Healthy Sleep, Orexin System and Addiction

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RESUMEN

Introducción: las alteraciones del sueño son frecuentemente reportadas en el contexto de depresión, ansiedad y trastorno por abuso de sustancias, observaciones que han fortalecido la noción de que existe un vínculo subyacente. El sistema orexinérgico inerva simultáneamente los núcleos conocidos por promover el sueño y la vigilia, además de los involucrados en el circuito mesolímbico de la recompensa, por lo que teóricamente, tiene la capacidad de promover tanto la vigilia como aspectos de la conducta adictiva. **Objetivo:** describir tanto el papel del sistema orexinérgico en las conductas de sueño y abuso de sustancias, como el potencial terapéutico de los moduladores orexinérgicos para el tratamiento de estas. **Método:** búsqueda de artículos científicos en bases de datos científicas (*PubMed*, *Scopus* y *Science Direct*) para encontrar información sobre el sueño, el sistema orexinérgico y los trastornos por abuso de sustancias. La información sobre ensayos clínicos con moduladores orexinérgicos fue obtenida en línea de la página web *clinicaltrials.gov* y el registro del *International Standard Randomized Controlled Trial Number* (ISRCTN). **Resultados:** evidencia experimental favorece la noción de que la hiperactividad del sistema orexinérgico puede conducir al insomnio e incrementar conductas de búsqueda de drogas, y que la modulación orexinérgica tiene amplio potencial terapéutico. **Discusión y conclusiones:** el trastorno de abuso de sustancias se presenta frecuentemente con desordenes del sueño, una relación que ha mostrado incrementar la tasa de recaídas. Los antagonistas orexinérgicos reducen la actividad del sistema orexinérgico, lo que incrementa la calidad de sueño y reduce la intensidad de los síntomas de abstinencia en pacientes. Por lo tanto, la hiperactividad del sistema orexinérgico se afianza como el mecanismo subyacente entre trastornos del sueño y abuso de sustancias.

Palabras clave: orexinas, sueño, trastornos por consumo de sustancias, DORAs, SORAs, agonista orexinérgico.

ABSTRACT

Introduction: sleep disturbances are often reported in the context of depression, anxiety, and substance abuse disorder, observations that have strengthened the idea that there is an underlying link between them. Recently, the orexinergic system has been proposed as a possible common regulator, as orexinergic innervation reaches both sleep and wake-promoting centers and the mesolimbic pathway, potentially allowing orexinergic stimuli to promote wakefulness and addiction concurrently. **Objective:** to describe the involvement of the orexinergic system in behaviors such as sleep and substance abuse disorders, and the therapeutical potential of orexin modulators for the treatment of such conditions. **Method:** a search in scientific databases (PubMed, Scopus and Science Direct) was carried out for information regarding sleep, the orexinergic system, and substance abuse disorders. Information regarding clinical trials for orexin modulators was extracted from the clinicaltrials.gov website and the International Standard Randomized Controlled Trial Number (ISRCTN) registry. Results: experimental evidence suggests that orexinergic hyperactivity can lead to insomnia and increase drug-seeking behavior. Therefore, orexin modulators are being tested for their potential as aid in the treatment of substance abuse disorders with alcohol, nicotine, and opioids, leading the ongoing clinical trials. **Discussion and conclusions:** substance abuse disorders are often accompanied by sleep disturbances, a relationship that has been proved to be a risk factor for relapse. In this regard, orexinergic antagonists reduce the activity of the orexinergic system in humans, increasing sleep quality and potentially reducing the intensity of withdrawal symptoms. Therefore, the orexinergic system could function as the proposed link between sleep and issues such as substance abuse, anxiety, and depression.

Keywords: orexins, sleep, substance use disorders, DORAs, SORAs, orexin agonist.

