist, reduces oxycodone self-administration and conditioned reinstatement in male and female rats. Front Pharmacol. 2023;14:1127735 https://doi.org/10.3389/fphar.2023.1127735
71. Schmeichel BE, Barbier E, Misra KK, Contet C, Schlosburg JE, Grigoriadis D, et al. Hypocretin receptor 2 antagonism dose-dependently reduces escalated heroin self-administration in rats. Neuropsychopharmacology. 2015;40:1123–9. https://doi.org/10.1038/npp.2014.293
72. Richardson NR, Roberts DC. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. J Neurosci Methods. 1996;66:1–11. https://doi.org/10.1016/0165-0270(95)00153-0
73. Bentzley BS, Fender KM, Aston-Jones G. The behavioral economics of drug self-administration: a review and new analytical approach for within-session procedures. Psychopharmacology. 2013;226:113–25. https://doi.org/10.1007/s00213-012-2899-2
74. Hursh SR, Silberberg A. Economic demand and essential value. Psychol Rev. 2008;115:186.
75. James MH, Bowrey HE, Stopper CM, Aston-Jones G. Demand elasticity predicts addiction endophenotypes and the therapeutic efficacy of an orexin/hypocretin-1 receptor antagonist in rats. Eur J Neurosci. 2019;50:2602–12. https://doi.org/10.1111/ejn.14166
76. Espana RA, Oleson EB, Locke JL, Brookshire BR, Roberts DC, Jones SR. The hypocretin-orexin system regulates cocaine self-administration via actions on the mesolimbic dopamine system. Eur J Neurosci. 2010;31:336–48. https://doi.org/10.1111/j.1460-9568.2009.07065.x
77. Zhou L, Smith RJ, Do PH, Aston-Jones G, See RE. Repeated orexin 1 receptor antagonism effects on cocaine seeking in rats. Neuropharmacology. 2012;63:1201–7. https://doi.org/10.1016/j.neuropharm.2012.07.044
78. James MH, Fragale JE, O'Connor SL, Zimmer BA, Aston-Jones G. The orexin (hypocretin) neuropeptide system is a target for novel therapeutics to treat cocaine use disorder with alcohol coabuse. Neuropharmacology. 2021;183:108359. https://doi.org/10.1016/j.neuropharm.2020.108359
79. Kawa AB, Bentzley BS, Robinson TE. Less is more: prolonged intermittent access cocaine self-administration produces incentive-sensitization and addiction-like behavior. Psychopharmacology. 2016;233:3587–602. https://doi.org/10.1007/s00213-016-4393-8
80. O'Neal TJ, Nooney MN, Thien K, Ferguson SM. Chemogenetic modulation of accumbens direct or indirect pathways bidirectionally alters reinstatement of heroin-seeking in high- but not low-risk rats. Neuropsychopharmacology. 2020;45:1251–62. https://doi.org/10.1038/s41386-019-0571-9
81. Brown RM, Dayas CV, James MH, Smith RJ. New directions in modelling dysregulated reward seeking for food and drugs. Neurosci Biobehav Rev. 2022;132:1037–48.
82. Zimmer BA, Oleson EB, Roberts D. The motivation to self-administer is increased after a history of spiking brain levels of cocaine. Neuropsychopharmacology. 2012;37:1901–10.

83. D'Ottavio G, Reverte I, Ragozzino D, Meringolo M, Milella MS, Boix F, et al. Increased heroin intake and relapse vulnerability in intermittent relative to continuous self-administration: sex differences in rats. Br J Pharmacol. 2023;180:910–26.
84. James MH, Bowrey HE, Stopper CM, Aston-Jones G. Demand elasticity predicts addiction endophenotypes and the therapeutic efficacy of an orexin/hypocretin-1 receptor antagonist in rats. Eur J Neurosci. 2019;50:2602–12.
85. Bossert JM, Marchant NJ, Calu DJ, Shaham Y. The reinstatement model of drug relapse: recent neurobiological findings, emerging research topics, and translational research. Psychopharmacology. 2013;229:453–76.
86. Venniro M, Banks ML, Heilig M, Epstein DH, Shaham Y. Improving translation of animal models of addiction and relapse by reverse translation. Nat Rev Neurosci. 2020;21:625–43.
