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REVIEW

Orexin Receptor Antagonists as Emerging Treatments for Psychiatric Disorders

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Abstract Orexins comprise two neuropeptides produced by orexin neurons in the lateral hypothalamus and are released by extensive projections of these neurons throughout the central nervous system. Orexins bind and activate their associated G protein-coupled orexin type 1 receptors (OX1Rs) and OX2Rs and act on numerous physiological processes, such as sleep-wake regulation, feeding, reward, emotion, and motivation. Research on the development of orexin receptor antagonists has dramatically increased with the approval of suvorexant for the treatment of primary insomnia. In the present review, we discuss recent findings on the involvement of the orexin system in the pathophysiology of psychiatric disorders, including sleep disorders, depression, anxiety, and drug addiction. We discuss the actions of orexin receptor antagonists, including selective OX1R antagonists (SORA1s), selective OX2R antagonists (SORA2s), and dual OX1/2R antagonists (DORAs), in the treatment of these disorders based on both preclinical and clinical evidence. SORA2s and DORAs have more pronounced efficacy in the treatment of sleep disorders, whereas SORA1s may be promising for the treatment of anxiety and drug addiction. We also discuss potential challenges and opportunities for the application of orexin receptor antagonists to clinical interventions.

Keywords Orexin · Insomnia · Depression · Anxiety · Drug addiction

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Introduction

Orexins and hypocretins were almost simultaneously discovered by Sakurai and de Lecea, respectively, in 1998 and were later shown to be the same neuropeptide [1, 2]. There are two types of orexins: orexin-A (hypocretin-1) and orexin-B (hypocretin-2). Both are produced from the same precursor peptide, prepro-orexin, by neuronal cleavage in the lateral and posterior hypothalamus, and orexin projections are found throughout the brain [1–3]. Orexin peptides are ligands for G protein-coupled orexin type 1 receptors (OX1Rs) and OX2Rs. Orexin-A activates both OX1Rs and OX2Rs with approximately equal potency, while orexin-B preferentially activates OX2Rs [4, 5]. The anatomical distribution of OX1Rs and OX2Rs in the brain shows partially overlapping and partially distinct patterns [4, 6–8] (Fig. 1A). Both receptors are expressed in the lateral hypothalamus (LH), medial prefrontal cortex (mPFC), hippocampus (Hip), central nucleus of the amygdala (CeA), bed nucleus of the stria terminalis (BNST), dorsal raphe (DR), ventral tegmental area (VTA), laterodorsal tegmental nucleus (LDT)/pedunculopontine nucleus (PPT), and nucleus of the solitary tract (NTS). OX1Rs are selectively expressed in the locus coeruleus (LC) and cingulate cortex, while OX2Rs are selectively
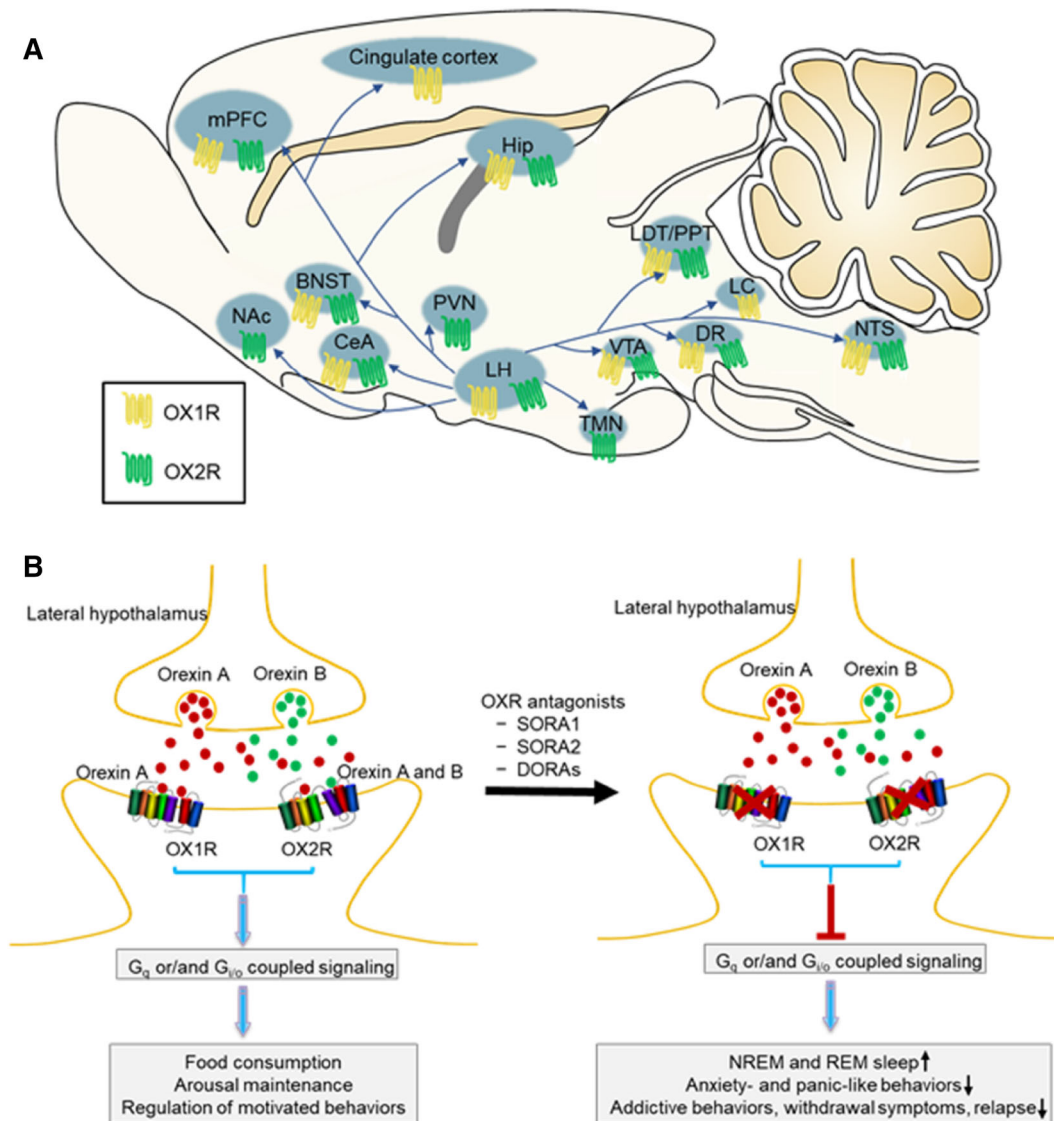
Fig. 1 Orexin receptor distribution and potential application of orexin receptor antagonists for the treatment of psychiatric disorders. **A** Orexin neurons in the lateral hypothalamus send extensive projections to brain areas associated with feeding, sleep-wake regulation, and motivated and emotional behaviors. The anatomical distribution of OX1Rs and OX2Rs in these regions is shown. **B** Orexin A and orexin B are hypothalamic neuropeptides. Their actions are mediated by G_q- and/or $G_{i/o}$-coupled OX1Rs and OX2Rs, playing important roles in many physiological processes, such as feeding, the sleep-to-wakefulness transition, and motivation. Antagonism of the orexin system increases NREM and REM sleep, decreases anxiety- and panic-like behaviors, and inhibits the reinforcing and motivational properties of addictive drugs. Orexin receptor antagonists may be promising for the treatment of psychiatric disorders, such as insomnia, anxiety, and drug addiction. BNST, bed nucleus of the stria terminalis; CeA, central nucleus of the amygdala; DORA, dual OX1/2R antagonist; DR, dorsal raphe; Hip, hippocampus; LC, locus coeruleus; LDT/PPT, laterodorsal tegmental nucleus/pedunculopontine nucleus; LH, lateral hypothalamus; mPFC, medial prefrontal cortex; NAc, nucleus accumbens; NREM, non-rapid-eye-movement; NTS, nucleus of the solitary tract; OX1R, orexin type 1 receptor; OX2R, orexin type 2 receptor; PVN, hypothalamic paraventricular nucleus; REM, rapid-eye-movement; SORA1, selective OX1R antagonist; SORA2, selective OX2R antagonist; TMN, tuberomammillary nucleus; VTA, ventral tegmental area.