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INTRODUCTION

The Importance of Healthy Sleep

Proper sleep is a vital part of a healthy lifestyle and should be promoted with the same enthusiasm as physical activity and correct nutrition. The American Academy of Sleep Medicine and the Sleep Research Society both agree that healthy sleep should be comprised of adequate duration, good quality, appropriate timing and regularity, and an absence of sleep disturbances or disorders (Watson et al., 2015). Regrettably, it is difficult to guarantee the fulfilment of these conditions in our modern society (Andersen & Tufik, 2015), since sleep has often been underestimated in such a way that an estimated 32% of adults worldwide do not sleep the recommended minimum of 7 hours per night (Coutrot et al., 2022), and many more suffer from difficulties with sleep or even have a diagnosed sleep disorder (Ohayon, 2011).

The negative consequences of not sleeping enough have been widely documented and it is now generally accepted that insufficient or bad quality sleep are a risk factor for many issues ranging from proneness to accidents, low performance, and cognitive impairment, to increased risk of several different medical conditions, including cardiovascular disease, diabetes, obesity, cancer and neurodegenerative diseases (Chattu et al., 2018; Hale et al., 2020).

Mental health has been shown to be particularly vulnerable to the effects of sleep disturbances, as reports have concluded that suboptimal sleep can lead to emotional distress and mood disorders, and the worsening of anxiety and depression (Medic et al., 2017), and that the severity of symptoms appears to be connected with the reported frequency of sleep issues (Tkachenko et al., 2014). Likewise, studies have shown that interventions aimed at improving sleep boost mental health (Scott et al., 2021), further underpinning the relationship between them.

Moreover, it has been noted that sleep impairments are commonly present in the context of substance use disorders, with reports indicating that almost 70% of patients admitted for detoxification complain of sleep problems (Roncero et al., 2012), and these same sleep problems have been identified as a risk factor for relapse (Brower, 2015; Garcia & Salloum, 2015).

Since its discovery at the turn of the century (de Lecea et al., 1998; Sakurai et al., 1998), the orexinergic system has garnered attention for its ability to sustain wakefulness (De Luca et al., 2022), but is now also subject of intense study for its possible link in reward-seeking behavior (Harris et al., 2005).

In this narrative review, we will cover the basics of sleep and its relationship with aspects of mental health and substance abuse, exploring the orexinergic system as the potential underlying factor and a promising therapeutic target.

METHOD

For this non-systematic narrative review, a literary research was carried out for topics relevant to sleep, mental health and substance abuse in articles published since the discovery of the orexinergic system in 1998, in the scientific databases PubMed, Scopus and Science Direct between October 2023 and March 2024. The keywords employed for the search were combinations of the following terms: orexin, hypocretin, antagonist, agonist, SORA, DORA, 1-SORA, 2-SORA, healthy sleep, sleep quality, sleep duration, sleep disorders, sleep disturbances, insomnia, narcolepsy, mental health, substance abuse disorder, withdrawal, relapse, alcohol, opioid, nicotine, cocaine, and morphine. Through this database search, we obtained a total of 83 records while 18 additional references were retrieved from our Mendeley library. Hits were screened by title and abstract and resulted in the elimination of 13 records that were either duplicates or behind a paywall. The remaining 88 articles were revised and another 14 were discarded for containing redundant information or covering topics out of the scope of this narrative review. See Figure 1 for the flow chart of the revision process.

In addition, information regarding clinical trials that involve orexin modulators was gathered from the clinicaltrials.gov and the International Standard Randomized Controlled Trial Number (ISRCTN) registry online databases. Terms used for this search included orexin, hypocretin, agonist, antagonist, suvorexant, lemborexant, daridorexant, vornorexant, seltorexant. All results gathered during the search were screened for identification of clinical trials that employed either orexin antagonists in the context of substance abuse disorders, or evaluation of orexin agonists as a possible treatment for narcolepsy. Trials not meeting these criteria were discarded (Figure 1).

