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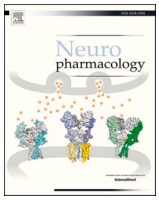

Clinical usefulness of dual orexin receptor antagonism beyond insomnia: Neurological and psychiatric comorbidities

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ABSTRACT

Orexin is a neurotransmitter produced by a small group of hypothalamic neurons. Besides its well-known role in the regulation of the sleep-wake cycle, the orexin system was shown to be relevant in several physiological functions including cognition, mood and emotion modulation, and energy homeostasis. Indeed, the implication of orexin neurotransmission in neurological and psychiatric diseases has been hypothesized via a direct effect exerted by the projections of orexin neurons to several brain areas, and via an indirect effect through orexin-mediated modulation of sleep and wake. Along with the growing evidence concerning the use of dual orexin receptor antagonists (DORAs) in the treatment of insomnia, studies assessing their efficacy in insomnia comorbid with psychiatric and neurological diseases have been set in order to investigate the potential impact of DORAs on both sleep-related symptoms and disease-specific manifestations. This narrative review aimed at summarizing the current evidence on the use of DORAs in neurological and psychiatric conditions comorbid with insomnia, also discussing the possible implication of modulating the orexin system for improving the burden of symptoms and the pathological mechanisms of these disorders. Target searches were performed on PubMed/MEDLINE and Scopus databases and ongoing studies registered on Clinicaltrials.gov were reviewed. Despite some contradictory findings, preclinical studies seemingly support the possible beneficial role of orexin antagonism in the management of the most common neurological and psychiatric diseases with sleep-related comorbidities. However, clinical research is still limited and further studies are needed for corroborating these promising preliminary results.

1. Introduction

Orexins, also known as hypocretins, are neuropeptides consisting of two isoforms, orexin A and orexin B, both synthesized by neurons located in the lateral and dorsal hypothalamic areas and firstly isolated in 1998 (de Lecea et al., 1998; Peyron et al., 1998; Sakurai et al., 1998). These neuropeptides exert their effects by binding to two distinct G-protein-coupled receptors, namely orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R), with OX1R exhibiting selective affinity for orexin A and OX2R displaying non-selective affinity for both orexin A and B (de Lecea et al., 1998; Sakurai et al., 1998).

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Abbreviations

AD	Alzheimer's disease
AHI	apnea-hypopnea index
ALS	amyotrophic lateral sclerosis
BD	bipolar disorder
BDNF	brain-derived neurotrophic factor
BED	binge eating disorder
CID	chronic insomnia disorder
CSF	cerebrospinal fluid
DLB	dementia with Lewy bodies
DORA	dual orexin receptor antagonist
EDS	excessive daytime sleepiness
FDA	Food and drug administration
GAD	Generalized anxiety disorder
GTCS	generalized tonic-clonic seizures
HD	Huntington's disease
ISWRD	irregular sleep-wake rhythm disorder
MDD	major depressive disorder
NREM	non-rapid-eye-movement
OSA	obstructive sleep apnea
OX1R	orexin receptor 1
OX2R	orexin receptor 2
PD	Parkinson's disease
PSG	polysomnography
PTSD	post-traumatic stress disorder
RBD	REM sleep behavior disorder
REM	rapid-eye-movement
RLS	restless leg syndrome
SE	sleep efficiency
SOL:	sleep onset latency
SORA	single orexin receptor antagonist
SUD	substance use disorder
TST	total sleep time
WASO	wakefulness after sleep onset

The orexin system is recognized for its pivotal role in modulating the sleep-wake cycle and contributing to the maintenance of wakefulness, indirectly influencing sleep regulation (de Lecea and Huerta, 2014; Sakurai et al., 2010). In particular, orexin promotes vigilance and co-operates with monoaminergic systems and the histamine pathway to regulate the wake state and synchronize the circadian rhythm of arousal and sleep (Belle et al., 2014; Kantor et al., 2009; Marston et al., 2008). Beyond its involvement in sleep-wake regulation, the orexin system also participates in various physiological functions, including mood, stress, reward, eating, and cognition (Butterick et al., 2013; Chen et al., 2015; Harris et al., 2005; Harris and Aston-Jones, 2006; Messina et al., 2014; Sakurai, 2014; Sargin, 2019; Shimizu et al., 2020; Willie et al., 2001). All these multifaceted functions are mediated by widespread orexin projections and receptors distributed across cortical, subcortical, and brainstem systems (Peyron et al., 1998; Sakurai et al., 2010).

Considering this distinctive role of orexin in participating in several physiological processes, the interest in modulating its output and function grew in the recent past. Accordingly, both agonism and antagonism to orexin receptors has been hypothesized for treating sleep disorders (Chow and Cao, 2016; Mieda and Sakurai, 2013). Mainly narcolepsy, a sleep disorder featured by a selective neuroimmune attack limited to orexin neurons (Nishino et al., 2000), and insomnia, a highly prevalent medical disorder featured by difficulties in initiating and maintaining sleep coupled with daytime impairment (Morin et al., 2015), were recognized as the main diseases to be targeted by the agonism and antagonism to orexin receptors, respectively (Janto et al., 2018; Pizza et al., 2022; Sakurai, 2013).

While the therapeutic potential of replenishing orexin function through receptor agonism is acknowledged in narcolepsy (Sakurai, 2013), current evidence on human patients is limited (Nepovimova et al., 2019; Pizza et al., 2022). Conversely, the clinical significance of targeting the orexin system by antagonizing its receptors for insomnia treatment is well-supported (Equihua et al., 2013; Janto et al., 2018; Kumar et al., 2016; Xue et al., 2022) and a comprehensive model outlining the role of orexin pathways in insomnia has recently been proposed (Palagini et al., 2023).

In the context of sleep regulation, both OX1R and OX2R have been shown to be involved in sleep initiation and maintenance (de Lecea and Huerta, 2014), with preclinical models demonstrating reciprocal interactions between these receptors (Dugovic et al., 2009). Notably, OX2R has been implicated in suppressing non-rapid eye movement (NREM) sleep, while both receptors contribute comparably to rapid eye movement (REM) sleep suppression (Mieda et al., 2011).

Additionally, the association linking sleep deprivation – whether partial, sustained, or total – and increased cerebrospinal fluid (CSF) orexin levels has been documented (Allen et al., 2002; Olsson et al., 2018; Pedrazzoli et al., 2004). Moreover, several animal studies showed that both total sleep deprivation and selective REM sleep deprivation are associated with a higher orexin tone, sustained by increased orexinergic neurons firing and projections (Alexandre et al., 2013; Briggs et al., 2019; Deboer et al., 2004; Mehta et al., 2015; Saper et al., 2001). Starting from these findings, the clinical potential of using the antagonism to orexin receptors in order to downregulate the orexin system and restore sleep in patients with insomnia has been substantiated by preclinical and clinical evidence (Janto et al., 2018; Winrow and Renger, 2014; Xue et al., 2022). Therefore, just under ten years ago, dual orexin receptor antagonists (DORAs) started to be used for treating insomnia in clinical trials and subsequently in real-world studies (Sullivan, 2012; Xue et al., 2022). At the moment, three DORAs have been approved by the Food and Drug Administration (FDA): suvorexant (Jacobson et al., 2014; Yang, 2014), lemborexant (Scott, 2020; Zammit and Krystal, 2021), daridorexant (Markham, 2022). Only the latter (daridorexant) has been also approved by the European Medicines Agency for the treatment of chronic insomnia disorder (CID) (dos Santos and da Silva, 2022).

CID is a frequently reported comorbidity of patients with neurologic or psychiatric disorders (Dauvilliers, 2007; Khurshid, 2018; Mayer et al., 2011, 2021; Riemann, 2007; Taylor et al., 2005). In fact, it frequently represents an unsatisfied complaint since the approved therapeutic opportunities are few and usually not targeted in patients with insomnia symptoms occurring in the clinical picture of other neurologic or psychiatric diseases.

Considering the significant contribution that DORAs may give to the clinical management of patients with CID, the opportunity to use this drug class in patients presenting insomnia as a symptom of neurologic or psychiatric diseases should be thoroughly investigated with specific clinical trials. Therefore, the aim of this narrative review is to share the recent evidence about the role of DORAs in psychiatric and neurological diseases presenting insomnia as a comorbidity, and the potential of targeting the orexin system in patients affected by insomnia comorbid with these disorders to treat sleep and improve the concomitant symptoms in light of the possible role of the orexin system in both sleep and non-sleep related clinical manifestations (Berteotti et al., 2021; Wang et al., 2018; Yeoh et al., 2014).

2. Methods

A comprehensive search for articles published in peer-reviewed

journals over the last decade from January 1, 2014 (year of FDA's first approval of DORA suvorexant) to May 31, 2023 was performed on PubMed/MEDLINE and Scopus databases. Searches were conducted using multiple combination of terms, and relevant articles investigating the use of DORAs on human patients were identified and included in the references of this review. Furthermore, ongoing clinical studies registered on Clinicaltrials.gov involving the principal known DORAs with no published results were searched and subsequently reviewed to explore current and future research directions. In order to retrieve studies on DORAs, the following keywords were used: 'orexin', 'hypocretin', 'suvorexant', 'lemborexant', and 'daridorexant'. In addition, specific keywords were used for target comorbid conditions in combination with 'insomnia'. For neurological and sleep-related disorders, the following terms were used: 'dementia', 'mild cognitive impairment', 'neurodegenerative disorder', 'Alzheimer's disease', 'Parkinson's disease', 'Huntington's disease', 'amyotrophic lateral sclerosis', 'epilepsy', 'migraine', 'obstructive sleep apnea', 'restless leg syndrome', 'sleep disorder'. As for psychiatric disorders, the following keywords were selected: 'psychiatric disorders', 'anxiety', 'post-traumatic stress disorder', 'depression', 'schizophrenia', 'eating disorders', and 'substance use'. Book chapters, monographs, theses, dissertations, non-peer-reviewed material, and non-English articles were excluded. Overall, this search strategy aimed at providing a comprehensive overview of the clinical research concerning the use of DORAs for treating insomnia in patients with neurological and psychiatric disorders and at reviewing current hypotheses on the role of the orexin system in these disorders. To facilitate the interpretation of the reported results, Box 1 features a brief outline of the objective assessment methods employed in sleep medicine, and information on the main sleep variables considered in the reviewed studies is reported in Box 2. A basic graphical representation of the hypothesized interactions between the orexin system and insomnia as a comorbidity of neurological and psychiatric diseases is depicted in Fig. 1.