87. Qi K, Wei C, Li Y, Sui N. Orexin receptors within the nucleus accumbens shell mediate the stress but not drug priming-induced reinstatement of morphine conditioned place preference. Front Behav Neurosci. 2013;7:144.
88. Guo SJ, Cui Y, Huang ZZ, Liu H, Zhang XQ, Jiang JX, et al. Orexin a-mediated AKT signaling in the dentate gyrus contributes to the acquisition, expression and reinstatement of morphine-induced conditioned place preference. Addict Biol. 2016;21:547–59.
89. Azizbeigi R, Haghparast A. Involvement of orexin-2 receptor in the ventral tegmental area in stress-and drug priming-induced reinstatement of conditioned place preference in rats. Neurosci Lett. 2019;696:121–6.
90. Illenberger JM, Flores-Ramirez FJ, Pascasio G, Matzeu A, Martin-Fardon R. Daily treatment with the dual orexin receptor antagonist DORA-12 during oxycodone abstinence decreases oxycodone conditioned reinstatement. Neuropharmacology. 2023;239:109685 https://doi.org/10.1016/j.neuropharm.2023.109685
91. Moorman DE, Aston-Jones G. Orexin-1 receptor antagonism decreases ethanol consumption and preference selectively in high-ethanol–preferring Sprague–Dawley rats. Alcohol. 2009;43:379–86. https://doi.org/10.1016/j.alcohol.2009.07.002
92. Ozdemir D, Allain F, Kieffer BL, Darcq E. Advances in the characterization of negative affect caused by acute and protracted opioid withdrawal using animal models. Neuropharmacology. 2023;232:109524.
93. Scicluna RL, Wilson BB, Thelaus SH, Arnold JC, McGregor IS, Bowen MT. Cannabidiol reduced the severity of gastrointestinal symptoms of opioid withdrawal in male and female mice. Cannabis Cannabinoid Res. 2024;9:547–60.
94. Tisdale RK, Sun Y, Park S, Ma SC, Haire M, Allocca G, et al. Biological sex influences sleep phenotype in mice experiencing spontaneous opioid withdrawal. J Sleep Res. 2024;33:e14037.
95. Kourosh-Arami M, Joghataei M-T, Komaki A, Gholami M, Najafi Z, Lavaie M. Persistent effects of the orexin-1 receptor antagonist SB-334867 on naloxone precipitated morphine withdrawal symptoms and nociceptive behaviors in morphine dependent rats. Int J Neurosci. 2021;132:67–76.
96. Ye H, Cao T, Shu Q, Chen Y, Lu Y, He Z, et al. Blockade of orexin receptor 1 attenuates morphine protracted abstinence-induced anxiety-like behaviors in male mice. Psychoneuroendocrinology. 2023;151:106080.
97. Davoudi M, Azizi H, Mirnajafi-Zadeh J, Semnanian S. The blockade of GABAA receptors attenuates the inhibitory effect of orexin type 1 receptors antagonist on morphine withdrawal syndrome in rats. Neurosci Lett. 2016;617:201–6.
98. Ahmadi-Soleimani SM, Ghaemi-Jandabi M, Azizi H, Semnanian S. Orexin type 1 receptor antagonism in Lateral Paragigantocellularis nucleus attenuates naloxone precipitated morphine withdrawal symptoms in rats. Neurosci Lett. 2014;558:62–66.
99. Hooshmandi M, Hosseinmardi N, Janahmadi M, Khakpai F, Rohampour K, Doostmohammadi J. Antagonism of orexin type-1 receptors (OX1Rs) attenuates naloxone-precipitated morphine withdrawal syndrome in rat dorsal hippocampus. Pharmacol Biochem Behav. 2017;158:39–48.
100. Hooshmand B, Azizi H, Javan M, Semnanian S. Intra-LC microinjection of orexin type-1 receptor antagonist SB-334867 attenuates the expression of glutamate-induced opiate withdrawal like signs during the active phase in rats. Neurosci Lett. 2017;636:276–81. https://doi.org/10.1016/j.neulet.2016.10.051
101. Bedard ML, Lord JS, Perez PJ, Bravo IM, Teklezghi AT, Tarantino LM, et al. Probing different paradigms of morphine withdrawal on sleep behavior in male and female C57BL/6J mice. Behav Brain Res. 2023;448:114441.