expressed in the tuberomammillary nucleus (TMN), hypothalamic paraventricular nucleus (PVN), and nucleus accumbens (NAc). These brain regions are major effector sites of orexin neurons in the LH, which is involved in feeding, sleep, and motivated behaviors [9–11].

Fasting has been shown to increase prepro-orexin mRNA levels, and the central administration of orexin-A and orexin-B stimulates food consumption, suggesting that they play important physiological roles in regulating feeding behavior [2]. Satiety activates anorexigenic pro-

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opiomelanocortin (POMC)-containing neurons and inhibites orexin-producing neurons in the hypothalamus, thus suppressing feeding and/or stimulating energy expenditure [12, 13]. However, orexin-A and OX1R stimulation have been shown to inhibit satiety-inducing POMC neurons and increase the motivation for food [14, 15]. The exogenous administration of orexin-A into the LH increases wakefulness in rats [16]. The selective optogenetic activation of orexin neurons in the LH increases the probability of the sleep-to-wakefulness transition, and OX1Rs and OX2Rs play differential roles in the regulation of rapid-eye-movement (REM) sleep and non-REM (NREM) sleep [17]. NREM sleep is mainly regulated by OX2Rs, but there are important synergistic effects of OX1R and OX2R signaling in this regulation [18, 19]. Many reviews have indicated that the orexin system is involved in the regulation of reward, motivated behaviors, and stress-related psychiatric disorders [6, 9, 20, 21].

Given the critical role of orexin in multiple physiological processes and the wide distribution of orexin receptors throughout the brain, compounds that target orexin receptors may be beneficial for the treatment of various disorders. A growing number of patents for orexin receptor antagonists has emerged for use in the areas of sleep disorders, anxiety, panic, and addictive disorders[22]. Orexin receptor antagonists are classified into selective OX1R antagonists (SORA1s), selective OX2R antagonists (SORA2s), and dual OX1/2R antagonists (DORAs), based on their binding affinities. Several DORAs and SORA2s have been translated from basic research to clinical interventions. They have been shown to have sustained clinical efficacy and are well-tolerated for the management of primary insomnia [23, 24]. The DORA suvorexant was the first orexin receptor antagonist approved by United States Food and Drug Administration (FDA) for the treatment of primary insomnia [25]. Another DORA, lemobrexant, has been shown to be effective for the treatment of insomnia disorder in randomized controlled clinical trials [23, 26]. In addition, orexin receptor antagonists have been extensively investigated for use in psychiatric disorders associated with the dysregulation of orexin function [10, 20, 21, 27] (Fig. 1B). In this review, we discuss the potential involvement of the orexin system in the pathophysiology of several psychiatric disorders, including sleep disorders, anxiety, and drug addiction, and summarize the progress of recent research on orexin receptor antagonists for the treatment of these disorders, from basic research to clinical studies.

From the Laboratory to the Clinic: Orexin Receptor Antagonists for the Treatment of Psychiatric Disorders

Although orexin neurons are concentrated only in the LH and adjacent areas, their nerve fibers project widely to much of the central nervous system, from the brainstem to the cortex. These widespread connections are involved in the regulation of feeding, sleep/wake states, stress, and reward processing [6, 9, 28, 29]. Specific hypothalamic nuclei, such as the LH and PVN, are often referred to as "centers" for hunger and satiety, and the activation of orexin projections to the NTS and NAc has been shown to increase food intake [9, 12, 30]. The effects of orexin neuropeptides on sleep-wake regulation may be reflected by their innervation of noradrenergic neurons in the LC, histaminergic neurons in the TMN, serotonergic neurons in the DR, and cholinergic neurons in the LDT/PPT [11, 31]. Orexin terminals are also expressed in the CeA, BNST, mPFC, and Hip, which are critical for the regulation of stress and anxiety-related responses [10, 32]. Orexin neurons also send projections to dopamine neurons in the VTA and NAc, which are well known to modulate reward processing [9, 21]. Accumulating evidence indicates that the orexin system contributes to the etiology of several psychiatric disorders. Orexin receptor antagonists have shown promise for the treatment of these disorders.