3. Orexin antagonism in insomnia comorbid with neurological disorders and other sleep disorders: rationale and current evidence

This section illustrates the current clinical evidence concerning the use of DORAs in the treatment of insomnia in comorbidity with several neurological and sleep-related conditions by reviewing the ongoing registered clinical trials and the results of published clinical studies. For each examined condition, the supposed role of the orexin system in its pathophysiology and the prevalence of comorbid sleep disturbances will be briefly outlined. Considering that the pivotal importance of orexin in narcolepsy has been extensively addressed elsewhere (Berteotti et al., 2021; Nishino et al., 2010; Sakurai, 2013) and given that orexin antagonism is not a plausible therapeutic strategy for this disease (Mahoney et al., 2020; Scammell and Winrow, 2011), only common sleep disorders mostly occurring in comorbidity with insomnia will be discussed. The main findings of the studies reviewed in this section are summarized in Table 1, whereas the ongoing clinical studies of interest registered on Clinicaltrials.gov are listed in Table 2.

3.1. Alzheimer's disease

Sleep disturbances including insomnia and sleep-wake rhythm disorders are extremely common among patients with Alzheimer's disease (AD) (Brzecka et al., 2018; Peter-Derex et al., 2015), with up to 39% of AD patients suffering from sleep disorders according to recent evidence (Zhao et al., 2016). Sleep problems frequently appear at an early stage of AD and are associated with an increased risk of institutionalization and worse cognitive decline (McCurry et al., 2000), consistently with the well-documented role of sleep in memory consolidation (Diekelmann and Born, 2010; Rauchs et al., 2010). In fact, sleep alterations may be critically involved in the pathophysiological mechanisms of AD, with chronic sleep disruption impairing the clearance function of the glymphatic system and enhancing the accumulation of amyloid-β (Brzecka et al., 2018; Mander et al., 2016). Degeneration of the hypothalamic orexin system has been reported in AD (Fronczek et al., 2012), and orexin dysfunction might be implicated in AD pathophysiology through several pathways involving a bidirectional relation with amyloid-β

Box 1
Objective sleep assessment: polysomnography and actigraphy

Polysomnography (PSG) is the gold standard method for objective sleep measurement. PSG assessment involves nightly continuous recordings of the electroencephalogram (EEG), electro-oculogram (EOG), and chin electromyogram (EMG) along with electrocardiogram (ECG), measures of respiratory effort, respiratory airflow, oxygen saturation, limb EMG, and video monitoring (videoPSG) (Rundo and Downey, 2019). A PSG study provides information about sleep architecture, and in particular the time spent in each Non-REM and REM sleep stage and other sleep parameters (including sleep onset latency - SOL, wakefulness after sleep onset - WASO, total sleep time - TST, and sleep efficiency - SE) as well as specific sleep measures such as periodic limb movements and the apnea-hypopnea index (AHI, total apneas plus hypopneas per hour of sleep). In clinical practice, PSG is a mandatory exam for the diagnosis of obstructive sleep apnea (OSA) and sleep-related breathing disorders (Kushida et al., 2005; Rundo and Downey, 2019) and is routinely indicated in the evaluation of narcolepsy (along with a multiple sleep latency test), periodic limb movement disorder, and parasomnias or disorders of arousals, and sleep-related hypermotor epilepsy (Kushida et al., 2005).

Actigraphy is a methodology based on small watch-like portable devices that collect movement information for extended periods. An actigraph typically consists of a triaxial accelerometer that quantifies movements, a photodiode that quantifies light exposure, a case temperature sensor to identify periods of device removal, and an event-marker button that the subjects can press to mark a range of events (e.g., the period in and out of bed, diurnal naps, drug intake). Actigraphs are usually worn on the non-dominant wrist and are particularly useful for ecological monitoring of sleep-wake patterns and rest-activity cycles. Actigraphy-based measures of TST and WASO showed high agreement with PSG-derived estimates (Marino et al., 2013), and the possibility to monitor subjects in their natural environment is the key advantage of actigraphy over PSG. Furthermore, along with conventional sleep quantity measures (SOL, WASO, time in bed, TST, and SE), actigraphy allows quantifying different features of the circadian rest-activity rhythm including intraday rhythm fragmentation (IV), day-to-day similarity of activity patterns (IS), relative amplitude of rest-activity rhythm (RA), least active hours (L5), and most active hours (M10) of the day. However, actigraphy does not measure sleep stages, and is not reliable in identifying sleep disorders for which a complete PSG monitoring is required such as OSA (Kushida et al., 2005). On the other hand, its use is recommended in monitoring circadian rhythm sleep disorders and shift work disorder, in characterizing sleep and circadian rhythm patterns in individual with insomnia or hypersomnia and particular populations such as older adults and children (Kushida et al., 2005; Liguori et al., 2023; Morgenthaler et al., 2007; Schutte-Rodin et al., 2008).

Box 2
Sleep variables and their definitions

Total sleep time (TST): time spent asleep from sleep onset to get-up.

Time in bed (TIB): time interval between bed time and get-up time.

Sleep onset latency (SOL): time from bed time to sleep onset.

Wakefulness after sleep onset: time spent awake after sleep onset.

Sleep efficiency index: ratio between TST and TIB expressed in percentage.

Non-REM sleep: time (absolute or percentage) of TST spent in non-rapid-eye-movement sleep stages (N1, N2, N3).

REM sleep: time (absolute or percentage) of TST spent in rapid-eye-movement sleep.

Apnea-hypopnea index (AHI): number of apnea events plus number of hypopnea events per hour of sleep. The AHI value is used to determine the severity of obstructive sleep apnea.

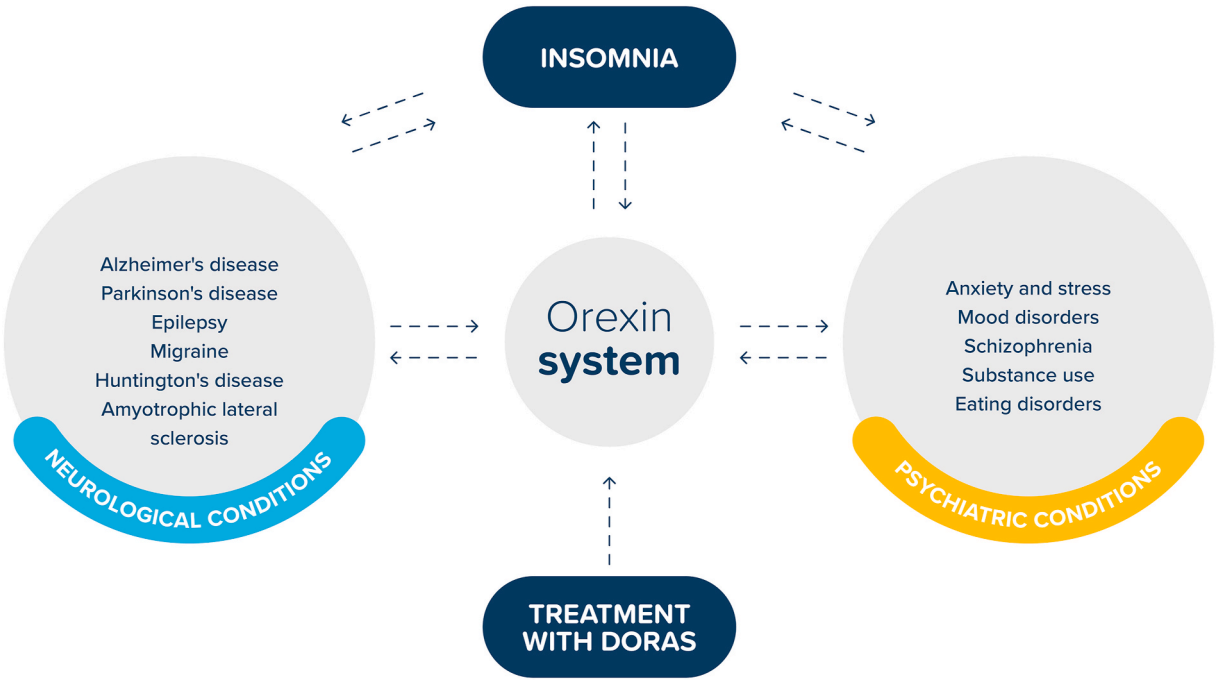

Fig. 1. Possible relations linking the orexin system to insomnia as a comorbidity in neurological and psychiatric disorders.

pathology (Berhe et al., 2020; Dufort-Gervais et al., 2019) (Fig. 2).

In particular, higher CSF level of orexins has been observed in AD patients with significant associations between orexin levels and disrupted sleep macrostructure, cognitive decline, and AD biomarkers (i.e., tau proteins and amyloid-β) (Liguori et al., 2014, 2016; Slats et al., 2012), and correlations between orexin A and amyloid-β and phosphorylated-tau were also found in healthy elderly subjects (Osorio et al., 2016). Furthermore, animal studies showed that direct intra-ventricular administration of orexin promotes wakefulness and increases amyloid-β levels in interstitial fluid and that daily treatment with almorexant (a DORA) reduces the formation of amyloid-β plaques in mice (Kang et al., 2009), while transgenic mice with knocked-out expression of the orexin gene exhibited less wakefulness and reduced amyloid-β (Roh et al., 2014).