RESULTS

The Basics of Sleep Regulation

Sleep forms part of the sleep-wake cycle (SWC), a circadian rhythm that is tightly regulated by homeostatic

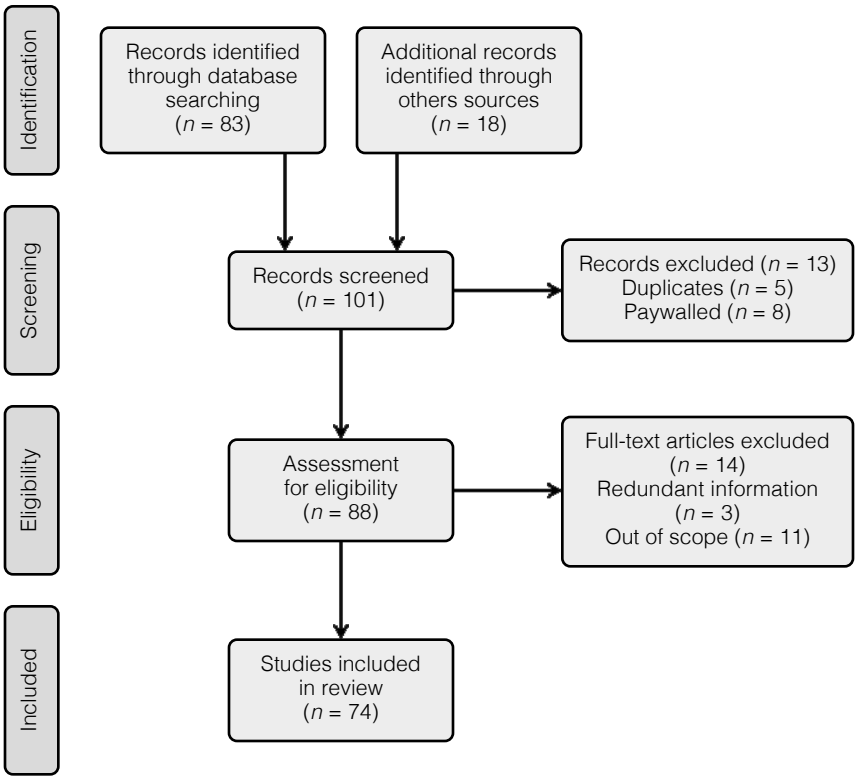

Figure 1. *PRISMA flow chart of the search procedure for this narrative review.*

and environmental factors. According to the two-process model of sleep regulation proposed by Borbély, the homeostatic factors accumulate as a function of time spent awake, increasing the pressure to sleep, and are referred to as process S, while environmental cues, such as the variation of available daylight, drive the circadian pacemaker and are known as process C (Borbély, 1982). Under this model, as process C descends (light of day weans) and process S increases (more time spent awake) a window of opportunity for sleep arises that reaches its peak when both processes are at their most opposite (Borbély et al., 2016). This model has been able to accurately predict sleeping behavior, explaining why we find it easier to sleep at certain hours and why we feel an increased need to sleep the longer we stay awake.

The introduction of the electroencephalogram (EEG) in 1924 by Hans Berger (Kaplan, 2011) has allowed the close examination of electrical brain activity, allowing for distinct sleep patterns to be identified and for sleep to be recognized as a highly active and organized state. Information gathered from these electrophysiological recordings now demonstrates the existence of brain activity that gives rise to two types of sleep, which are referred to as non-rapid eye movement (NREM) sleep and rapid eye movement (REM) sleep (Aserinsky & Kleitman, 2003). While we sleep, REM and NREM appear at regular intervals in a sequential manner, forming cycles throughout the night (Luppi & Fort, 2019; Siegel, 2004).

In addition to the electrophysiological recordings that helped catalyze the science of sleep, biomedical research has been conducted in order to better understand the specific brain structures involved in the genesis of sleep, the maintenance of wakefulness, and the control of phase alternation. This data has now been integrated into what is known as the flip-flop switch model of sleep (Saper, 2013). This model borrows its working idea from the electrical concept of a bistable circuit, a type of system where two stable states (such as on-off or 1 and 0) exist, and transitions are swift and complete once a change is forced. Transferring this idea to the SWC, we find that there are wake and sleep-promoting neurons that form a mutually inhibitory circuit, and the behavioral state of the individual will depend on the group of neurons with prevailing activity (Saper et al., 2001); a similar arrangement has been proposed as regulating the transitions between NREM and REM sleep (Lu et al., 2006).