Sleep Disorders, Especially Primary Insomnia

The discovery of selective orexin neuron loss in narcolepsy sparked great research interest in the sleep field and raised the possibility of an alternative approach of treating the symptoms of insomnia with orexin receptor antagonists [11]. The number of orexin neurons is selectively reduced in human narcolepsy, and canine narcolepsy is caused by a mutation of the OX2R gene [33, 34]. Intranasal administration of orexin peptide, orexin neuron transplants, and orexin gene therapy are promising approaches to the treatment of narcolepsy [35, 36]. The selective OX2R agonist YNT-185 has been shown to ameliorate cataplexy-like episodes in a mouse model of narcolepsy [37]. OX2R agonists (a modified orexin-B peptide) have also been reported to promote resilience to stress and have anxiolytic and anti-depressive effects [38, 39]. Inactivation of each orexin receptor subtype is required to induce narcoleptic effects, but OX1Rs and OX2Rs play distinct roles in gating NREM and REM sleep. OX2Rs are the pivotal receptors that regulate wakefulness and NREM sleep, whereas REM sleep is controlled by both receptor subtypes [19]. The selective inhibition of OX2Rs results in an increase in NREM sleep and a decrease in the latency to NREM sleep,

but no effect on REM or NREM sleep occurs when OX1Rs are selectively inhibited [40–42]. Although OXR1s do not have a direct action on regulating sleep, almorexant has been shown to enhance the total REM sleep time in OX1R-knockout mice compared with wild-type mice, thus indicating that OX1Rs play additional roles in REM sleep [43]. Knockdown of OX1Rs in the LC selectively increases the time spent in REM sleep during the dark period [44]. The SORA1 JNJ-54717793 has minimal effects on spontaneous sleep in rats and wild-type mice, but JNJ-54717793 administration in OX2R-knockout mice selectively reduces REM sleep latency and increases REM sleep duration [45]. Pharmacological experiments have also shown that co-administration of an OX1R antagonist and an OX2R antagonist reduces REM sleep latency and increases REM sleep duration [18]. However, another study have showed that the inhibition of OX1Rs attenuates the increase in REM sleep time that is induced by selective OX2R antagonism, which appeared to be correlated with dopaminergic neurotransmission [46]. These reports suggest that OX2Rs play a dominant role in regulating sleep, while OX1Rs alone only make a minimal contribution to sleep induction but exert synergistic effects with OX2Rs to regulate REM sleep.

DORAs block the activity of both OX1Rs and OX2Rs and result in a rapid transition to sleep. Administered orally, the DORA suvorexant significantly and dose-dependently reduces locomotor activity and promotes both NREM and REM sleep in rats, dogs, and rhesus monkeys [47]. Suvorexant promotes sleep primarily by increasing REM sleep duration and reducing the latency to REM sleep [48]. It also increases NREM sleep and improves the impairment in glucose tolerance in an animal model of diabetes mellitus [49]. These studies suggest that DORAs effectively improve sleep without significantly disrupting its architecture. Treatment with the DORA MK6096 and the SORA2 MK1064 but not a SORA1 stabilizes sleep and improves sleep-dependent memory function [50]. Fos immunohistochemistry showed that the DORA almorexant does not block the sleep deprivation-induced activation of wake-promoting cell groups in the LH, TMN, or basal forebrain, which suggests a mechanism by which almorexant causes less cognitive impairment than the benzodiazepine receptor agonist zolpidem [51].

Consistent cross-species evidence for the sleep-promoting effects of orexin receptor antagonists spurred the pharmaceutical development of new orexin-targeted treatments for insomnia. Almorexant was the first-in-class compound that targeted the orexin system and the first DORA to proceed to Phase II sleep disorder studies in 2007, but investigations of almorexant were halted during Phase III trials for undisclosed reasons. Currently, the most advanced DORA is suvorexant, which was approved by the FDA in 2014 for the treatment of insomnia [25]. Several meta-analyses and reviews of clinical trials support the efficacy of suvorexant for the treatment of insomnia [52–55]. Randomized controlled clinical trials have reported that suvorexant generally improves sleep maintenance and onset over 3 months of nightly treatment and is well-tolerated in both adult and elderly patients with primary insomnia [56–59]. DORA treatment results in significant and dose-related improvements in both subjective and objective sleep [26, 60, 61]. A meta-analysis and several clinical trials found that suvorexant is associated with significant improvements in subjective time to sleep onset, subjective total sleep time, and subjective sleep quality [24, 62–64]. Statistically significant sleep-promoting effects on both REM and NREM sleep have been reported, and sleep architecture and the power spectral profile are not disrupted in patients with primary insomnia or healthy people who are treated with suvorexant [23, 60, 65, 66]. The DORA SB-649868 has been shown to increase total sleep time and REM sleep duration and reduce waking after sleep onset, the latency to persistent sleep, and the latency to REM sleep in healthy men in a model of situational insomnia and men with primary insomnia [67, 68]. Another DORA, lemborexant, improves sleep efficiency, decreases the latency to persistent sleep, decreases the latency to subjective sleep onset, and decreases waking after sleep onset in adults and elderly individuals with insomnia disorder [26].

In addition to treating primary insomnia, the DORA suvorexant has been evaluated for the treatment of insomnia symptoms in patients with psychosis and physical disease. Suvorexant is effective for the treatment of insomnia in patients with Alzheimer's disease, but whether it influences Alzheimer's disease itself remains unclear [69]. Suvorexant significantly increases sleep efficiency and decreases glucose levels in individuals with insomnia symptoms and type 2 diabetes mellitus, and these effects are consistent with the effects of suvorexant in an animal model [49, 70]. Combination therapy with suvorexant and ramelteon improves subjective sleep quality without inducing delirium in acute stroke patients [71]. Some case reports have also suggested that suvorexant treatment is useful in patients with schizophrenia [72] and Parkinson's disease [73], but its efficacy in these patients remains unclear and needs further validation. Overall, DORAs have shown efficacy for the treatment of primary insomnia and insomnia symptoms. Several studies have focused on suvorexant for the treatment of patients with sleep apnea, but it lacks clinically important respiratory effects during sleep [74–76]. The SORA2 seltorexant has also been found to decrease the latency to persistent sleep and increase total sleep time and sleep efficiency in patients with major depressive disorder (MDD) and persistent insomnia who

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are being treated with antidepressants and individuals with insomnia disorder without psychiatric comorbidity [77, 78].

Data from a Japanese post-marketing survey suggested that adverse effects of suvorexant are rare, with an incidence of 8.8%. Next-day somnolence is the most commonly reported side-effect, which may be an inevitable consequence of pharmacological interventions that promote sleep in some patients [79]. Suvorexant is generally effective and well tolerated. However, compared with traditional sleep agents (e.g., benzodiazepines), the efficacy of suvorexant requires further validation [80, 81]. Some studies have reported infrequent but notable side-effects of suvorexant in the treatment of insomnia disorder, such as abnormal dreams, sleep paralysis, over-sedation, the acute worsening of depressive symptoms, and suicidal thoughts [82–84].