Current evidence on the pharmacological treatment of insomnia in AD patients is limited, with contrasting results regarding the efficacy of melatonin (Dowling et al., 2008; Gehrman et al., 2009) and sedative antidepressant (trazodone) or ramelteon (a melatonin agonist) (Camargos et al., 2014; Cordone et al., 2019; Scoralick et al., 2017) and concerns regarding safety and side effects of long-term administration of hypnotics and antipsychotics (Ellul et al., 2006; Peter-Derex et al., 2015). Given the growing body of literature demonstrating the efficacy of DORAs in the management of CID (Wu et al., 2022; Xue et al., 2022) and the previously mentioned association between orexin system dysregulation and AD pathology, recent research has focused on assessing the efficacy and safety of DORAs in AD patients with insomnia. Two studies presented findings from dedicated clinical trials. The first was a double-blind clinical trial that investigated the efficacy of suvorexant in comparison to a placebo on polysomnographic (PSG) sleep measures in patients with probable AD dementia and insomnia ($n = 285$ randomized patients; suvorexant, n=142; placebo, n=143) (Herring et al., 2020). The second study was a phase 2 trial that evaluated the effect of various lemborexant dosages versus placebo on actigraphic parameters in patients with mild-to-moderate AD with irregular sleep-wake rhythm disorder (ISWRD; n = 62 randomized patients; lemborexant 2.5 mg, n = 12; lemborexant 5 mg, $n = 13$; lemborexant 10 mg, $n = 13$; lemborexant 15 mg, n = 12; placebo, n = 12) (Moline et al., 2020). Specifically, Herring et al. (2020) found that suvorexant 10 mg significantly decreased PSG-measured wakefulness after sleep onset (WASO) and increased total sleep time (TST) in comparison with placebo after four

Table 1
Published studies investigating the effect of DORAs in patients diagnosed with a neurological or a sleep-related condition.

Country	Condition	Study design	Administered DORA	Sample	Assessment	Main findings	References	Clinicaltrials.gov identifier
USA	AD with insomnia	RCT	Suvorexant (SUV) 10 mg vs. placebo	$n = 285$ randomized patients; SUV, $n = 142$; placebo, $n = 143$	PSG	Reduced WASO and increased TST measured with PSG in patients receiving SUV after four weeks of treatment. No significant alterations in sleep architecture observed.	Herring et al. (2020)	NCT02750306
USA	AD with ISWRD	RCT	Lemborexant (LEM) 2.5, 5, 10, 15 mg vs. placebo	$n = 62$ randomized patients; LEM 2.5 mg, $n = 12$; LEM 5 mg, $n = 13$; LEM 10 mg, $n = 13$; LEM 15 mg, $n = 12$; placebo, $n = 12$	Actigraphy	Reduced actigraphy-measured least active 5 h and more stable rest-activity rhythm in patients receiving LEM after four weeks of treatment. LEM 5 mg was the most effetive dosage.	Moline et al. (2020)	NCT03001557
USA	Healthy volunteers	RCT	Suvorexant (SUV) 10, 20 mg vs. placebo	$n = 38$ randomized participants; SUV 10 mg, $n = 13$; SUV 20 mg, $n = 12$; placebo, $n = 13$	PSG; CSF amyloid-β and tau levels	No significant differences in sleep parameters after a single-dose administration (SUV vs. placebo). Decrease in amyloid-β observed in participants receiving SUV 10 mg or 20 mg and decrease in the ratio of phosphorylated tau-threonine-181 to unphosphorylated tau-threonine-181in participants administered SUV 20 mg.	Lucey et al. (2023)	NCT03077620
USA	Migraine	RCT	Filorexant (FIL) 10 mg vs. placebo	$n = 235$ randomized patients; FIL, $n = 120$; placebo, $n = 115$	Self-reported electronic headache and sleep diary	No observed differences between patients receiving FIL and those receiving placebo in migraine and headache outcomes and self-reported sleep measures.	Chabi et al. (2015)	NCT01513291
USA	Mild to moderate OSA	RCT	Suvorexant (SUV) 40 mg vs. placebo	$n = 26$ randomized patients; suvorexant to placebo, $n = 13$; placebo to suvorexant, $n = 13$	PSG with finger pulse oximetry	No significant differences in AHI and SpO_2 on day 1 (single dose) and on day 4. Slightly higher AHI on day 4 in patients receiving SUV. Increased REM sleep and TST on day 1 and day 4, increased NREM and SEI on day 1, and decreased WASO on day 1 were observed in the SUV group.	Sun et al. (2016)	NCT01300455
USA	Mild OSA	RCT	Lemborexant (LEM) 10 mg vs. placebo	$n = 39$ randomized patients; placebo to lemborexant, $n = 19$; lemborexant to placebo, $n = 20$	PSG with finger pulse oxymetry	No significant differences in AHI and SpO_2 were observed for LEM vs. placebo following a single dose (day 1) or multiple doses (day 8). No significant differences in percentage of TST during which SpO_2 was below predefined critical thresholds.	Cheng et al. (2020)	NCT03471871
Germany	Mild to moderate OSA	RCT	Daridorexant (DAR) 50 mg vs. placebo	$n = 28$ randomized patients; daridorexant to placebo, $n = 14$; placebo to daridorexant, $n = 14$	PSG with finger pulse oxymetry	No clinically relevant effect of DAR on AHI or SpO_2 during TST was observed after single (day 1) and repeated (day 5) administration. DAR compared with placebo increased TST and SEI and decreased WASO on both day 1 and day 5.	Boof et al. (2021)	NCT03765294
USA	Shift work related sleep difficulties	RCT	Suvorexant (SUV) 10 mg–20 mg vs. placebo	$n = 19$ randomized patients; suvorexant, $n = 8$; placebo, $n = 11$	Actigraphy and self-reported sleep diary	Significant increase in self-reported and actigraphy-measured TST in subjects receiving SUV after one week of treatment and after three weeks of treatment.	Zeitzer et al. (2020)	NCT02491788
Japan	AD with nocturnal delirium	Case-series	Suvorexant (SUV) 15 mg	$n = 4$ hospitalized patients	Clinical observation	Immediate sleep improvement was observed in all cases after SUV administration. In one case, treatment discontinuation led to symptoms recurrence reversed by recommencing SUV.	Hanazawa and Kamijo (2019)	–

Note. AD: Alzheimer's disease; ISWRD: irregular sleep wake rhythm disorder; OSA: obstructive sleep apnea; RCT: randomized controlled trial; PSG: polysomnography; AHI: apnea-hypopnea index; SpO_2: oxygen saturation; TST; total sleep time; SEI: sleep efficiency index; WASO: wakefulness after sleep onset.

week of treatment with mild-to-moderate somnolence being the most common side effect (reported by 4.2% of the patients in the suvorexant group). The authors also observed that suvorexant was mostly effective in mild AD patients, had its largest effect on sleep maintenance in the latter part of the night, and did not significantly alter the overall sleep architecture. As regards the lemborexant study, Moline et al. (2020) reported a decrease in actigraphy-measured least active 5 h (indicating more restful night-time sleep) and a more stable rest-activity rhythm

Table 2
Ongoing studies registered on Clinicaltrials.gov investigating the use of DORAs in patients with insomnia comorbid with neurological and psychiatric disorders.

Trial title	Conditions	DORA	Status	Clinicaltrials.gov identifier
Sleep Trial to Prevent Alzheimer's Disease (SToP-AD)	Sleep; Alzheimer's disease (amyloid positive healthy subjects)	Suvorexant	Recruiting	NCT04629547
A Pilot Study of Suvorexant for Insomnia in Parkinson Disease	Insomnia	Suvorexant	Recruiting	NCT02729714
A Study to Evaluate the Respiratory Safety of Lemborexant in Adult and Elderly Participants With Moderate to Severe Obstructive Sleep Apnea, and in Adult and Elderly Participants With Moderate to Severe Chronic Obstructive Pulmonary Disease	Obstructive sleep apnea; Chronic obstructive pulmonary disease	Lemborexant	Completed	NCT04647383
A Study to Investigate the Effects of Daridorexant on Nighttime Breathing in Patients With Shallow or Paused Breath During Sleep	Obstructive sleep apnea	Daridorexant	Recruiting	NCT05458193
Efficacy of Suvorexant in Patients With Effectively Treated Restless Legs Syndrome and Persistent Chronic Insomnia	Restless leg syndrome; Insomnia; Sleep disorder	Suvorexant	Recruiting	NCT04706091
Treatment of Restless Legs Syndrome With the Hypocretin Antagonist Suvorexant	Restless Legs Syndrome	Suvorexant	Unknown	NCT03755310
Lemborexant Shift Work Treatment Study	Shift-work related sleep disturbance	Lemborexant	Recruiting	NCT05344443
Lemborexant in Delayed Sleep Phase Syndrome	Delayed sleep phase syndrome	Lemborexant	Recruiting	NCT05463861
Suvorexant in the Management Comorbid Sleep Disorder and Alcohol Dependence	Insomnia; Alcohol use disorder	Suvorexant	Recruiting	NCT03897062
The Efficacy of Suvorexant in Treatment of Patients With Substance Use Disorder and Insomnia: A Pilot Open Trial (Suvsubuse)	Sleep disturbance; Craving, Cortisol hypersecretion	Suvorexant	Enrolling by invitation	NCT03412591
Medical Management of Sleep Disturbance During Opioid Tapering	Opioid dependence; Opioid withdrawal; Sleep disturbance	Suvorexant	Completed	NCT03789214
Suvorexant and Sleep's Benefits to Therapeutic Exposure for Posttraumatic Stress Disorder	Posttraumatic stress disorder	Suvorexant	Completed	NCT02849548
Suvorexant: A Dual Orexin Receptor Antagonist for Treating Sleep Disturbance in Posttraumatic Stress	Sleep initiation and maintenance disorders; Posttraumatic stress disorder	Suvorexant	Recruiting	NCT03642028
A Six Week, Randomized, Double-Blind Placebo-Controlled, Suvorexant Augmentation Study of Antidepressant Treatment of Major Depressive Disorder With Residual Insomnia	Depression/Major depressive disorder; Insomnia	Suvorexant	Recruiting	NCT02669030
Suvorexant and Cocaine	Cocaine use disorder	Suvorexant	Completed	NCT03937986
Lemborexant Augmentation of Naltrexone for Alcohol Craving and Sleep	Alcohol Use Disorder	Lemborexant	Not yet recruiting	NCT05458609
Drug-drug Interaction Study of Lemborexant as an Adjunctive Treatment for Buprenorphine/Naloxone for Opioid Use Disorder	Drug Interaction; Analgesics, Opioid (Opioid Use Disorder)	Lemborexant	Recruiting	NCT04818086

after four weeks of treatment in patients receiving lemborexant 2.5, 5, 10, or 15 mg versus placebo. In this trial, lemborexant 5 mg appeared to be the most effective dosage in improving circadian rhythm, and no serious adverse events or worsening of cognitive functions were observed.