102. Li Y-J, Zhong F, Yu P, Han J-S, Cui C-L, Wu L-Z. Electroacupuncture treatment normalized sleep disturbance in morphine withdrawal rats. Evid Based Complement Alternat Med. 2011;2011:361054.
103. Winrow CJ, Gotter AL, Cox CD, Doran SM, Tannenbaum PL, Breslin MJ, et al. Promotion of sleep by suvorexant—a novel dual orexin receptor antagonist. J Neurogenet. 2011;25:52–61.
104. Hoyer D, Dürst T, Fendt M, Jacobson LH, Betschart C, Hintermann S, et al. Distinct effects of IPSU and suvorexant on mouse sleep architecture. Front Neurosci. 2013;7:235.
105. Gotter AL, Forman MS, Harrell CM, Stevens J, Svetnik V, Yee KL, et al. Orexin 2 receptor antagonism is sufficient to promote NREM and REM sleep from mouse to man. Sci Rep. 2016;6:27147.
106. Huhn AS, Dunn KE. The orexin neurotransmitter system as a target for medication development for opioid use disorder. Neuropsychopharmacology. 2024;49:329–30. https://doi.org/10.1038/s41386-023-01679-0
107. You WR, Lin LC, Lin WC, Tsai MC. Differences in orexin-A level in the functional brain network of HUD patients undergoing harm reduction therapy. Medicine. 2022;101:e30093. https://doi.org/10.1097/md.0000000000030093
108. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: an American Academy of Sleep Medicine Clinical Practice Guideline. J Clin Sleep Med. 2017;13:307–49. https://doi.org/10.5664/jcsm.6470
109. Hasler BP, Smith LJ, Cousins JC, Bootzin RR. Circadian rhythms, sleep, and substance abuse. Sleep Med Rev. 2012;16:67–81. https://doi.org/10.1016/j.smrv.2011.03.004
110. White AM, Eglovitch M, Parlier-Ahmad AB, Dzierzewski JM, James M, Bjork JM, et al. Insomnia symptoms and neurofunctional correlates among adults receiving buprenorphine for opioid use disorder. PLoS One. 2024;19:e0304461.
111. Guo R, Vaughan DT, Rojo ALA, Huang YH. Sleep-mediated regulation of reward circuits: implications in substance use disorders. Neuropsychopharmacology. 2023;48:61–78. https://doi.org/10.1038/s41386-022-01356-8
112. Fragale, J. E., M. H. James, J. A. Avila, A. M. Spaeth, R. N. Aurora, D. Langleben and G. Aston-ones. The Insomnia-Addiction Positive Feedback Loop: Role of the Orexin System. Front Neurol Neurosci. 2021;45:117–127
113. Suchting R, Yoon JH, Miguel GGS, Green CE, Weaver MF, Vincent JN, et al. Preliminary examination of the orexin system on relapse-related factors in cocaine use disorder. Brain Res. 2020;1731:146359. https://doi.org/10.1016/j.brainres.2019.146359
114. Strickland JC, Hatton KW, Hays LR, Rayapati AO, Lile JA, Rush CR, et al. Use of drug purchase tasks in medications development research: orexin system regulation of cocaine and drug demand. Behav Pharmacol. 2023;34:275–86. https://doi.org/10.1097/fbp.0000000000000731
115. Stoops WW, Strickland JC, Hatton KW, Hays LR, Rayapati AO, Lile JA, et al. Suvorexant maintenance enhances the reinforcing but not subjective and physiological effects of intravenous cocaine in humans. Pharmacol Biochem Behav. 2022;220:173466. https://doi.org/10.1016/j.pbb.2022.173466
116. Meyer PJ, King CP, Ferrario CR. Motivational processes underlying substance abuse disorder. Curr Top Behav Neurosci. 2016;27:473–506. https://doi.org/10.1007/7854_2015_391
117. Kosten TR, Baxter LE. Review article: effective management of opioid withdrawal symptoms: a gateway to opioid dependence treatment. Am J Addict. 2019;28:55–62. https://doi.org/10.1111/ajad.12862