Overall, several SORA2s and DORAs that are clinically used for patients with primary insomnia have been shown to be safe and effective (Table 1). Additional orexin-targeted drugs are expected to be approved by the FDA for clinical use. Further studies are needed to evaluate the action of orexin receptor antagonists in the treatment of other sleep disorders and mental illnesses.

Mood Disorders

Orexin receptor antagonists have been implicated in the treatment of depression and anxiety (Table 2). Acute restraint stress activates orexin neurons in the LH and increases orexin-A levels in the VTA [85]. OX1R gene variants are associated with the development of MDD and depressive symptom severity [86]. Systemic administration of the SORA2 LSN2424100 has dose-dependent antidepressant-like effects in a delayed-reinforcement of low-rate assay in rodents, and the SORA2 seltorexant has a tendency to improve mood in antidepressant-treated MDD patients with persistent insomnia [77, 87]. The DORA almorexant prevents chronic unpredictable mild stress-induced depressive-like behavior in mice but does not affect hippocampal cell proliferation or neurogenesis [88]. Suvorexant has also been shown to improve sleep quality and mood in psychiatric inpatients with insomnia symptoms [89]. Another Phase 2 clinical trial reported inconsistent results, in which 6 weeks of treatment with the DORA filorexant did not have significant effects in patients with MDD, but this study had limitations with regard to enrollment challenges and insufficient statistical power, the results of which should be interpreted with caution [90].

Orexin modulates neuronal circuitry that is implicated in the expression and extinction of conditioned fear, suggesting that it may be a promising target for the treatment of anxiety disorders [10, 91]. Panic disorder is a common disabling anxiety disorder characterized by recurrent panic attacks. The orexin system in the medial hypothalamus and orexin-related molecular mechanisms in the amygdala–hippocampus–prefrontal cortex pathway are involved in the behavioral expression of panic disorder [92, 93]. Orexin-related pharmacological targets may be promising for the treatment of panic attacks. Orexin neurons are activated in a rat model of panic disorder, and the orexin levels in cerebrospinal fluid (CSF) increase in humans with panic-related anxiety [94]. OX1R gene variations are associated with the development of panic disorder and the treatment response to cognitive behavioral therapy [95]. Systemic administration of the SORA1 SB-334867 and silencing the orexin gene in the hypothalamus block panic responses and anxiety-like behavior in a rat model of CO_2- and sodium lactate-induced panic [94, 96]. Intracerebroventricular injection of SB-334867 decreases seizures and anxiety in pentylenetetrazol-kindled rats [97]. Systemic SB-334867 administration has no effect on anxiety-like behavior in the open field, whereas microinjection of SB-334867 into the trigeminal nucleus caudalis reduces orofacial pain-induced anxiety-like behavior in rats [98, 99]. SB-334867 treatment also attenuates FG-7142-induced anxiety-like behavior, increases heart rate, and increases neuronal activation in anxiety- and stress-related brain regions, such as the CeA and BNST [100].

The novel brain-penetrant SORA1 JNJ-54717793 attenuates CO_2- and sodium lactate-induced panic-like behavior and cardiovascular responses [45]. The SORA1 compound 56 also attenuates this behavior and cardiovascular responses without altering baseline locomotor or autonomic activity, while the SORA2 JNJ10397049 has no effects on panic-like responses [101, 102]. The antagonism of OX1Rs in the hypothalamus has been shown to treat panic disorder. However, a previous study showed that OX1R transcript levels increase and OX2R transcripts decrease in the basolateral amygdala in chronic social defeat-susceptible mice. Knockdown of either orexin receptor in the BLA has no effects on depressive-like behavior, whereas OX2R knockdown in the BLA increases anxiety-like behavior [103]. Therefore, the roles of the two orexin receptor subtypes in depressive- and anxiety-like behaviors may be brain region-specific.

Drug Addiction

Some addictive drugs act both locally on orexin neurons in the LH and at orexin terminals in the VTA. Orexin system activation promotes drug-seeking by stimulating postsynaptic OX1Rs and modulating the drug-induced glutamatergic synaptic plasticity in dopamine neurons in the VTA [21]. Hypothalamic orexin neurons co-release orexin and dynorphin in the VTA, and the SORA1 SB334867 has

Table 1 Summary of recent findings on orexin receptor antagonists for the treatment of sleep disorders.

Manipulation and target	Subjects	Findings	References
Filorexant (MK-6096) DORA	Rats and dogs	Dose-dependently reduced locomotor activity and increased sleep in rats and dogs.	Winrow *et al.* [151]
	Mice	Stabilized sleep and improved sleep-dependent memory function.	Li *et al.* [50]
	Patients (18–65 years old) with primary insomnia	Increased SE, decreased WASO, and decreased the latency to persistent sleep onset.	Connor *et al.* [61]
Suvorexant (MK-4305) DORA	Rats, dogs, and rhesus monkeys	Reduced locomotor activity and promoted sleep in rats, dogs, and rhesus monkeys.	Winrow *et al.* [47]
	Mice	Disturbed sleep architecture by selectively increasing REM sleep and decreasing wake time.	Hoyer *et al.* [48]
	Type 2 diabetic db/db mice	Increased NREM sleep and improved impairment in glucose tolerance in db/db mice.	Tsuneki *et al.* [49]
	Non-elderly patients with primary insomnia	Increased SE, decreased LPS, and decreased WASO	Herring *et al.* [152]
	Patients with primary insomnia	Showed greater efficacy than placebo in improving subjective TST and subjective TSO; was generally safe and well tolerated over 1 year of nightly treatment.	Michelson *et al.* [64]
	Nonelderly and elderly patients with insomnia.	Improved sleep onset and maintenance over 3 months of nightly treatment and was generally safe and well tolerated.	Herring *et al.* [57]
	Patients with insomnia	Increased TST (average increase ≤ 3.9% in REM sleep) and reduced REM sleep latency.	Snyder *et al.* [66]
	Elderly patients with insomnia	Generally improved sleep maintenance and onset over 3 months of nightly treatment and was well-tolerated.	Herring *et al.* [56]
	Elderly and nonelderly insomnia patients	Generally effective and well tolerated in both women and men with insomnia.	Herring *et al.* [59]
	Psychiatric inpatients with insomnia	Overall improvement in the quality of sleep and the severity of anxiety and depression.	Nakamura *et al.* [89]
	Adolescent patients with insomnia	Improved sleep quality in adolescent insomnia.	Kawabe *et al.* [62]
	Japanese elderly patients with chronic insomnia	Appeared to be more cost-effective than the alternative zolpidem in a virtual cohort.	Nishimura and Nakao [153]
	Elderly and non-elderly insomnia patients	Improved sleep to a greater extent than placebo as assessed by the ISI.	Herring *et al.* [63]
	Insomnia patients	Reduced WASO by reducing the number and time spent in long wake bouts.	Svetnik *et al.* [154]
	Healthy young men (18–45 years old)	Decreased LPS and wake after sleep onset time and increased SE; did not affect EEG frequency bands.	Sun *et al.* [60]
	Patients with primary insomnia	Limited effects on EEG power spectral density compared with placebo.	Ma *et al.* [65]
	Alzheimer's disease patients with insomnia	Adequate efficacy for the treatment of insomnia in patients with Alzheimer's disease.	Hamuro *et al.* [69]
	Patients with type 2 diabetes mellitus and insomnia	Increased TST and SE and decreased glucose levels.	Toi *et al.* [70]
	COPD patients	Did not have an overt respiratory depressant effect.	Sun *et al.* [76]
	Healthy adult men and women	Lacked clinically important respiratory effects during sleep.	Uemura *et al.* [74]
	Patients (18–65 years old) with OSA	Did not appear to have clinically important respiratory effects during sleep.	Sun *et al.* [75]