For sleep promotion, the ventrolateral preoptic (VLPO) and median preoptic (MnPO) nuclei are thought to be the most relevant. Located in the anteri-

or hypothalamus, they are rich in the inhibitory neurotransmitters gamma-aminobutyric acid (GABA) and galanin, respectively (Saper, 2013). On the other hand, wake-promoting nuclei are primarily found in the brainstem and are collectively known as the ascending reticular activating system (ARAS) (Moruzzi & Magoun, 1949). Nuclei of the ARAS include the monoaminergic nuclei *locus coeruleus* (noradrenaline), dorsal raphe (serotonin), tuberomammillary nucleus (histamine), the cholinergic pedunculopontine and laterodorsal tegmentum and the glutamatergic precoeruleus and parabrachial, in addition to the more rostral basal forebrain (rich in acetylcholine and GABA) (Equihua-Benítez et al., 2017).

Besides the above-mentioned nuclei, neurons from the lateral hypothalamus (LH) perform a stabilizing function for the switch with orexinergic cells that maintain wakefulness by increasing the activity of wake-promoting neurons and melanin-concentrating hormone (MCH) producing neurons that promote sleep by inhibiting these same neurons (Hassani et al., 2009; Saper, 2013).

The Orexinergic System and Its Therapeutic Potential

Among the structures mentioned as relevant in the control of the SWC, one has been the subject of intense study since the beginning of the century for its involvement in the maintenance of wakefulness; we are talking about the orexinergic system. Initially, this system was first described, almost simultaneously, by two different groups that suggested orexins played a role in the feeding and energy balance; it has ever since been indistinctly called the orexinergic (Sakurai et al., 1998) or hypocretinergic (de Lecea et al., 1998) system. Shortly after its first description, it was established that the sleep disorder known as narcolepsy was associated with defects in this system in both dogs (Lin et al., 1999) and humans (Mignot et al., 2002; Thannickal et al., 2000), and soon after researchers were able to replicate aspects of the narcoleptic phenotype in mice by targeting the orexinergic system (Chemelli et al., 1999; De la Herrán-Arita et al., 2011; Hara et al., 2001).

The orexinergic system is comprised of somas located in the LH and perifornical dorsomedial hypothalamus, from where they extensively innervate the central nervous system and exert their excitatory action through two G-coupled receptors known as orexin receptor type 1 (OX1R) and type 2 (OX2R) (Peyron et al., 1998). Since their first description, evidence has consistently shown that orexins play a pivotal role in the stability of the SWC, where orexinergic stimulation promotes arousal (Adamantidis et al., 2007; Mieda et al., 2011), while orexin antagonism induces somnolence (Hoever et al., 2012). These findings have given rise to a whole new branch of sleep research, and targeting the orexin system has become the aim of a new class of drugs that have already started to benefit patients suffering from insomnia and have the potential of also aiding narcoleptic patients.

Narcolepsy is a sleep disorder where excessive daytime sleepiness, cataplexy, sleep paralysis and hypnagogic hallucinations are frequent complaints. Using the diagnostic criteria of the International Classification of Sleep disorders 3rd edition (ICSD-3), narcolepsy is classified as either type 1 (NT1) or type 2 (NT2) (Sateia, 2014). This diagnosis, while similar in aspects such as the presence of complaints of excessive somnolence and of sleep onset rapid eye movement periods (SOREMPs), differ in that NT1 requires evidence of low concentrations of orexin A in cerebrospinal fluid (such as ≤ 110 pg/mL when using the Stanford reference sample) and/or cataplexy, while NT2 does not (Scammell, 2018).