118. Newton TF, De La Garza R 2nd, Kalechstein AD, Tziortzis D, Jacobsen CA. Theories of addiction: methamphetamine users' explanations for continuing drug use and relapse. Am J Addict. 2009;18:294–300. https://doi.org/10.1080/10550490902925920
119. Strang J, Volkow ND, Degenhardt L, Hickman M, Johnson K, Koob GF, et al. Opioid use disorder. Nat Rev Dis Prim. 2020;6:3. https://doi.org/10.1038/s41572-019-0137-5
120. Stumbo SP, Yarborough BJ, McCarty D, Weisner C, Green CA. Patient-reported pathways to opioid use disorders and pain-related barriers to treatment engagement. J Subst Abuse Treat. 2017;73:47–54. https://doi.org/10.1016/j.jsat.2016.11.003
121. Cicero TJ, Lynskey M, Todorov A, Inciardi JA, Surratt HL. Co-morbid pain and psychopathology in males and females admitted to treatment for opioid analgesic abuse. Pain. 2008;139:127–35. https://doi.org/10.1016/j.pain.2008.03.021
122. Ahmadi-Soleimani SM, Mianbandi V, Azizi H, Azhdari-Zarmehri H, Ghaemi-Jandabi M, Abbasi-Mazar A, et al. Coregulation of sleep-pain physiological interplay by orexin system: an unprecedented review. Behav Brain Res. 2020;391:112650. https://doi.org/10.1016/j.bbr.2020.112650
123. Roehrs T, Hyde M, Blaisdell B, Greenwald M, Roth T. Sleep loss and REM sleep loss are hyperalgesic. Sleep. 2006;29:145–51. https://doi.org/10.1093/sleep/29.2.145
124. Schuh-Hofer S, Wodarski R, Pfau DB, Caspani O, Magerl W, Kennedy JD, et al. One night of total sleep deprivation promotes a state of generalized hyperalgesia: a surrogate pain model to study the relationship of insomnia and pain. Pain. 2013;154:1613–21. https://doi.org/10.1016/j.pain.2013.04.046
125. Staffe AT, Bech MW, Clemmensen SLK, Nielsen HT, Larsen DB, Petersen KK. Total sleep deprivation increases pain sensitivity, impairs conditioned pain modulation and facilitates temporal summation of pain in healthy participants. PLoS One. 2019;14:e0225849. https://doi.org/10.1371/journal.pone.0225849

126. Sun Y, Laksono I, Selvanathan J, Saripella A, Nagappa M, Pham C, et al. Prevalence of sleep disturbances in patients with chronic non-cancer pain: a systematic review and meta-analysis. Sleep Med Rev. 2021;57:101467. https://doi.org/10.1016/j.smrv.2021.101467
127. Tang NK. Insomnia co-occurring with chronic pain: clinical features, interaction, assessments and possible interventions. Rev Pain. 2008;2:2–7. https://doi.org/10.1177/204946370800200102
128. Wilkerson AK, McRae-Clark AL. A review of sleep disturbance in adults prescribed medications for opioid use disorder: potential treatment targets for a highly prevalent, chronic problem. Sleep Med. 2021;84:142–53. https://doi.org/10.1016/j.sleep.2021.05.021
129. Razavi BM, Hosseinzadeh H. A review of the role of orexin system in pain modulation. Biomed Pharmacother. 2017;90:187–93. https://doi.org/10.1016/j.biopha.2017.03.053
130. Kang X, Tang H, Liu Y, Yuan Y, Wang M. Research progress on the mechanism of orexin in pain regulation in different brain regions. Open Life Sci. 2021;16:46–52.
131. Chavan P, Chikahisa S, Shiuchi T, Shimizu N, Dalanon J, Okura K, et al. Dual orexin receptor antagonist drug suvorexant can help in amelioration of predictable chronic mild stress-induced hyperalgesia. Brain Res Bull. 2022;188:39–46.
132. Hoffmann J, Supronsinchai W, Akerman S, Andreou AP, Winrow CJ, Renger J, et al. Evidence for orexinergic mechanisms in migraine. Neurobiol Dis. 2015;74:137–43.