Table 1 continued

Manipulation and target	Subjects	Findings	References
Almorexant (ACT-078573) DORA	Healthy male participants	Equivalent to zolpidem with regard to subjectively assessed alertness.	Hoever *et al.* [155]
	Mice	Increased REM and NREM sleep in wild-type mice but not in OX2R-knockout mice.	Mang *et al.* [43]
	Mice	Promoted sleep and exacerbated cataplexy in a mouse model of narcolepsy.	Black *et al.* [156]
	Rats	Promoted sleep without impairing memory performance.	Morairty *et al.* [157]
	Rats	Promoted sleep but was permissive for the activation of wake-promoting systems.	Parks *et al.* [51]
	Male and female adult patients with primary insomnia	Decreased subjective WASO, decreased objective and subjective LPS, decreased the latency to sleep onset, and increased objective and subjective TST.	Black *et al.* [158]
	Elderly patients with primary insomnia	Increased TST, decreased WASO, and decreased LPS.	Roth *et al.* [159]
SB-649868 DORA	Healthy male volunteers	Increased TST and REM sleep duration, decreased WASO and LPS, and decreased the latency to REM sleep; did not affect SWS or EEG power spectra in NREM sleep.	Bettica *et al.* [67]
	Male patients with primary insomnia	Decreased LPS, decreased WASO, increased TST, increased REM sleep, and decreased REM sleep latency.	Bettica *et al.* [68]
Lemborexant (E2006) DORA	Mice	Efficacy demonstrated in an *in vivo* study that used objective sleep parameter measurements.	Yoshida *et al.* [160]
	Adults and elderly subjects with insomnia	Improved SE and subjective SE, decreased LPS and subjective sleep onset latency, and decreased WASO and subjective WASO.	Murphy *et al.* [26]
Seltorexant (JNJ-42847922 and MIN 202) SORA2	Rats, mice, and healthy humans	Reduced latency to NREM sleep and prolonged NREM sleep duration in rats but not in OX2R-knockout mice; increased somnolence in healthy humans.	Bonaventure *et al.* [102]
	Individuals with insomnia	Increased TST, decreased LPS, and decreased WASO in individuals with insomnia without psychiatric comorbidity.	De Boer *et al.* [78]
	MDD patients with persistent insomnia	Decreased LPS and increased TST and SE, accompanied by a tendency to subjectively improved mood in antidepressant-treated MDD patients with persistent insomnia.	Brooks *et al.* [77]
MK-1064 SORA2	Rats, dogs, and healthy humans	Increased NREM and REM sleep.	Gotter *et al.* [42]
JNJ-54717793 SORA1	Rats and mice	Minimal effects on spontaneous sleep in rats and wild-type mice; selectively promoted REM sleep in OX2R-knockout mice.	Bonaventure *et al.* [45]
IPSU SORA2	Mice	Influenced sleep only during the active phase and induced sleep by increasing NREM sleep.	Hoyer *et al.* [48]
Compound 5 DORA	Rats	Decreased locomotor activity and the time awake and increased REM sleep and delta sleep.	Whitman *et al.* [161]
3,9-diazabicyclo[4.2.1]nonanes DORA	Rats	Better oral bioavailability and exerted sleep-promoting activity in a rat EEG model.	Coleman *et al.* [162]

COPD, chronic obstructive pulmonary disease; DORA, dual orexin receptor 1/2 antagonist; E2006, (1*R*,2*S*)-2-{[(2,4-dimethylpyrimidin-5-yl)oxy]methyl}-2-(3-fluorophenyl)-*N*-(5-fluoropyridin-2-yl)cyclopropanecarboxamide; EEG, electroencephalogram; IPSU, 2-([1H-Indol-3-yl]methyl)9-(4-methoxypyrimidin-2-yl)-2,9-diazaspiro[5.5]undecan-1-one; ISI, Insomnia Severity Index; LPS, latency to persistent sleep; MDD, major depressive disorder; NREM, non-rapid-eye-movement; OSA, obstructive sleep apnea; OX1R, orexin type 1 receptor; OX2R, orexin type 2 receptor; REM, rapid-eye-movement; SE, sleep efficiency; SORA1, selective orexin receptor 1 antagonist; SORA2, selective orexin receptor 2 antagonist; TSO, time to sleep onset; TST, total sleep time; WASO, wake after sleep onset.