Due to narcolepsy development being closely related to the loss of orexinergic cells, orexin replacement therapy has long been thought of as a viable therapeutic option (Mieda et al., 2004), nonetheless it has been observed that orexin peptides do not efficiently cross the blood-brain barrier Fujiki et al., 2003), significantly reducing their clinical potential and therefore creating a need for synthetic compounds. On this point, YNT-185 was the first orexin receptor agonist to be reported (Nagahara et al., 2015), and after evaluation in animal models, it showed promise for reducing cataplectic events and promoting wakefulness through stimulation of OX2R (Irukayama-Tomobe et al., 2017). Since then, several orexinergic agonists have started to emerge and have quickly progressed to clinical studies, some of which are aimed at evaluating their therapeutic potential for narcolepsy (Table 1). Among these, the selective OX2R agonist TAK-994 appeared to be specially promising. Regrettably, however, phase 2 clinical trials were recently halted due to concerns of hepatotoxicity (Dauvilliers et al., 2023). Nonetheless, there are still ongoing trials for other compounds of the same class (see Table 1) such as TAK-861, which has recently been advanced to phase 3 trials for the treatment of NT1, and ALKS 2680, which successfully completed phase 1 trials (Yee et al., 2023) and thus there are plans for starting phase 2 trials sometime during the year 2024.

Notably, new molecules with different mechanisms of action have also started to emerge, such as the novel dual receptor agonist RTOXA-43, that is currently being tested in a preclinical stage and has

Table 1
Clinical trials for Orexin receptor agonists

Compound	*Condition*	*Clinical trial identifier*	*Phase*	*Status*
TAK-994	NT1	NCT04820842	2	terminated
TAK-861		NCT05816382	3	recruiting
ALKS 2680		ISRCTN98204977	1	completed
TAK-861	NT2	NCT05687916	2	active, not recruiting

Note: the revelation that lack of orexin stimulation leads to narcolepsy has long substantiated the notion that orexin replacement therapy will be an effective treatment for this condition. Nonetheless, while initial clinical evidence supports the effectiveness of orexin agonists for sleep consolidation, to date no compound has been granted approval due to safety concerns. NT1 = narcolepsy type 1; NT2 = narcolepsy type 2.

shown to improve wakefulness in aged mice (Zhang et al., 2021), and the first selective OX1R agonist (R)-YNT-3708, which has been recently synthesized (Iio et al., 2023). Due to promising results in the field, researchers are confident that in the next 5 years or so a treatment for narcolepsy which targets the orexinergic system will become available (Table 1).

On the other hand, orexin antagonists have already proven to be useful for the treatment of insomnia, one of the most common medical complaints (Bonnet & Arand, 2018). Orexin antagonists inhibit the orexinergic system by binding to either or both orexin receptors and thus are known as single or double orexin receptor antagonists, or SORAs and DORAs, respectively. Furthermore, SORAs can either be 1-SORAs if they display selectivity for OX1R, or 2-SORAs when they favor OX2R. So far, only DORAs have received the Food and Drug Administration (FDA) approval for the treatment of insomnia, namely suvorexant, lemborexant, and daridorexant (Coleman et al., 2017; Saitoh & Sakurai, 2023), with a fourth DORA, vornorexant (TS-142), expected to follow soon, as results from phase 2 trials were promising (Uchiyama et al., 2022) and phase 3 trials have already been completed. DORAs reduce the orexinergic system's activity, impeding wakefulness and allowing sleep to occur. This is a different mechanism of action from the other therapeutic options available for insomnia, such as benzodiazepine receptor agonists and sedating antidepressants, which induce sedation and are often received with complaints of daytime drowsiness and can be habit-forming (Shaha, 2023).

Although so far only DORAs have reached the market, evidence suggests there's potential for the use of SORAs in the clinical setting, such as the 2-SORAs, seltorexant (JNJ-42847922), that has shown to improve sleep efficiency and appears to be distinctly promising for patients suffering from both depression and insomnia (Jha, 2022), and JNJ-48816274, which has undergone phase 1 trials in an attempt to evaluate its potential effectiveness for the treatment of insomnia. Regarding 1-SORAs, nivorexant (ACT-539313) is the first one to enter clinical testing, albeit for binge-eating disorder (Williams et al., 2024).