133. Roehrs T, Withrow D, Koshorek G, Verkler J, Bazan L, Roth T. Sleep and pain in humans with fibromyalgia and comorbid insomnia: double-blind, crossover study of suvorexant 20 mg versus placebo. J Clin Sleep Med. 2020;16:415–21. https://doi.org/10.5664/jcsm.8220
134. Ueno K, Hitoaki S, Nomura Y, Obata N, Satoshi M. Improvement of sleep and pain with lemborexant administration in patients with chronic pain: a Retrospective Observational Study. Pain Med. 2023;25:139–43. https://doi.org/10.1093/pm/pnad126
135. Chabi A, Zhang Y, Jackson S, Cady R, Lines C, Herring WJ, et al. Randomized controlled trial of the orexin receptor antagonist filorexant for migraine prophylaxis. Cephalalgia. 2015;35:379–88. https://doi.org/10.1177/0333102414544979
136. Muthulingam D, Bia J, Madden LM, Farnum SO, Barry DT, Altice FL. Using nominal group technique to identify barriers, facilitators, and preferences among patients seeking treatment for opioid use disorder: a needs assessment for decision making support. J Subst Abuse Treat. 2019;100:18–28. https://doi.org/10.1016/j.jsat.2019.01.019
137. Muehlan C, Vaillant C, Zenklusen I, Kraehenbuehl S, Dingemanse J. Clinical pharmacology, efficacy, and safety of orexin receptor antagonists for the treatment of insomnia disorders. Expert Opin Drug Metab Toxicol. 2020;16:1063–78. https://doi.org/10.1080/17425255.2020.1817380
138. Vermeeren A, Sun H, Vuurman EF, Jongen S, Van Leeuwen CJ, Van Oers AC, et al. On-the-road driving performance the morning after bedtime use of suvorexant 20 and 40 mg: a study in non-elderly healthy volunteers. Sleep. 2015;38:1803–13. https://doi.org/10.5665/sleep.5168
139. Vermeeren A, Vets E, Vuurman EF, Van Oers AC, Jongen S, Laethem T, et al. On-the-road driving performance the morning after bedtime use of suvorexant 15 and 30 mg in healthy elderly. Psychopharmacology. 2016;233:3341–51. https://doi.org/10.1007/s00213-016-4375-x
140. Seol J, Fujii Y, Park I, Suzuki Y, Kawana F, Yajima K, et al. Distinct effects of orexin receptor antagonist and GABA(A) agonist on sleep and physical/cognitive functions after forced awakening. Proc Natl Acad Sci USA. 2019;116:24353–8. https://doi.org/10.1073/pnas.1907354116
141. Kaufmann P, Ort M, Golor G, Kornberger R, Dingemanse J. Multiple-dose clinical pharmacology of the selective orexin-1 receptor antagonist ACT-539313. Prog Neuropsychopharmacol Biol Psychiatry. 2021;108:110166. https://doi.org/10.1016/j.pnpbp.2020.110166
142. van der Ark PD, Golor G, van Nueten L, Nandy P, de Boer P. Multiple daytime administration of the selective orexin-2 receptor antagonist JNJ-42847922 induces somnolence in healthy subjects without residual central effects. J Psychopharmacol. 2018;32:1330–40. https://doi.org/10.1177/0269881118791521
143. Hoever P, de Haas SL, Dorffner G, Chiossi E, van Gerven JM, Dingemanse J. Orexin receptor antagonism: an ascending multiple-dose study with almorexant. J Psychopharmacol. 2012;26:1071–80. https://doi.org/10.1177/0269881112448946
144. Herring WJ, Ceesay P, Snyder E, Bliwise D, Budd K, Hutzelmann J, et al. Polysomnographic assessment of suvorexant in patients with probable Alzheimer's disease dementia and insomnia: a randomized trial. Alzheimers Dement. 2020;16:541–51. https://doi.org/10.1002/alz.12035
145. Muehlan C, Roch C, Vaillant C, Dingemanse J. The orexin story and orexin receptor antagonists for the treatment of insomnia. J Sleep Res. 2023;32:e13902.
146. White JM, Irvine RJ. Mechanisms of fatal opioid overdose. Addiction. 1999;94:961–72.
147. Jones JD, Mogali S, Comer SD. Polydrug abuse: a review of opioid and benzodiazepine combination use. Drug Alcohol Depend. 2012;125:8–18.
148. Young JK, Wu M, Manaye KF, Kc P, Allard JS, Mack SO, et al. Orexin stimulates breathing via medullary and spinal pathways. J Appl Physiol. 2005;98:1387–95.