Building on the preclinical and observational literature regarding the link between dysregulated orexin expression, amyloid-β accumulation, and tau pathology, a recent study investigated the impact of suvorexant on tau phosphorylation and amyloid-β concentrations in a randomized controlled trial comparing acute administration of two suvorexant dosages (10 mg and 20 mg, with $n = 13$ and $n = 12$ respectively) against a placebo ($n = 13$) in 38 cognitively unimpaired volunteers aged 45–65 years without diagnosed or self-reported sleep disorders (Lucey et al., 2023). Notably, no significant differences in sleep parameters were observed among the three groups. However, participants treated with suvorexant 20 mg exhibited a 10–15% decrease in the ratio of phosphorylated tau-threonine-181 to unphosphorylated tau-threonine-181 (a measure of phosphorylation) when compared to the placebo group, while both suvorexant groups displayed a 10–20% reduction in amyloid-β levels in comparison to the placebo. No decrease was observed at the two other investigated phosphosites (tau-serine-202 and tau-threonine-217).

Future studies should be designed to confirm these promising findings and to investigate the efficacy of other DORAs in the management of insomnia or SWRD in AD patients as well as their impact on other manifestations of the disease and on its pathological processes. In fact, preliminary evidence from a case-series study points out the possible usefulness of suvorexant for the management of nocturnal delirium in AD (Hanazawa and Kamijo, 2019), and an ongoing clinical trial (Clinicaltrials.gov identifier NCT05307692) aims at evaluating the efficacy of the selective single OX2R antagonist (2-SORA) seltorexant in reducing agitation symptoms, aggressive behaviors, and sleep disturbances in AD patients. Furthermore, in line with Lucey et al.'s work (2023), an ongoing clinical study (SToP-AD; Clinicaltrials.gov identifier NCT04629547) is currently investigating whether long-term treatment with suvorexant 20 mg could potentially decelerate amyloid-β accumulation in the brain of cognitively intact subjects with biomarkers consistent with AD pathology, further investigating the potential of DORAs as a preventing treatment for AD.

3.2. Parkinson's disease and dementia with lewy bodies

Sleep disorders represent one of the most common non-motor manifestation of Parkinson's disease (PD), with an overall prevalence ranging between 40% and 90% (Suzuki et al., 2011). Reduced sleep efficiency and increased sleep fragmentation have been observed in PD patients (Zhang et al., 2020), and high rates of circadian dysfunction and sleep disorders such as REM sleep behavior disorder (RBD), restless leg syndrome (RLS), excessive daytime sleepiness (EDS), and insomnia have been reported (Chahine et al., 2017; Peeraully et al., 2012). Notably, RBD has been extensively investigated in PD patients and is currently recognized as a clinical biomarker of synucleinopathies such as PD and dementia with Lewy bodies (DLB) (Chahine et al., 2017; Kim and Jeon, 2014; Liguori et al., 2019). On the other hand, insomnia is highly common in PD with up to 60% of all patients reporting insomnia symptoms due to sleep fragmentation (Mizrahi-Kliger et al., 2022) and yield a major impact on patients' quality of life (Shafazand et al., 2017). Nonetheless, the evidence concerning effective pharmacological management of insomnia in PD patients is scarce, with limited support for the use of dopaminergic medications and mixed results regarding hypnotics (eszopiclone and doxepin) and melatonin (Wallace et al., 2020).

Deterioration of the orexin system has been shown in human PD patients (Drouot et al., 2003; Fronczek et al., 2007; Thannickal et al., 2007) as well as in DLB patients (Lessig et al., 2010). Indeed, the main

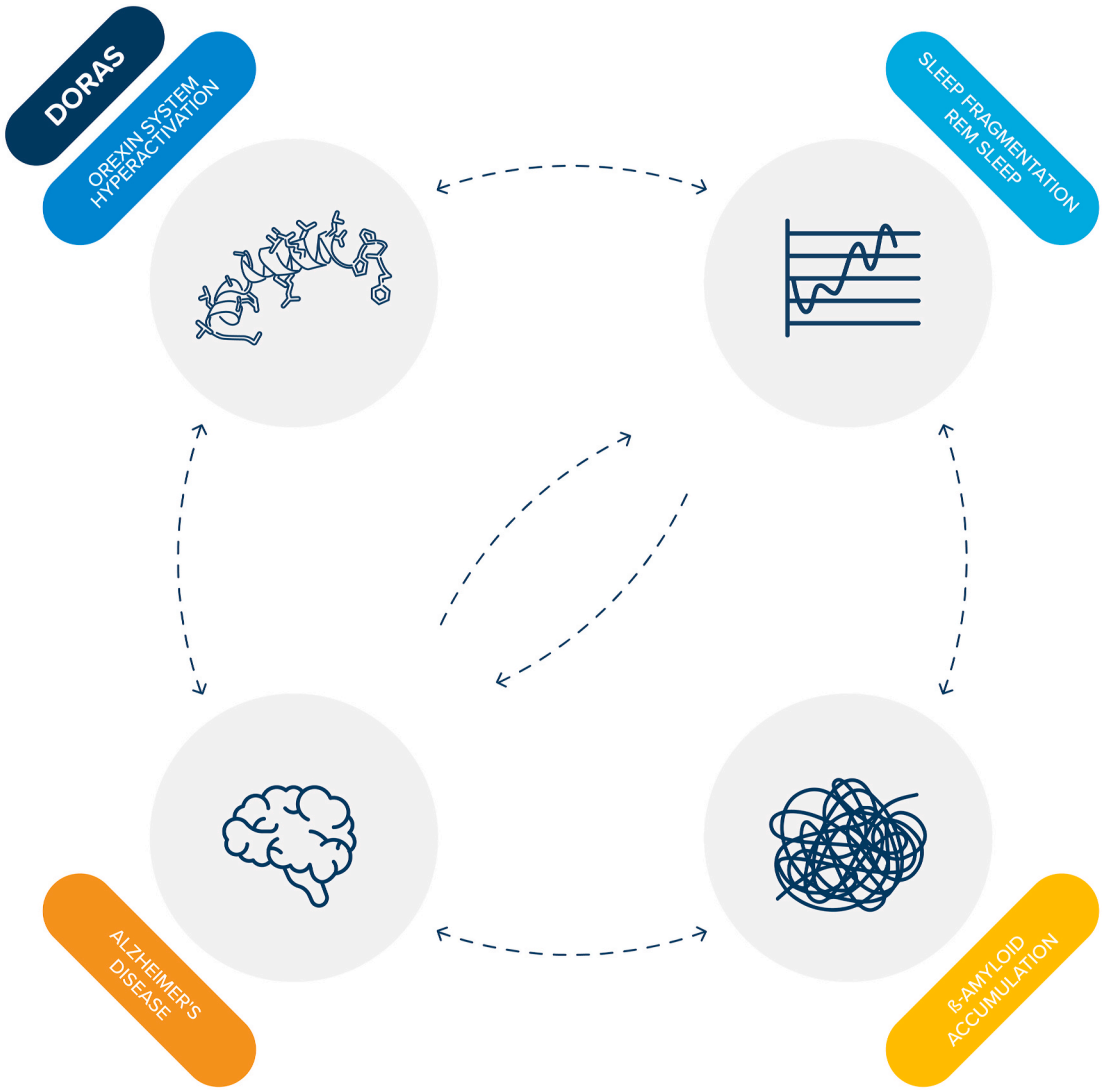

Fig. 2. The hypothesized vicious cycle involving sleep fragmentation, REM sleep impairment, and orexin system hyperactivation in the AD neurodegenerative process. DORAs may reduce orexin system hyperactivity, thus improving sleep and possibly counteracting AD neuropathology.

brain structures implied in motor control are innervated by orexinergic neurons and presents a high expression of orexin receptors (Hu et al., 2015; Xue et al., 2016). Consistently, Hadadianpour et al. (2017) showed that orexin A administration improves motor functions, whereas the administration of the selective OX1R antagonist SB-334867 apparently yields a detrimental effect on motor performance in a rat model of PD. An increase in the firing activity of nigral dopaminergic neurons subsequent to the administration of both orexin A and orexin B was also observed in rodents (Liu et al., 2018). This enhancement of dopamine tone might prevent degeneration of dopamine neurons, playing a protective role in PD. Moreover, orexins' neuroprotective function in synucleinopathies may also involve different mechanism, possibly including the enhancement of brain-derived neurotrophic factor biosynthesis and the induction of hypoxia inducible factor 1 alpha (Berhe et al., 2020).

Concerning the implication of orexins regarding sleep disorders in PD patients, an association among the orexin depletion documented in PD brain, fragmented sleep and EDS has been hypothesized, although current evidence is ambiguous (Baumann et al., 2004; Compta et al., 2009; Wienecke et al., 2012).

Overall, considering the well-documented involvement of the orexin system in PD and synuclein-related pathologies, research on the treatment of insomnia in PD or DLB patients with DORAs should be conducted to evaluate both their efficacy and their safety. In particular, the impact of DORAs on EDS and REM-related sleep disruption should be thoroughly investigated. Currently, no published clinical studies addressed these issues and a single registered pilot clinical trial aiming at assessing the effectiveness and safety of suvorexant 10 mg versus placebo in the treatment of PD patients with insomnia is recruiting patients (Clinicaltrials.gov identifier NCT02729714).