Among the benefits of the use of DORAs for the treatment of insomnia, there is no evidence of insomnia rebound or withdrawal, and almost no potential for abuse (Herring et al., 2012). The evidence further suggests that orexin agonists have the potential for reducing drug-seeking behavior, as is the case for suvorexant, which has shown promise in the treatment of opiate withdrawal in patients (Huhn et al., 2022), and a reduction of alcohol self-administration in rats (Flores-Ramirez et al., 2022).

These findings, in addition to the observations that narcoleptic patients seldom abuse their long-term stimulant medication (Brown & Guilleminault, 2011), have added to the notion that the orexinergic system plays a role in the establishment of addictive disorders.

Overlap Between Sleep and the Reward Circuit: The Orexinergic System

The widespread distribution of orexinergic axons allows orexins to participate in several physiological functions besides wakefulness, including feeding behavior, energy homeostasis, thermoregulation, and addiction (Inutsuka & Yamanaka, 2013). Their role in addiction is thought to be related to the orexinergic innervation of the mesolimbic pathway, including the ventral tegmental area (VTA) and nucleus accumbens (NAc) (Peyron et al., 1998), a circuit known to be involved in reward-seeking behavior.

As mentioned earlier, in addition to accumulating sleep debt and increasing the risk of health issues, poor sleep has been found to be associated with substance use (Garcia & Salloum, 2015). In this respect, it is possible that hyperactivity of the orexinergic system underlies both these issues, as studies

have shown that sustained wakefulness, such as that imposed by our modern society, increases orexinergic activation (Zeitzer et al., 2003) which can in turn lead to overstimulation of the limbic system because of the activation of the VTA through OX1R, the subtype of receptors most densely expressed in this region (Marcus et al., 2001). This would lead to the activation of dopaminergic VTA neurons and dopamine release into the NAc and prefrontal cortex, a sequence that can facilitate the establishment of reward-seeking behaviors. This mechanism has been tested in rodents, through the modulation of the orexinergic system, which can promote or diminish the consumption of rewards. For example, agonism of OX1R can increase food intake (Terrill et al., 2016), while the effect of OX1R antagonists has shown to be helpful in reducing the adverse effects associated with withdrawal of drugs such as methamphetamine, nicotine, cocaine, and morphine (Pantazis et al., 2022; Winrow et al., 2010; Ye et al., 2023; Zamanirad et al., 2023).

Evidence suggests that blocking the activity of OX1R can reduce the intensity of withdrawal symptoms, thus it is possible that this therapeutical approach could aid patients struggling with substance abuse disorder since withdrawal avoidance is an important factor behind many cases of relapse, as evidenced in the case of alcohol and opioid abuse (Becker, 2008; Kosten & George, 2002).

DISCUSSION AND CONCLUSIONS

Sleep and Mental Health Are Intrinsically Linked

Since its discovery at the wake of the century, the orexinergic system has propelled the field of sleep research by increasing our understanding of the SWC, and it has also steadily become clear that it is involved in many other physiological processes, including mental health and addiction (Chieffi et al., 2017). Thus, the orexinergic system rises as an underlying link among these different spheres of behavior, and both researchers and clinicians have started to look more closely at the state of sleeping habits among patients as a risk factor for different complications such as anxiety, depression, and relapse. Reports indicate that insomnia is one of the most common sleep disorders observed among patients of substance use disorders (Garcia & Salloum, 2015) and that there is a bidirectional relationship between insomnia, anxiety, and depression (Alvaro et al., 2013). The synergy of these health issues raises additional concerns about increasing the susceptibility of developing a substance abuse disorder. For example, research suggests that insomniacs turn to alcohol use as a hypnotic aid, where there is an initial increase in sleep satisfaction that is quickly followed by the development of tolerance and a subsequent increase in dosage (Roehrs & Roth, 2018), conversely, suffering from insomnia has been observed to increase the likelihood of a relapse to alcohol use (Brower, 2003).