149. Fukushi I, Yokota S, Takeda K, Terada J, Umeda A, Yoshizawa M, et al. Dual orexin receptor blocker suvorexant attenuates hypercapnic ventilatory augmentation in mice. Brain Res. 2022;1795:148061.
150. Xu L, Krishna A, Stewart S, Shea K, Racz R, Weaver JL, et al. Effects of sedative psychotropic drugs combined with oxycodone on respiratory depression in the rat. Clin Transl Sci. 2021;14:2208–19.
151. Moreira-Junior EDC, Rowlett JK, Berro LF. Suvorexant enhances oxycodone-induced respiratory depression in male rats. Drug Alcohol Depend. 2024;264:112434.
152. Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities. Annu Rev Pharmacol Toxicol. 2011;51:243–66.
153. Sun H, Palcza J, Rosenberg R, Kryger M, Siringhaus T, Rowe J, et al. Effects of suvorexant, an orexin receptor antagonist, on breathing during sleep in patients with chronic obstructive pulmonary disease. Respir Med. 2015;109:416–26.
154. Sun H, Palcza J, Card D, Gipson A, Rosenberg R, Kryger M, et al. Effects of suvorexant, an orexin receptor antagonist, on respiration during sleep in patients with obstructive sleep apnea. J Clin sleep Med. 2016;12:9–17.
155. Boof M-L, Dingemanse J, Lederer K, Fietze I, Ufer M. Effect of the new dual orexin receptor antagonist daridorexant on nighttime respiratory function and sleep in patients with mild and moderate obstructive sleep apnea. Sleep. 2021;44:zsaa275.
156. Boof M-L, Ufer M, Fietze I, Pepin J-L, Guern A-S, Lemoine V, et al. Assessment of the effect of the dual orexin receptor antagonist daridorexant on various indices of disease severity in patients with mild to moderate obstructive sleep apnea. Sleep Med. 2022;92:4–11.
157. Cheng JY, Filippov G, Moline M, Zammit GK, Bsharat M, Hall N. Respiratory safety of lemborexant in healthy adult and elderly subjects with mild obstructive sleep apnea: a randomized, double-blind, placebo-controlled, crossover study. J sleep Res. 2020;29:e13021.
158. Uemura N, McCrea J, Sun H, Donikyan M, Zammit G, Liu R, et al. Effects of the orexin receptor antagonist suvorexant on respiration during sleep in healthy subjects. J Clin Pharmacol. 2015;55:1093–1100.
159. Tolentino JC, Schmidt SL. DSM-5 criteria and depression severity: implications for clinical practice. Front Psychiatry. 2018;9:450. https://doi.org/10.3389/fpsyt.2018.00450
160. Savitz A, Wajs E, Zhang Y, Xu H, Etropolski M, Thase ME, et al. Efficacy and safety of seltorexant as adjunctive therapy in major depressive disorder: a phase 2b, randomized, placebo-controlled, adaptive dose-finding study. Int J Neuropsychopharmacol. 2021;24:965–76. https://doi.org/10.1093/ijnp/pyab050
161. Connor KM, Mahoney E, Jackson S, Hutzelmann J, Zhao X, Jia N, et al. A phase II dose-ranging study evaluating the efficacy and safety of the orexin receptor antagonist filorexant (MK-6096) in patients with primary insomnia. Int J Neuropsychopharmacol. 2016;19:pyw022. https://doi.org/10.1093/ijnp/pyw022
162. Brooks S, Jacobs GE, de Boer P, Kent JM, Van Nueten L, van Amerongen G, et al. The selective orexin-2 receptor antagonist seltorexant improves sleep: an exploratory double-blind, placebo controlled, crossover study in antidepressant-treated major depressive disorder patients with persistent insomnia. J Psychopharmacol. 2019;33:202–9. https://doi.org/10.1177/0269881118822258
163. Recourt K, de Boer P, Zuiker R, Luthringer R, Kent J, van der Ark P, et al. The selective orexin-2 antagonist seltorexant (JNJ-42847922/MIN-202) shows antidepressant and sleep-promoting effects in patients with major depressive disorder. Transl Psychiatry. 2019;9:216. https://doi.org/10.1038/s41398-019-0553-z
164. Gorka SM, Khorrami KJ, Manzler CA, Phan KL. Acute orexin antagonism selectively modulates anticipatory anxiety in humans: implications for addiction and anxiety. Transl Psychiatry. 2022;12:308. https://doi.org/10.1038/s41398-022-02090-x
165. Russell JL, Spiller HA. Retrospective assessment of toxicity following exposure to orexin pathway modulators modafinil and suvorexant. Toxicol Commun. 2019;3:33–36.