3.3. Other neurodegenerative disorders: amyotrophic lateral sclerosis and Huntington's disease

The above recapitulated implications of orexins in the physiopathology of major neurodegenerative disorders warrant research efforts addressing the possible role of the orexin system in other neurodegenerative disorders such as amyotrophic lateral sclerosis (ALS) and Huntington's disease (HD) (Berhe et al., 2020). However, current evidence is limited and somewhat ambiguous. Concerning ALS, normal orexin levels were observed in patients' CSF (Van Rooij et al., 2009), but significant atrophy of the hypothalamus with loss of lateral hypothalamic orexinergic neurons in comparison with controls was also reported and related to behavioral alterations (i.e., abnormal eating behavior) (Gabery et al., 2021). In addition, orexins up-regulation with increased wakefulness and reduced sleep-time was observed in a mouse model of

ALS (Liu et al., 2015), linking a possible disruption of orexinergic transmission with sleep disturbances in this disease.

Similar conflicting findings have been reported for HD, with patients showing normal orexin levels in the CSF (Baumann et al., 2004; Gaus et al., 2005; Meier et al., 2005) as well as significant loss of orexinergic neurons and reduction in orexinergic signaling (Aziz et al., 2008; Petersén et al., 2005; Roos and Aziz, 2007). A complex dysfunction of the hypothalamus and the limbic system may play a role in the occurrence of the disease's non-motor features, including sleep and circadian rhythm disorders (Petersén and Gabery, 2012). In fact, an abnormal circadian activity profile misaligned from that of the suprachiasmatic nucleus was observed in a murine model of HD (Williams et al., 2011).

Considering this compelling evidence and the reported high prevalence of sleep disorders in both ALS (Ahmed et al., 2016; Boentert, 2019) and HD (Herzog–Krzywoszanska and Krzywoszanski, 2019), the possible role of DORAs in treating comorbid insomnia and ameliorating sleep quality in ALS and HD patients should be evaluated. Clinical studies might be particularly relevant for the management of insomnia symptoms in ALS patients, considering the high frequency of sleep disordered breathing in this population possibly making traditional hypnotics contraindicated. However, no clinical studies investigating the use of DORAs in patients with ALS or HD have been conducted and no ongoing clinical trials are currently registered on Clinicaltrials.gov.

3.4. Epilepsy

Epilepsy is associated with increased risk for many comorbid conditions including sleep disorders (Gilliam et al., 2005; Manni and Terzaghi, 2010). High frequency of insomnia symptoms has been reported among people with epilepsy (PWE), with prevalence rates ranging from 36% to 74% for the diagnosis of insomnia (Macêdo et al., 2017), and the presence of insomnia complaints was shown to be related with higher levels of depressive symptoms and worse quality of life (Quigg et al., 2016). Furthermore, sleep deprivation has been associated with an increased risk of seizures in PWE (Grigg-Damberger and Ralls, 2014; Malow, 2004; Mattson et al., 1965). Therefore, a bidirectional link between epilepsy and sleep has long been recognized and widely described in clinical studies showing an interdependent association between seizures and sleep disorders, where the occurrence of one can exacerbate the other. Specifically, on the one hand, considering the effect of REM sleep on seizures, interictal epileptiform discharges, and high-frequency oscillations, and on the other hand, the increase seizure propensity due to insufficient sleep, sleep deprivation, sleep instability, and selective REM sleep deprivation (Malow and Aldrich, 2000; Ochi et al., 2011), the investigation of the possible role of neurotransmitter systems involved in sleep regulation, such as the orexinergic system, in the pathophysiology of epilepsy is needed (Berteotti et al., 2023). In fact, there is growing evidence that the orexinergic system may play a key role in the onset of seizures, with higher seizure propensity when orexin level is high (i.e., prolonged wakefulness with sleep deprivation, or transition from REM sleep to wakefulness) (Berhe et al., 2020; Ng, 2017). However, available in vivo studies on patients are limited and not conclusive in this regard. One of the main findings emerging from the literature is reported in a large case-control study designed to detect CSF orexin levels in a sample of patients with different neurological conditions, in which authors showed moderate decrease of CSF orexin A after generalized tonic-clonic seizures (GTCSs) in three out of seven epileptic patients (Ripley et al., 2001). In a subsequent research, CSF orexin A concentrations from 21 patients with single and repetitive GTCSs were found to be significantly lower compared to 19 controls, with the lowest levels detected in a subgroup of patients with repetitive GTCSs (Rejdak et al., 2009).

These results point out the complex nature of the relationship between orexin transmission and seizures in epilepsy. Implications for the treatment of PWE should be further investigated. Preclinical studies showed that administration of the DORA almorexant reduced epileptic activities in a mouse model of epilepsy (Roundtree et al., 2016) and that the selective OX1R antagonist SB-334867 elevated seizure threshold in mice undergoing acute seizure threshold tests (Socała et al., 2016). Considering this preliminary evidence and the above outlined implication of the orexin system in epilepsy, the possible role of DORAs in the management of insomnia comorbid with epilepsy should be thoroughly investigated to evaluate both their efficacy and safety in reducing sleep symptoms and their possible direct and indirect effect on seizures frequency and severity. Nonetheless, no studies addressing these issues are currently available and no clinical trials seeking to investigate the efficacy of DORAs in PWE are registered on Clinicaltrials.gov at the moment.

3.5. Migraine

Sleep complaints are common in patients presenting with migraine and headaches, with an increased rate of RLS (Schürks et al., 2014) and highly frequent insomnia complaints (Kelman and Rains, 2005; Rains, 2018) in this clinical population. Furthermore, sleep problems predict new onset or exacerbation of migraine (Boardman et al., 2006), and poor sleep is one of the most common triggers for headache attacks (Pellegrino et al., 2018; Rains, 2018). In turn, migraine patients seemingly use sleep as a relieving strategies for headaches (Haque et al., 2012) and previous research showed that behavioral interventions targeting sleep may be effective in preventing chronic migraine (Yang and Wang, 2017). This well-established bidirectional relation between sleep problems and migraine supports the hypothesis that both sleep disruption and headache might be expression of a common pathophysiological process in which orexins might be implicated. In fact, the hypothalamus is involved in both the modulation of sleep and circadian rhythms and the regulation of multiple pain systems (including the trigeminovascular system (Ashina et al., 2019)), and hypothalamic neuropeptides (i.e., pituitary adenylate cyclase activating protein, oxytocin, and neuropeptide Y) most likely playing a relevant role in migraine symptomatology. In particular, the orexin systems projects to brain areas involved in nociceptive processes including the paraventricular thalamic nuclei, the periaqueductal gray, and the spinal and trigeminal dorsal horns (Holland and Goadsby, 2007), and hence its disruption might alter homeostatic processes in these brain regions contributing to migraine-related pain (Strother et al., 2018). Somewhat consistently, higher CSF levels of orexin were found in patients with chronic migraine and medication overuse, whereas lower levels were observed in patients with episodic migraine (Sarchielli et al., 2008). Furthermore, migraine prevalence has been shown to be significantly increased in patients with narcolepsy (Dahmen et al., 1999, 2003), which is notoriously characterized by an extensive loss of orexinergic neurons (Thannickal et al., 2000). These findings support a complex dysfunction of the orexinergic transmission which might represent a target for migraine treatments directed at the management of both headache and sleep-related symptoms. Indeed, preclinical studies on rodents investigated the effect of both orexin agonism and antagonism on trigeminal nociception. Administration of orexin A (but not orexin B) modulated the pain-related activation of neurons in the trigeminal nucleus caudalis and reduced neurogenic dural vasodilation in rat models of migraine, and OX1R antagonist SB-334867 reversed both the effects (Holland et al., 2005, 2006). On the other hand, the precursor of suvorexant DORA-12 was demonstrated to suppress nocifensive inflammatory response in the trigeminal ganglion induced with the injection of complete Freund's adjuvant (Cady et al., 2014) and to attenuate trigeminal nociceptive activity inducing at the same time an elevation of the threshold for the induction of a KCl-evoked cortical spreading depression in a rat model of migraine aura (Hoffmann et al., 2015).

These last findings suggest that besides their documented effect on insomnia symptoms, non-selective antagonist of OX1R and OX2R could be a viable treatment for migraine pain. Nonetheless, only one clinical study has been conducted on migraine patients (Chabi et al., 2015) to

investigate the effectiveness and safety of the DORA filorexant (which was subsequently showed to be effective in improving sleep efficiency in patients with CID (Connor et al., 2016)) for migraine prophylaxis. In this double blind, randomized clinical trial ($n = 235$ randomized patients; filorexant, $n = 120$; placebo, $n = 115$) (Chabi et al., 2015), patients with migraine received filorexant 10 mg or placebo nightly for three months. Change in mean monthly migraine days was considered as the primary efficacy endpoint, whereas change from baseline subjective sleep parameters as measured with a sleep diary was analyzed as an exploratory efficacy endpoint. At the end of the trial, no significant differences were observed between treatments on migraine or headache outcomes or on self-reported sleep measures. However, filorexant was well tolerated, with no serious adverse events. Somnolence and fatigue were the most common adverse events in the filorexant group (occurring in 13.3% and 8.3% of the patients respectively). Given that this preliminary investigation failed at showing the efficacy of filorexant in migraine management, the authors and subsequent reviews pointed out that the nighttime administration (which was indeed necessary to avoid sedation and somnolence during the day) and the short half-life of filorexant might have overshadowed its possible effect on migraine symptoms and suggest that other pharmacological solutions involving orexin such as selective agents targeting single receptors should be evaluated (Goadsby, 2015; Strother et al., 2018). However, DORAs might still be effective in the treatment of insomnia in migraine patients, possibly resulting in alleviation of pain symptoms via an indirect mechanism. Of particular interest for the purposes of this review, subgroup analyses in the filorexant trial reported by Chabi et al. (2015) showed that a small group of twenty-five patients with self-reported insomnia at baseline obtained a greater benefit from treatment in comparison with patients without insomnia, showing a more pronounced reduction in mean monthly migraine days. Hence, more controlled studies are needed to further evaluate the role of DORAs in insomnia comorbid with migraine. Nonetheless, there are currently no ongoing clinical trials with this aim registered on Clinicaltrials.gov.