To explain this relationship, Brower proposed a reciprocal causal model, where alcohol use disorder develops after prolonged self-medication for sleep disturbances, which in turn induces maladaptive changes in sleep circuits that eventually cause the development of insomnia (Brower, 2003). Taking into account evidence regarding the neuroplasticity of the orexinergic system, such as the documented upregulation of orexinergic cells observed in both animal models of cocaine, alcohol and opioid consumption (Matzeu & Martin-Fardon, 2022) and in postmortem brain samples of patients of heroin use disorder (Thannickal et al., 2018), as well as the abovementioned increased orexinergic activity after sustained wakefulness, it is possible that the orexinergic system helps sustain an insomnia-substance use disorder loop (Fragale et al., 2021), an observation further cemented by the suppressive effects in drug seeking behavior achieved by systemic administration of 1-SORAs such as SB-334867 (Harris et al., 2005).

While experimental evidence supports the notion that the orexinergic role in motivation and reward is mostly mediated by the activity of OX1R, the majority of current clinical research aimed at evaluating the therapeutic effect of orexin antagonists in various conditions of substance use disorder has been carried out using DORAs and can be consulted in Table 2.

Since DORAs act upon both orexin receptors and several studies support the notion that OX1R and OX2R perform distinct physiological roles (e.g. reward and motivation *vs.* sleep-wake regulation; Perrey & Zhang, 2020), feedback from the current clinical trials will most likely be positive, but it will also face complaints of sleepiness, drowsiness, and tiredness, among others, as these are often reported in the context of their use for insomnia treatment. This suggests 1-SORAs can offer an advantage over DORAs in the treatment of substance use disorders, as they can theoretically offer relief without the drawbacks of sleep regulation issues. For this purpose, there are several newer 1-SORAs that have recently become available and display higher selectivity profiles (Perrey & Zhang, 2020) than those being

Table 2
Clinical trials for orexin receptor antagonists and substance abuse conditions

Compound	*Condition studied*	*Clinical trial identifier*	*Phase*	*Status*
Suvorexant	Substance abuse disorder	NCT03412591	2, 3	completed
	Alcohol use disorder	NCT05656534	1	recruiting
		NCT03897062	2	terminated
		NCT04229095	2	completed
	Cocaine use disorder	NCT03937986	1	completed
		NCT02785406	2	completed
	Methamphetamine use disorder	NCT05711862	2	recruiting
	Nicotine dependence	NCT03999099	1	unknown
		NCT05630781	not applicable	recruiting
		NCT04234997	2	recruiting
	Opioid use disorder	NCT05546515	2	recruiting
		NCT04262193	2	recruiting
		NCT04287062	2	recruiting
		NCT05145764	2	recruiting
		NCT03789214	2	completed
		NCT05829655	early phase 1	recruiting
Lemborexant	Alcohol use disorder	NCT05458609	3	enrolling by invitation
	Opioid use disorder	NCT04818086	1, 2	completed

Note: orexin antagonists have already proven to be effective for the improvement of primary and comorbid insomnia but are now also being investigated for their potential in the context of substance abuse, as evidenced by the many trials evaluating them. Both suvorexant and lemborexant are dual orexin receptor antagonists (DORAs), meaning they inhibit the activity of both orexin receptors (OX1R and OX2R).

typically used, such as SB-334867, one of the most widely used 1-SORA in research that has a reported ~50-fold selectivity for OX1R, meaning it also has relevant effect upon OX2R.

Final comments

Modulation of the orexinergic system has already proven to offer relief for patients suffering from insomnia, and will probably soon be able to aid narcoleptic patients. In addition, experimental evidence makes a strong case for the use of orexin antagonists as therapeutical aids in substance use disorders, and there are currently several clinical trials underway that aim to test this theory in the clinical setting, as evidenced by the compilation in Table 2. As such, it is reasonable to expect orexin antagonists to be soon awarded approval for the treatment of such conditions, which will in turn provide an increase in the available clinical information regarding the orexinergic system's involvement in conditions related to substance use disorders.

It is also worth noting that as the use of orexin modulators becomes more widespread, the evidence will accumulate in favor of their use for the treatment of psychiatric disorders such as depression and anxiety, both of which have strong relationships with sleep.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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