166. Ito H, Ogawa Y, Shimojo N, Kawano S. Suvorexant poisoning in a patient with cirrhosis and renal failure. Cureus. 2021;13:e14329 https://doi.org/10.7759/cureus.14329
167. Dallmann R, Brown SA, Gachon F. Chronopharmacology: new insights and therapeutic implications. Annu Rev Pharmacol Toxicol. 2014;54:339–61. https://doi.org/10.1146/annurev-pharmtox-011613-135923
168. Khoshnevis S, Smolensky MH, Haghayegh S, Castriotta RJ, Hermida RC, Diller KR. Recommended timing of medications that impact sleep and wakefulness: a review of the American Prescribers' digital reference. Sleep Med Rev. 2023;67:101714 https://doi.org/10.1016/j.smrv.2022.101714

169. Rhyne DN, Anderson SL. Suvorexant in insomnia: efficacy, safety and place in therapy. Ther Adv Drug Saf. 2015;6:189–95. https://doi.org/10.1177/2042098615595359
170. Michelson D, Snyder E, Paradis E, Chengan-Liu M, Snavely DB, Hutzelmann J, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2014;13:461–71. https://doi.org/10.1016/S1474-4422(14)70053-5
171. Herring WJ, Connor KM, Ivgy-May N, Snyder E, Liu K, Snavely DB, et al. Suvorexant in patients with insomnia: results from two 3-month Randomized Controlled Clinical Trials. Biol Psychiatry. 2016;79:136–48. https://doi.org/10.1016/j.biopsych.2014.10.003
172. Schoedel KA, Sun H, Sellers EM, Faulknor J, Levy-Cooperman N, Li X, et al. Assessment of the abuse potential of the orexin receptor antagonist, suvorexant, compared with zolpidem in a randomized crossover study. J Clin Psychopharmacol. 2016;36:314–23. https://doi.org/10.1097/jcp.0000000000000516
173. Ufer M, Kelsh D, Schoedel KA, Dingemanse J. Abuse potential assessment of the new dual orexin receptor antagonist daridorexant in recreational sedative drug users as compared to suvorexant and zolpidem. Sleep. 2022;45:zsab224 https://doi.org/10.1093/sleep/zsab224
174. Tubbs AS, Ghani SB, Naps M, Grandner MA, Stein MD, Chakravorty S. Past-year use or misuse of an opioid is associated with use of a sedative-hypnotic medication: a US National Survey on Drug Use and Health (NSDUH) study. J Clin Sleep Med. 2022;18:809–16. https://doi.org/10.5664/jcsm.9724
175. Guo R, Wang Y, Yan R, Chen B, Ding W, Gorczyca MT, et al. Rapid eye movement sleep engages melanin-concentrating hormone neurons to reduce cocaine seeking. Biol Psychiatry. 2022;92:880–94.
176. Chen B, Wang Y, Liu X, Liu Z, Dong Y, Huang YH. Sleep regulates incubation of cocaine craving. J Neurosci. 2015;35:13300–10.
177. Wiskerke et al. Brain Research. 2020 https://pubmed.ncbi.nlm.nih.gov/31002819/

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AUTHOR CONTRIBUTIONS

JSR contributed to conceptualization of the scope of the review, conducted the literature search, organized and managed sources, wrote initial drafts of sections of the manuscript, revised and restructured the manuscript, created the table, and helped to coordinate communications and submission. RDV contributed to the initial conceptualization of the review and wrote some initial draft sections of the review. JP contributed to the initial conceptualization of the review, revised and proofread the manuscript, and provided guidance and supervision of the project. MHJ contributed to the conceptualization of the scope of the review, contributed to initial drafts of sections of the manuscript, revised and restructured the manuscript, provided guidance and supervision of the project, and coordinated communications and submission.

COMPETING INTERESTS

JSR and RDV declare no competing financial interests. MHJ is an inventor on US Patent submissions PCT/US23/27918 and 63/601,522. JP is a consultant for Delix Therapeutics, Inc.

ADDITIONAL INFORMATION

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