3.6. Other sleep disorders

CID and obstructive sleep apnea (OSA) are the most common sleep disorders in the general population. Consistently, OSA and insomnia can frequently co-occur (COMISA, co-morbid insomnia and sleep apnea) (Janssen et al., 2019; Ong and Crawford, 2013; Sweetman et al., 2019) exacerbating patients' sleep impairment and leading to challenges in the therapeutic management of both sleep disorders. Continuous positive airway pressure (CPAP) therapy is the gold standard treatment for moderate to severe OSA, however, it is not well tolerated by patients with COMISA (Sweetman et al., 2017; Wickwire et al., 2010). Although benzodiazepines and Z-drugs are the most commonly used drugs for insomnia treatment (Sateia et al., 2017), controversial data reported the association between Z-drugs use and decreased oxygen saturation during night-time in patients with OSA, whereas a general agreement advises against the use of benzodiazepines in COMISA (George, 2000; Guilleminault, 1990; Mason et al., 2015). Hence, there is a need for safe sleep medications that does not impact nocturnal breathing in patients with COMISA. Accordingly, the effect of DORAs has been investigated on night-time respiratory function in patients with OSA since it has been suggested that orexin may play a relevant role in the regulation of respiration (Carrive and Kuwaki, 2016).

One recent study reported the results of a double-blind, crossover clinical trial investigating the effects of suvorexant versus placebo on PSG sleep measures and oxygen saturation in patients with OSA ($n = 26$ randomized patients; suvorexant to placebo, $n = 13$; placebo to suvorexant, $n = 13$) (Sun et al., 2016). This trial showed that suvorexant did not have clinically important respiratory effects during sleep in patients with mild to moderate OSA at 40 mg dosage after four days of administration. Increase in REM sleep and TST on both day 1 (after a single dose) and day 4 and in Non-REM sleep and SE on day 1 with a decrease in WASO on day 1 were also observed in the group receiving suvorexant. No serious adverse events were reported, with somnolence occurring in 19% of the patients receiving suvorexant. Nonetheless, it is important to note that patients were included in the study regardless of whether or not they had insomnia, and only one patient reported comorbid insomnia. Moreover, a phase 1, randomized, double-blind, placebo--controlled, two-period crossover study evaluated the effect of lemborexant versus placebo on respiratory safety in mild OSA ($n = 39$ randomized patients; placebo to lemborexant, $n = 19$; lemborexant to placebo, $n = 20$) (Cheng et al., 2020). No impairment in night-time respiratory function (i.e., apnea-hypopnea index and peripheral capillary oxygen saturation) was observed with lemborexant dose of 10 mg in mild OSA. No relevant adverse events were observed, with participants reporting similar rates of adverse events while receiving lemborexant and placebo administration. Regarding the effects of lemborexant in moderate to severe OSA, although a study has been concluded, the results have not yet been made public (Clinicaltrials.gov identifier NCT04647383). Similarly to these previous findings, in a recent crossover randomized controlled trial daridorexant ($n = 28$ randomized patients; daridorexant to placebo, $n = 14$; placebo to daridorexant, $n = 14$) did not worse disease severity, improved sleep efficiency, and reduced WASO in mild or moderate OSA patients after five days of administration (Boof et al., 2021). No serious adverse events were observed in this study, with similar incidence following the administration of daridorexant and placebo. Another study is currently ongoing with the aim of further investigating the respiratory safety of daridorexant on severe OSA patients (Clinicaltrials.gov identifier NCT05458193). Overall, the findings of these trials suggest that DORAs improve sleep efficiency and do not worse disease severity in patients with insomnia and either mild or moderate OSA.

In light of the high prevalence of insomnia comorbid with other sleep disorders, two ongoing clinical studies are evaluating the impact of suvorexant on restless leg syndrome (RLS). In particular, one of them (Clinicaltrials.gov identifier NCT04706091) is investigating the effect of suvorexant on actigraphy-derived TST in patients with effectively treated RLS with persistent insomnia, whereas the other (Clinicaltrials.gov identifier NCT03755310) aims at determining whether suvorexant administration over two weeks improves PSG-measured WASO, leg movements, and overall symptoms severity in patients with RLS.

Finally, the use of DORAs in circadian rhythm disorders and related conditions is currently under investigation. A recent randomized controlled study evaluated the effect of suvorexant (three weeks administration, with 10 mg daily dose in the first week and 20 mg daily dose in the next two weeks) versus placebo in a sample of shift workers reporting difficulty sleeping ($n = 19$; suvorexant, $n = 8$; placebo, $n = 11$) (Zeitzer et al., 2020). In this study, suvorexant significantly improved subjective sleep duration in comparison with placebo, with participants in the suvorexant group showing significant and progressive increases in both self-reported and actigraphy-measured total sleep times at the end of the first week of treatment (with 10 mg dosage) and at the end of the third week of treatment (with 20 mg dosage from week 2). In addition, two ongoing clinical studies are recruiting participants to evaluate the effectiveness of lemborexant in increasing daytime sleep in night shift workers with difficulty sleeping during the daytime (Clinicaltrials.gov identifier NCT05344443) and in reducing sleep onset latency in patients with delayed sleep phase syndrome (Clinicaltrials.gov identifier NCT05463861).

Overall, further clinical studies are warranted in order to thoroughly evaluate the effectiveness and safety of DORAs in common sleep and circadian-related condition as well as confirm the promising results obtained on patients with co-occurring insomnia and OSA.

4. Orexin antagonism in insomnia comorbid with psychiatric disorders: rationale and current evidence

This section presents the current clinical evidence about the use of

DORAs in the treatment of insomnia in comorbidity with psychiatric conditions. Insomnia may play an important role as a risk factor, a comorbid condition, and a transdiagnostic symptom in many mental disorders including mood and anxiety disorders, schizophrenia, and substance use disorder (Hertenstein et al., 2019; Palagini et al., 2022). In fact, insomnia is currently considered a complex stress-related sleep disorder with the dysregulation of arousal system being the key component and playing a role in the pathogenesis of mental disorders (Palagini et al., 2022; Riemann et al., 2022). Recently, it has been hypothesized that an orexins overactivation may be associated with stress-related hyperarousal and with the hyperactivation of arousal promoting systems in insomnia (Palagini et al., 2023). Insomnia may also play a role as a marker of disrupted neuroplasticity contributing to dysregulate different neurobiological mechanisms involved in these different mental conditions. By reviewing the ongoing registered clinical trials and the results of published clinical studies for each examined condition, we also reviewed the role of insomnia and the orexin system in the pathophysiology of these mental conditions. The results of the studies reviewed in this sections are briefly reported in Table 3 and pertinent underway studies registered on Clinicaltrials.gov are listed in Table 2.

4.1. Anxiety and stress-related disorders

Anxiety-related conditions are the most common mental health disorders worldwide with a global prevalence of ~25% (American Psychiatric Association, 2022). Anxiety disorders are characterized by persistent feelings of fear and worry with impaired daily functioning and include generalized anxiety disorder (GAD), panic disorder, specific phobias, agoraphobia, social anxiety disorder, and separation anxiety disorder. Insomnia is a major predictor for the onset of anxiety (Hertenstein et al., 2019) and is highly prevalent in individuals experiencing anxiety affecting more than 80% of patients with GAD and 70% of those with panic disorder. Furthermore, comorbid insomnia is an indicator of increased morbidity and low responsiveness to treatment and was shown to be related to the severity of worry, fear, and hypervigilance (Chellappa and Aeschbach, 2022; Palagini et al., 2022). Similarly, a bidirectional relation has been hypothesized between sleep disturbances and stress-related disorder including posttraumatic stress disorder (PTSD). In PTSD, insomnia is an hallmark and is listed among the diagnostic criteria with prevalence rates as high as 90% and a close relationship with disease severity and suicidal risk (American Psychiatric Association, 2022; Richards et al., 2020).

Anxiety and stress-related disorders are caused by a combination of genetic variations and exposure to environmental stressors leading to maladaptive expressions of fearful and anxious responses, potentially linked to deficits in the regulation of prefrontal-cortex-amygdala networks (Schiele and Domschke, 2018). Accumulating findings underscore the significant involvement of sleep-arousal systems in anxiety and stress-related disorders, revealing potential overlaps in neural circuitries regulating both sleep and anxiety (Chellappa and Aeschbach, 2022).

In the context of insomnia, the hyperactivation of stress and inflammatory systems may impair the regulation of prefrontal-cortex-amygdala networks, resulting in functional impairments in the top-down regulation of emotions (Palagini et al., 2022; Riemann et al., 2015). Consequently, insomnia may exert an anxiogenic impact on brain circuitry (Van Someren, 2021). Recent hypotheses suggest that orexin dysfunction plays a role in the hyperactivation of arousal-promoting systems in insomnia (Palagini et al., 2023) as well as in the pathophysiology of stress response and anxiety (Harris et al., 2005; Sargin, 2019).

Although orexinergic neuronal projections are present throughout the brain, they exhibit particularly dense concentrations in areas implicated in various components of anxiety, including the stress and arousal systems with projection to the medial prefrontal cortex (Johnson et al., 2012). Notably, the corticotropin-releasing factor (CRF) system, which mediates the stress response, directly projects to orexinergic neurons. This interaction results in the release of orexins, likely contributing to sustained stress responses with increased levels of arousal (Winsky-Sommerer et al., 2004). Consequently, orexin dysregulation may overlap in insomnia, anxiety, and stress-related disorders, leading to increased orexin release in brain limbic regions that regulate emotion and stress response (Johnson et al., 2012).