been shown to decrease reward thresholds, impulsive-like behavior, and cocaine self-administration, and these effects are reversed by dynorphin blockade with nor-binaltorphimine [21, 104]. Cocaine has been shown to modulate the σ1 receptor–corticotropin-releasing factor-1 receptor–OX1R complex. The SORA1 SB-334867 blocks the reinstatement of cocaine-induced conditioned place preference (CPP) that is induced by an intra-VTA microinjection of orexin-A [85, 105]. A recent study showed that intermittent access to cocaine produces a multi-endophenotype addiction-like state and persistently increases the number of orexin neurons and orexin neuron activity in the LH. The pharmacological blockade of OX1Rs with SB-334867 and the selective knockdown of orexin neurons in the LH reduce the motivation for cocaine and attenuate the addiction-like phenotype [106]. SB-334867 decreases cocaine self-administration in both rats and female rhesus monkeys. It also reduces the motivation for cocaine-associated cues and blocks the cue-induced reinstatement of cocaine-seeking behavior [107–109]. SB-334867 and almorexant, but not the SORA2 4PT, attenuate the cocaine-induced inhibition of dopamine uptake and reduce cocaine self-administration [110]. Prolonged access to cocaine self-administration enhances γ-aminobutyric acid neurotransmission in the medial CeA, and intra-CeA microinjections of SB-334867 reduce cocaine intake and attenuate the yohimbine-induced reinstatement of cocaine-seeking [111]. Systemic administration of the SORA2 RTIOX-276 decreases responding for cocaine under high-effort conditions and attenuates the cocaine-induced inhibition of dopamine uptake [112]. The DORA suvorexant attenuates the motivational and hedonic properties of cocaine and impulsive cocaine-seeking [113, 114]. The overall abuse liability of suvorexant has been shown to be low in both rodents and healthy recreational polydrug users with a history of sedative and psychedelic drug use [115, 116].

The orexinergic system has been implicated in the motivational effects of alcohol and opioids as well as other addictions [21, 117]. The SORA1s SB-334867 and GSK1059865 decrease alcohol intake and preference and reduce relapse to alcohol drinking but have no effects on sucrose intake [118–120]. SB-334867 selectively reduces alcohol self-administration and cue-induced reinstatement in highly-motivated rats [121]. SB-334867 inhibits the acquisition and expression of locomotor sensitization induced by morphine and amphetamine [122, 123]. SB-334867 also significantly attenuates morphine-induced CPP but does not affect morphine-induced hyperactivity [124]. SB-334867 reduces the motivation for the opioid remifentanil and reduces the cue-induced reinstatement of remifentanil-seeking in low takers [125]. Systemic SB-334867 administration significantly attenuates naloxone-induced morphine withdrawal symptoms and blocks

activation of the NAc shell [126]. Intra-LC microinjections of SB-334867 significantly attenuate the somatic signs of morphine withdrawal, and this is blocked by the GABA_A receptor antagonist bicuculline [127, 128]. Intra-VTA microinjections of SB-334867 and the DORA2 TCS-OX2-29 significantly attenuate the acquisition and expression of morphine-induced CPP [129]. Intra-dentate gyrus administration of SB-334867 and TCS-OX2-29 attenuates morphine priming-induced reinstatement and the acquisition and expression of LH stimulation-induced CPP in rats [130, 131].

Alcohol intake increases the mRNA levels of OX2Rs but not OX1Rs in the anterior paraventricular thalamus, and microinjections of TCS-OX2-29 but not SB-334867 into this nucleus decrease intermittent-access alcohol drinking [132]. Extended access to intravenous heroin self-administration increases OX2R mRNA levels in the CeA, and systemic administration of the SORA2 NBI-80713 dose-dependently decreases heroin self-administration in prolonged-access rats [133]. The DORA almorexant interferes with the expression of morphine-induced locomotor sensitization, attenuates the expression of cocaine- and amphetamine-induced CPP, and decreases alcohol self-administration [134, 135]. Almorexant does not potentiate the cognitive-impairing effects of alcohol in humans and does not affect motor performance in rats [136, 137]. Sleep disturbances occur during both alcohol exposure and withdrawal. Suvorexant decreases the latency to sleep onset but also exacerbates sleep fragmentation in rats exposed to chronic intermittent alcohol vapor and protracted withdrawal, which may help prevent relapse to alcohol use [138, 139].

Nicotine withdrawal increases the activation of orexin neurons in the LH and activates the PVN. Intra-PVN microinjections of the SORA1 SB334867 attenuate the somatic signs of nicotine withdrawal, but the SORA2 TCS-OX2-29 has no effect [140]. A genome-wide association study showed that the OX2R gene polymorphism Val308Ile is associated with nicotine dependence [141]. The DORA TCS1102 has no significant effects on palatable food self-administration or reinstatement in either hungry or sated rats and does not affect the reinstatement of nicotine-seeking [142, 143]. Administration of the SORA1 SB-334867 and knockdown of the orexin gene in the LH decrease responding for food under both variable-ratio and progressive-ratio schedules of reinforcement (i.e., impair the reinforcing and motivational properties of food) [144]. Contingent self-administration of the synthetic cannabinoid agonist WIN55,212-2 increases the activation of orexin neurons in the LH, and systemic administration of the SORA1 SB334867 but not SORA2 TCS-OX2-29 reduces the reinforcing and motivational properties of WIN55,212-2 [145].

Table 2 Summary of recent findings on orexin receptor antagonists for the treatment of depression and panic/anxiety.