In studies involving individual with anxiety disorders higher serum and CSF orexin levels were documented in comparison with controls, suggesting a possible hyperactivity state of the orexin system (Akça et al., 2020; Johnson et al., 2010). Moreover, another study in human subjects reported that variations in OX1R gene, which mediates hyperarousal, was associated with the etiology of panic disorder and agoraphobia. Specifically, the presence of OX1R gene rs2271933 allele was significantly associated with panic disorder and agoraphobia, with the association being more evident in women (Gottschalk et al., 2019). In sum, current evidence clearly indicates that orexin plays a critical role in arousal-based anxiety and suggests that orexin antagonism may be an effective strategy for reducing chronic hyper-arousal and disrupting the negative reinforcement cycle of anxiety. Accordingly, the latest preclinical findings confirmed and expanded previous promising indications of OX1R antagonists as novel-mechanism-based anti-anxiety compounds (Katzman and Katzman, 2022). Similar results have been reported for PTSD and stress-related disorders (Kaplan et al., 2022). In a study conducted on healthy volunteers, suvorexant 10 mg was associated with decreased startle reactivity during anticipatory anxiety but not with fear or no-threat conditions in comparison with placebo (Gorka et al., 2022). In two other studies conducted on patients with insomnia, anxiety, and depression, suvorexant improved not only insomnia symptoms but also anxiety symptoms (Nakamura and Nagamine, 2017; Shigetsura et al., 2022). Conversely, in a randomized controlled trial conducted on patients with trauma-related insomnia, suvorexant reduced both PTSD and sleep-related symptoms, but the same effect was observed for placebo (Mellman et al., 2022).

In this framework, it is likely that targeting insomnia symptoms with DORAs might help to target anxiety as well through the rebalance of the sleep system.

4.2. Mood disorders

Mood disorders are caused by an interplay of biological, psychological, and social factors and include a broad spectrum of conditions encompassing elevated mood, such as mania/hypomania, and depressed mood. Severe presentations, such as major depressive unipolar and bipolar disorders, are amongst the most prevalent and serious diseases with a tendency to be recurrent, chronic and disabling, and associated with a high suicide risk (American Psychiatric Association, 2022).

Insomnia is a frequent comorbid condition in mood disorders and a clinically significant feature highly prevalent across their entire course, as many as 80%–100% of people experiencing insomnia symptoms during the depressive episode and 45%–55% during the bipolar interepisode period. Insomnia was shown to be with illness severity, more adverse course, lower response rates to treatment, and increased suicidal risk (Palagini et al., 2019, 2022). In addition, it plays an important role in relapses and recurrences and is considered an independent risk factor for unipolar and bipolar depression (Hertenstein et al., 2019). Furthermore, persistent hyperactivity in the ventral emotional system that includes the amygdala and the ventral anterior cingulate cortex in insomnia-related hyperarousal (Riemann et al., 2022) might be related to disturbances in affect, including depressed mood, and several other potential mechanisms through which insomnia might increase the risk or perpetuation of mood disorders have been hypothesized and include the dysregulation of multiple systems involved in mood disorders (Palagini et al., 2019).

Several lines of evidence implicate the orexin system in the pathophysiology of major depression (Fagan et al., 2022; Katzman and

Table 3
Published studies investigating the effect of DORAs on patients diagnosed with a psychiatric condition.

Country	Condition	Study design	Administered DORA	Sample	Assessment	Main findings	References	Clinicaltrials.gov identifier
Japan	Diverse psychiatric diagnoses (mainly mood disorders or schizophrenia) with insomnia	Prospective	Suvorexant (SUV) 15 or 20 mg	$n = 40$ psychiatric inpatients	Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder-7 (GAD-7), and Patient Health Questionnaire-9 (PHQ-9)	Improved sleep quality after two weeks of treatment with SUV. Improved self-reported sleep duration and reduced severity of anxiety and depression symptoms after four weeks. Reduced cortisol levels and white blood cell count after eight weeks of treatment.	Nakamura and Nagamine (2017)	–
Japan	Diverse psychiatric diagnoses (mainly MDD, BD, and schizophrenia) with insomnia symptoms	Prospective single-arm clinical trial	Suvorexant (SUV) 15 or 20 mg (15 mg if age ≥65 years, 20 mg otherwise)	$n = 57$ psychiatric outpatients	Self-reported sleep diary, sleep satisfaction visual analog scale	SUV improved self-reported sleep measures (TST, TSO, WASO, and sleep satisfaction) after seven consecutive nightly administrations.	Kishi et al. (2019)	–
Japan	MDD with insomnia symptoms	RCT	Suvorexant (SUV) 15 or 20 mg vs. eszopiclone (2 or 3 mg)	$n = 18$ randomized patients	Insomnia Severity Index (ISI), Pittsburgh Sleep Quality Index (PSQI), Generalized Anxiety Disorder-7 (GAD-7), Beck Depression Inventory II (BDI-II)	After receiving benzodiazepine for more than two weeks, patients were randomized to four weeks of SUV or eszopiclone. Both treatments improved insomnia symptoms and tended to improve symptoms of depression and anxiety after two and four weeks with no relevant adverse events.	Shigetsura et al. (2022)	–
USA	MDD	RCT	Filorexant (FIL) 10 mg vs. placebo	$n = 128$ randomized patients; FIL, n = 64; placebo, n = 64	DSM-IV-TR criteria, Montgomery Asberg Depression Rating Scale (MADRS)	No significant difference in change in MADRS score after six weeks of treatment. Somnolence and suicidal ideation were the most common adverse events.	Connor et al. (2017)	NCT01554176
USA	Trauma-related insomnia	RCT	Suvorexant (SUV) 10 mg increasing to 20 mg after one week vs. placebo	$n = 37$ randomized patients	Clinical interview, Duke Sleep Disorders Interview, Polysomnography	Significant improvement in sleep and PTSD symptoms in both treatment groups. No differences in polysomnographic measures.	Mellman et al. (2022)	NCT02704754
USA	Substance use disorder (cocaine) (non-treatment seeking)	Experimental	Suvorexant (SUV) 5, 10, 20 mg vs. placebo	$n = 7$ subjects	Computerized Structured Clinical Interview for DSM-5 (SCID)	Subjects received SUV or placebo for at least three days before experimental sessions involving cocaine self-administration (of 0, 10 and 30 mg/70 kg) in a drug vs. money choice task. SUV increased self-administration of 10 mg/70 kg cocaine and decreased oral temperature. No other alterations in cocaine effects were observed.	Stoops et al. (2022)	–
Japan	Schizophrenia	Case report	Suvorexant (SUV) 20 mg	$n = 1$ outpatient in once-monthly aripiprazole treatment (300 mg)	Positive and Negative Syndrome Scale (PANSS), Clinical Global Impression-Severity (CGI-S), Athens Insomnia Scale (AIS)	Short-term suvorexant administration improved insomnia symptoms after eight weeks with no adverse events.	Suzuki et al. (2017)	–

Note. MDD: major depressive disorder; BD: bipolar disorder; RCT: randomized controlled trial; TST: total sleep time; TSO: time to sleep onset; WASO: wakefulness after sleep onset.

Katzman, 2022; Khairuddin et al., 2020). In animal studies, increased levels of orexin A have been reported in models of depression (Katzman and Katzman, 2022; Khairuddin et al., 2020). In clinical populations, the increase in CSF Orexin A concentration was found in patients with major depression and bipolar depression, with higher levels corresponding to higher suicide risk (Fagan et al., 2022; Li et al., 2021). However, some studies also reported no orexin levels alterations in major depression (Fagan et al., 2022). Interestingly, two case control studies showed an association between orexin receptor type 1 gene variants and major depression (Fagan et al., 2022). Thus, the dysregulation of the orexin system associated with insomnia might contribute to the onset and maintenance of mood disorders. Accordingly, orexin receptor antagonists have been proposed for the treatment of depression showing antidepressant-like activity in animal models (Fagan et al., 2022; Han et al., 2020). In humans, the efficacy of suvorexant has been investigated in psychiatric inpatients with insomnia in a prospective study conducted by Nakamura and Nagamine (2017) and in patients with major depressive disorder in a randomized clinical trial by Shigetsura et al. (2022), and an improvement in insomnia, depression, and anxiety was found in both studies. Similarly, Kishi et al. (2019) found a significant improvement in self-reported sleep quality, sleep duration, and sleep continuity after one week of treatment with suvorexant 20 mg if ages 18–64 or 15 mg if age $\geq$65 years in 57 psychiatric outpatients reporting insomnia symptoms. Sleepiness and fatigue were the most common adverse events in this study being reported respectively by 29% and 12% of the patients, and no significant psychiatric adverse events were reported. On the other hand, somewhat inconsistently with these findings, the DORA filorexant 10 mg administered at bedtime for 6 weeks showed no efficacy on depressive symptoms in a phase II study by Connor et al. (2017).

The SORA seltorexant, which selectively binds the OX2R, might also be effective in the treatment of insomnia and depressive symptoms (for an overview see Fagan et al., 2022).

Considering this evidence, DORAs might exert a positive effect on depression comorbid with insomnia mainly through their action on the sleep-wake system.

4.3. Schizophrenia

Schizophrenia is a severe and chronic mental disorder with a heterogenous combination of symptoms (i.e. 'positive' symptoms such as hallucinations and delusions and 'negative' symptoms such as emotional withdrawal and cognitive dysfunction; American Psychiatric Association, 2022). Insomnia symptoms are common in patients with schizophrenia and psychotic spectrum disorders with prevalence estimates ranging from 36% to 80% (Cohrs, 2008). In fact, the relation between insomnia and schizophrenia is likely bidirectional, with insomnia worsening schizophrenia symptoms and *viceversa* (Hertenstein et al., 2019). Insomnia might emerge during any stage of the illness, including the prodrome, first episode, acute recurrence, and even during remission stages. In addition, severe insomnia is a major risk factor for relapse of psychosis, and in particular for positive symptoms (including delusions, hallucinations, disorganized thinking and behavior), negative symptoms, and cognitive dysfunctions (Palagini et al., 2022).