Disorder	Manipulation	Target	Subjects	Findings	References
Depression	LSN2424100	OX2R	Rats	Systemic administration dose-dependently produced antidepressant-like activity.	Fitch *et al.* [87]
	Seltorexant	OX2R	MDD patients with persistent insomnia	Induced a tendency toward subjective improvements in mood in antidepressant-treated MDD patients with insomnia.	Brooks *et al.* [77]
	Almorexant	dual OX1/2R	Mice	Induced a robust antidepressant-like effect in the CUMS model of depression, and this effect was neurogenesis-independent.	Nollet *et al.* [88]
	Filorexant (MK-6096)	dual OX1/2R	Patients with MDD	No significant difference was found in the primary endpoint of change after 6 weeks of treatment.	Connor *et al.* [61]
	Suvorexant	dual OX1/2R	Psychiatric patients with insomnia	Overall improvement in the quality of sleep and the severity of anxiety and depression.	Nakamura *et al.* [89]
Panic/ anxiety	JNJ-54717793	OX1R	Rats	Attenuated CO_2- and sodium lactate-induced panic-like behaviors and cardiovascular responses.	Bonaventure *et al.* [45]
	Compound 56	OX1R	Rats	With a DORA, attenuated CO_2-induced anxiety-like behaviors; Compound 56 attenuated CO_2-induced cardiovascular responses; the SORA2 JnJ10397049 had no effect on panic-like responses.	Johnson *et al.* [101]
	SB-334867	OX1R	Rats	Intracerebroventricular injections decreased seizures and anxiety in pentylenetetrazol-kindled rats.	Kordi Jaz *et al.* [97]
	Compound 56	OX1R	Rats and mice	Attenuated sodium lactate-induced panic-like behaviors and cardiovascular responses.	Bonaventure *et al.* [102]
	SB-334867	OX1R	Rats	Systemic administration blocked panic-like responses.	Johnson *et al.* [94]
	SB-334867	OX1R	Rats	Systemic administration attenuated CO_2-induced pressor and anxiety-like responses.	Johnson *et al.* [96]
	SB-334867	OX1R	Rats	Attenuated FG-7142-induced anxiety-like behaviors and increased heart rate.	Johnson *et al.* [100]
	SB-334867	OX1R	Rats	Microinjection into the trigeminal nucleus caudalis inhibited orofacial pain-induced anxiety-like behavior in rats.	Bahaaddini *et al.* [99]
	SB-334867	OX1R	Rats	Systemic administration had opposite effects on arousal in adolescent and adult males and had no effect on anxiety-like behavior.	Blume *et al.* [98]

OX1R, orexin type 1 receptor; OX2R, orexin type 2 receptor; MDD, major depressive disorder; CUMS, chronic unpredictable mild stress; CO_2, carbon dioxide; SORA2, selective orexin receptor 2 antagonist; DORA, dual orexin receptor 1/2 antagonist.

Overall, OX1R antagonists may be useful for the treatment of cocaine and other drug addictions [146, 147] (Table 3).

Further Challenges and Unique Opportunities for the Application of Orexin Receptor Antagonists to Treating Psychiatric Disorders

Significant progress has been made in understanding the role of the orexin system in physiological processes and pathological behaviors. Hypothalamic orexin neurons have extensive projections throughout the central nervous system and act as regulators of sleep-to-wake transitions, emotion, and motivation [6]. Technical advances have allowed more precise manipulation of orexin neurons and their target brain regions, revealing the dysregulation of orexin function in various psychiatric disorders. Targeting the orexin system may be a promising strategy for the treatment of such disorders. Suvorexant has been found to promote sleep and was the first orexin receptor antagonist to be approved by the FDA in 2014 for the treatment of primary insomnia [25, 148]. The approval of suvorexant for the treatment for insomnia has helped pave the way for the development of more orexin receptor antagonists for the treatment of other disorders, such as anxiety and addiction.

Table 3 Summary of recent findings on orexin receptor antagonists for the treatment of drug addiction.

Addictive drug	Manipulation	Target	Subjects	Findings	References
Cocaine	Suvorexant	dual OX1/2R	Rats	Attenuated acute cocaine-induced impulsivity when administered systemically or directly into the ventral tegmental area.	Gentile *et al.* [113]
	Suvorexant	dual OX1/2R	Rats	Attenuated motivational and hedonic properties of cocaine.	Gentile *et al.* [114]
	SB-334867	OX1R	Rats	Reduced the acquisition and expression of cocaine self-administration and expression of amphetamine-induced conditioned place preference.	Hutcheson *et al.* [108]
	SB-334867	OX1R	Rats	Systemic administration decreased cocaine intake specifically in prolonged-access rats; microinjections into the central nucleus of the amygdala reduced cocaine intake in prolonged-access rats and attenuated yohimbine-induced reinstatement of cocaine seeking.	Schmeichel *et al.* [111]
	SB-334867	OX1R	Mice	Intra-ventral tegmental area microinjections of orexin-A reinstated extinguished cocaine-induced conditioned place preference in wildtype mice, which was blocked by SORA1 SB-334867.	Tung *et al.* [85]
	SB-334867	OX1R	Mice	Intra-ventral tegmental area injections decreased cocaine self-administration, lateral hypothalamus self-stimulation, and impulsive-like behavior, which were reversed by dynorphin antagonism.	Muschamp *et al.* [104]
	SB-334867	OX1R	Rats	Reduced the motivation for cocaine and attenuated the addiction phenotype.	James *et al.* [106]
	SB-334867	OX1R	Female rhesus monkeys	Decreased cocaine self-administration.	Foltin *et al.* [107]
	SB-334867	OX1R	Rats	Reduced cocaine demand in the presence of cocaine-associated cues and blocked cue-induced reinstatement.	Bentzley *et al.* [109]
	SB-334867	OX1R	Rats	SB-334867 but not the SORA2 4PT attenuated the cocaine-induced inhibition of dopamine uptake and reduced cocaine self-administration.	Prince *et al.* [110]
	Almorexant	dual OX1/2R	Rats	Attenuated the cocaine-induced inhibition of dopamine uptake and reduced cocaine self-administration.	Prince *et al.* [110]
	RTIOX-276	OX1R	Rats	Systemic administration decreased high-effort responding for cocaine and reduced the inhibition of cocaine-induced dopamine uptake.	Levy *et al.* [112]
Alcohol	Suvorexant	dual OX1/2R	Rats	Dose-dependently decreased the latency to REM sleep and SWS onset and produced REM sleep and SWS fragmentation in rats exposed to chronic intermittent alcohol and protracted withdrawal.	Sanchez-Alavez *et al.* [138]
	Almorexant	dual OX1/2R	Healthy humans	Did not potentiate impairing effects of alcohol.	Hoch *et al.* [137]
	Almorexant	dual OX1/2R	Rats	Systemic or intra-ventral tegmental area administration decreased alcohol self-administration.	Srinivasan *et al.* [135]
	Almorexant	dual OX1/2R	Rats	Did not interfere with forced motor performance or grip strength in rats and did not further increase the sedative effects of alcohol.	Steiner *et al.* [136]
	SB-334867	OX1R	Rats	Intra-nucleus accumbens infusions decreased alcohol intake and preference.	Mayannavar *et al.* [118]
	SB-334867	OX1R	Rats	Reduced alcohol relapse drinking.	Dhaher *et al.* [120]
	SB-334867	OX1R	Rats	Attenuated alcohol self-administration and the cue-induced reinstatement of alcohol-seeking in highly motivated rats.	Moorman *et al.* [121]

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Table 3 continued

Addictive drug	Manipulation	Target	Subjects	Findings	References
	GSK1059865	OX1R	Mice	Reduced alcohol drinking in alcohol-dependent mice but had no effect on sucrose intake.	Lopez et al. [119]
	TCS-OX2-29	OX2R	Rats	Microinjections of TCS-OX2-29 but not SB-334867 into the anterior paraventricular nucleus of the thalamus decreased intermittent-access alcohol drinking.	Barson et al. [132]
Opioids	SB-334867	OX1R	Mice	Inhibited the acquisition of morphine-induced locomotor sensitization.	Łupina et al. [123]
	SB-334867	OX1R	Rats	Intra-locus coeruleus microinjections significantly attenuated somatic signs of naloxone-induced morphine withdrawal, which was blocked by the GABA$_A$ receptor antagonist bicuculline.	Davoudi et al. [127]
	SB-334867	OX1R	Rats	Intra-locus coeruleus microinjections attenuated the expression of glutamate-induced morphine withdrawal during the active phase.	Hooshmand et al. [128]
	SB-334867	OX1R	Mice	Systemic administration significantly attenuated naloxone-induced morphine withdrawal symptoms.	Sharf et al. [126]
	SB-334867	OX1R	Mice	Significantly attenuated morphine-induced conditioned place preference but not morphine-induced hyperactivity or sensitization.	Sharf [144]
	SB-334867	OX1R	Rats	Intra-ventral tegmental area microinjections significantly attenuated the acquisition and expression of morphine-induced conditioned place preference.	Farahimanesh et al. [129]
	SB-334867	OX1R	Rats	Intra-dentate gyrus administration dose-dependently attenuated morphine priming-induced reinstatement.	Ebrahimian et al. [130]
	SB-334867	OX1R	Rats	Reduced motivation and the cue-induced reinstatement of remifentanil-seeking in low takers.	Porter-Stransky et al. [125]
	NBI-80713	OX2R	Rats	Systemic administration dose-dependently decreased heroin self-administration in prolonged-access rats and had no effect on food pellet self-administration.	Schmeichel et al. [133]
	TCS-OX2-29	OX2R	Rats	Intra-ventral tegmental area microinjections significantly attenuated the acquisition and expression of morphine-induced conditioned place preference.	Farahimanesh et al. [129]
	TCS-OX2-29	OX2R	Rats	Intra-dentate gyrus administration dose-dependently attenuated morphine priming-induced reinstatement.	Ebrahimian et al. [130]
Amphetamine	Almorexant	dual OX1/2R	Rats	Attenuated the expression of cocaine- and amphetamine-induced conditioned place preference but not morphine-induced conditioned place preference; interfered with the expression of morphine-induced locomotor sensitization but not cocaine- or amphetamine-induced locomotor sensitization.	Steiner et al. [134]
	SB-334867	OX1R	Rats	Reduced amphetamine-induced dopamine outflow in the nucleus accumbens shell and decreased the expression of amphetamine sensitization.	Quarta et al. [122]
Cannabis	SB334867	OX1R	Mice	Systemic SB334867 administration but not the SORA2 TCSOX229 reduced the reinforcing and motivational properties of the synthetic cannabinoid agonist WIN55,212-2.	Flores et al. [145]
Nicotine	TCS 1102	dual OX1/2R	Rats	No effect on the reinstatement of nicotine seeking.	Khoo et al. [143]
	SB334867	OX1R	Mice	SB334867 but not the SORA2 TCS-OX2-29 attenuated somatic signs of nicotine withdrawal.	Plaza-Zabala et al. [140]

OX1R, orexin type 1 receptor; OX2R, orexin type 2 receptor; REM, rapid-eye-movement; SWS, slow-wave sleep; SORA1, selective orexin receptor 1 antagonist; SORA2, selective orexin receptor 2 antagonist; DORA, dual orexin receptor 1/2 antagonist.

Further research is needed to optimize orexin receptor antagonists across diverse structural classes with better physicochemical properties (e.g., better solubility, higher functional and binding potencies at orexin receptors), and better pharmacokinetics (e.g., slower blood clearance, faster distribution, higher oral bioavailability, a plasma half-life that is appropriate for rapid sleep onset and maintenance, brain penetration, and *in vivo* activity) [149].

Hypothalamic orexin neurons have extensive projections to stress-sensitive brain regions, including the amygdala, BNST, and mPFC. The orexin system plays a critical role in the pathophysiology of stress-related psychiatric disorders [20, 32]. Patients with panic-related anxiety exhibit elevated orexin-A levels in the CSF, and patients with depression have low CSF orexin-A levels [20]. Given the role of the orexin system in the modulation of stress reactivity and fear responses, orexin-related pharmacological targets may represent promising opportunities for the treatment of depression and anxiety. However, clinical trials have reported inconsistent effects in the case of depression. Suvorexant attenuates anxiety and depressive symptoms in psychiatric patients with insomnia, and seltorexant has a tendency to subjectively improve depressive symptoms in antidepressant-treated MDD patients with persistent insomnia, whereas filorexant is not effective in patients with MDD [77, 89, 90]. Orexin system function is downregulated under conditions of chronic stress [20, 150], which may limit the application of orexin receptor antagonists for depression treatment. Nonetheless, SORA1s have been reported to consistently reduce panic- and anxiety-like behaviors in rodents. Further clinical trials are warranted to evaluate their efficacy in patients with anxiety and panic disorders.

Accumulating evidence indicates that the orexin system plays an important role in cocaine, opioid, alcohol, and other addictions. Orexin receptor antagonists, especially SORA1s, reduce drug-induced CPP and decrease the reinforcing and motivational properties of addictive drugs and relapse. Exposure to addictive drugs activates orexin neurons in the LH and regulates glutamatergic or GABAergic neurotransmission within orexin neuron-projecting brain regions, such as the VTA and CeA [104, 106, 111]. Orexin receptor antagonism in these regions also attenuates drug-seeking behavior and relapse. However, most of the currently available data have been derived from preclinical studies, and future work is needed to evaluate the efficacy of orexin receptor antagonists for the clinical treatment of addiction.

In conclusion, orexin receptor antagonism appears to be a very promising therapeutic avenue for the treatment of insomnia and other psychiatric disorders. Targeting the orexin system represents a breakthrough in our understanding of sleep disorders and the treatment of anxiety and drug addiction, although more preclinical and clinical studies are clearly needed.

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