The etiology of schizophrenia is complicated and linked to many interactions between genetic susceptibility and environmental factors. One of the main etiological hypotheses concerning schizophrenia stresses the role of the hyperactivity of subcortical dopaminergic functions (Jauhar et al., 2022). Several neurobiological mechanisms may explain the comorbid insomnia observed in patients with schizophrenia. Proposed mechanisms include dopamine dysregulation in schizophrenia and its simultaneous role in the sleep-wake cycle. Human and animal model studies have shown that elevated dopamine levels in the brain may disrupt sleep and circadian rhythms, whereas sleep disruption also increases dopamine release and sensitivity (Ashton and Jagannath, 2020). There is a strong interaction between orexin and dopaminergic neurons in midbrain, thalamocortical, and amygdala suggesting the potential role of orexinergic neurons in modulating dopaminergic neurons and in negative and cognitive symptoms in schizophrenia. Although preclinical data suggest a deficit of orexins in schizophrenia, a recent meta-analysis showed that patients with schizophrenia did not show abnormal plasma levels of orexin A while orexins in CSF have not been evaluated in schizophrenia (Li et al., 2022). According to the results of preclinical studies, drugs activating orexin neurons may be useful in treating the negative symptoms and cognitive deficits in schizophrenia (for a review see Li et al., 2022). On the other hand, DORAs may be useful in the treatment of insomnia comorbid with schizophrenia. Manipulations of sleep can positively impact the treatment of schizophrenia by promoting the restorative effects of sleep on cognition, metabolism, and immune function and by decreasing hyperarousal (Brown et al., 2022). No clinical trials were conducted on the efficacy of DORAs in treating insomnia comorbid with schizophrenia, but the use of suvorexant was reported in a case report on a patient with schizophrenia in treatment with aripiprazole (Suzuki et al., 2017). In this case, short term administration was effective in treating insomnia symptoms without impairment of cognitive functions. However, more studies on insomnia treatment in patients with schizophrenia are needed to understand the potential role of DORAs.

4.4. Substance use disorder

Systematic and narrative literature reviews highlight a bidirectional relationship between substance use and insomnia (Pasman et al., 2020; Provencher et al., 2020). Sleep complaints can be present before substance dependence or abuse, and they are intricately associated to withdrawal and relapse (Provencher et al., 2020), with prevalence estimates for insomnia in individuals with substance use disorder (SUD) ranging from 30% to 85% depending on the specific substance of abuse. Conversely, individuals with insomnia symptoms exhibit a higher frequency of substance use, including alcohol, cocaine, and heroin, compared to those with good sleep patterns (Dolsen and Harvey, 2017; Roehrs and Roth, 2016).

Orexin system overactivation may offer a compelling explanation for this relationship. In fact, the hypothesized activation of the orexin system in insomnia may contribute to drug-seeking behavior by dysregulating motivational and reward circuits (Harris and Aston-Jones, 2006). In the context of SUD, it is conceivable that the orexin system loses its adaptive capacity and orexin peptide production becomes persistently upregulated. As a consequence, hypermotivation for drugs and compulsive behaviors might be enhanced (James and Aston-Jones, 2022). Consistently, the hyperactivation of the orexinergic system has been implicated in the motivational effects of alcohol and opioids as well as other addictive substances (Han et al., 2020).

In humans, orexin serum levels are considered potential biomarker predicting the timing and risk of nicotine relapse in smoking cessation efforts. Similarly, orexin serum levels are increased in chronic alcoholism and positively correlated with the severity of alcohol withdrawal, with the alleviation of withdrawal symptoms linked to a reduction in orexin serum levels (Pan et al., 2018). Consequently, the use of orexin receptor antagonists is emerging as a promising strategy for treating drug addiction (Al-Kuraishy et al., 2020; Han et al., 2020) and DORAs stand out as potential therapeutic agents, particularly in alcohol use disorder, in which their effect on alcohol-related sleep disruption has the potential to mitigate relapse risk (Campbell et al., 2020).

Within this framework, animal studies showed the efficacy of DORAs in attenuating acute cocaine-induced impulsivity, reducing the motivational and hedonic properties of cocaine, diminishing relapse from alcohol and morphine, and ameliorating disrupted sleep related to alcohol withdrawal (Al-Kuraishy et al., 2020; Han et al., 2020). Specifically, various suvorexant dosages (5 mg/kg, 10 mg/kg, and 20 mg/kg) decreased alcohol self-administration and suvorexant 5 mg/kg prevented the reinstatement of alcohol-seeking behavior after extinction

training in male rats with a history of alcohol dependence (Flores-Ramirez et al., 2022), whereas suvorexant 20 mg/kg reduced oxycodone self-administration and reinstatement of oxycodone-seeking in male and female rats after extinction of discriminative stimulus-induced oxycodone consumption (Illenberger et al., 2023).

While several human studies on this topic are currently underway (see Table 3), only three have been completed. Two studies focused on the administration of daridorexant (Berger et al., 2020) or suvorexant (Sun et al., 2015) with alcohol in healthy subjects, and the third study involved the administration of suvorexant to subjects with cocaine use disorder in an experimental protocol detailed in Table 2 (Stoops et al., 2022). Additionally, an ongoing study (Clinicaltrials.gov identifier NCT03937986) aims to further investigate the impact of suvorexant on motivation for cocaine and other clinical outcomes. However, while these studies collectively provide valuable insights, available reports altogether do not provide direct evidence concerning the clinical effectiveness of DORAs in SUD.

In light of this considerations, DORAs emerge as a promising resource in the treatment of drug addiction, targeting both specific mechanisms and comorbid or withdrawal-related sleep problems (Hamidovic, 2022; Khoo and Brown, 2014). Nonetheless, further studies are needed to comprehensively assess their efficacy and safety in patients with SUD.

4.5. Eating disorders

Eating disorders are characterized by abnormal eating behaviors (American Psychiatric Association, 2022) and include bulimia nervosa (binge eating episodes—i.e., consuming an objectively large amount of food in a 2-h period accompanied by a loss of control—coupled with inappropriate compensatory behaviors, such as vomiting, laxative abuse, or excessive exercise), anorexia nervosa characterized as an inability to maintain a healthy body weight, and binge eating disorder (BED) defined by episodes of eating an objectively large quantity of food in a short period of time ($\leq$2 h), coupled with feelings of loss of control over eating. Affected individuals often eat in the absence of hunger and typically experience significant psychological distress after binge eating episodes. Insomnia and eating disorders have a bidirectional relation. Insomnia is related to an increased risk of eating disorders, while in eating disorders a disrupted sleep is present, and comorbid insomnia is also linked to poorer treatment outcomes for eating disorders (Allison et al., 2016).

Since the orexin system is involved in the regulation of both sleep-wake and appetite and increased orexin signaling promotes greater wakefulness and feeding, it has been hypothesized that levels of orexins are increased during the hunger state to promote wakefulness and incite the body to search for food. In this context, even though data on orexin plasma level are controversial in patients with anorexia nervosa, an overactivation of the orexin system has been correlated with both anorexia severity and insomnia severity (Allison et al., 2016). Hence, DORAs may be useful in the clinical management of anorexia nervosa by normalizing sleep, decreasing orexinergic activity, and possibly reducing eating behavior dysregulation. However, no studies have been conducted yet to assess the efficacy of DORAs in patients with anorexia nervosa and sleep problems.

Orexin dysregulation has been also hypothesized in BED, a clinical condition characterized by a compulsivity to eat as such that some proposed that these disorder reflects an “addiction” to food. There is some evidence to indicate that sleep dysregulation itself may contribute to altered feeding behavior, possibly via a reduction in top-down executive control and increased impulsivity. The potential involvement of the orexin system as a common mediator of both compulsive eating and sleep dysregulation in BED raises the possibility that more effective clinical management of BED might be achieved via pharmacotherapies designed to reduce orexin signaling (for an overview see Mehr et al., 2021). In this framework, DORAs might be useful in treating insomnia and improving BED symptoms. A single animal study supports this point, but there are currently no studies investigating the use of DORAs in patients with BED (Mehr et al., 2021).

Indeed, one report showed the efficacy of suvorexant in patients with nighttime eating (Kotorii, 2015), suggesting that DORAs might reduce binge eating by simultaneously reducing food craving via direct actions on OX1R and normalizing sleep by reducing OX2R receptor signaling (Mehr et al., 2021). Further clinical studies should be conducted to confirm this preliminary evidence.

5. Conclusion

The crucial role of sleep in both brain and mental health has been widely acknowledged, and insomnia represents both a risk and a precipitating factor for several neurological and psychiatric disorders. This review comprehensively evaluated the possible beneficial role of orexin antagonism not only on the comorbid insomnia symptoms but also on the other clinical manifestations of major neurological and psychiatric diseases. Moreover, the role of orexin neurotransmission in the disease pathophysiology was examined in order to identify potential preventive strategies and treatments possibly including the use of DORAs. In agreement with the studies reviewed here, since orexin dysregulation and overactivation may be involved in both insomnia and brain or mental disorders, it is indeed conceivable that neurologic and psychiatric disorder may also be treated by targeting insomnia symptom using DORAs in order to positively interfere with their trajectories. In keeping with this hypothesis, Figs. 2 and 3 depict the proposed relationship linking orexin system hyperactivation to AD pathology and anxiety disorder, with the intervening mediation of sleep impairment and fragmentation.

Considering the burden of dementias and neurodegenerative disorders, the high prevalence of epilepsy and migraine in the general population, and the widespread disabling mental disorders affecting the young and the elderly such as depression, SUD, anxiety and stress–related disorders, therapeutic solutions should be expanded with new strategies based on pathophysiological mechanisms. In this context, targeting insomnia and sleep by using DORAs can be considered a promising therapeutic approach in neurological and psychiatric disorders. Indeed, the recent literature reviewed here provided preliminary evidence supporting the use of DORAs in these complex conditions, with several ongoing trials aiming at further investigating and confirming the clinical usefulness of this drug class.

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Data statement

The data supporting the findings of this study are available within the article. The corresponding author can be contacted for further inquiries.

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CRediT authorship contribution statement

Matteo Carpi: Data curation, Investigation, Writing – original draft, Writing – review & editing, Conceptualization. **Laura Palagini:** Conceptualization, Investigation, Supervision, Writing – original draft, Writing – review & editing. **Mariana Fernandes:** Investigation, Writing – original draft. **Carmen Calvello:** Investigation, Writing – original draft. **Pierre Alexis Geoffroy:** Supervision. **Mario Miniati:** Supervision.

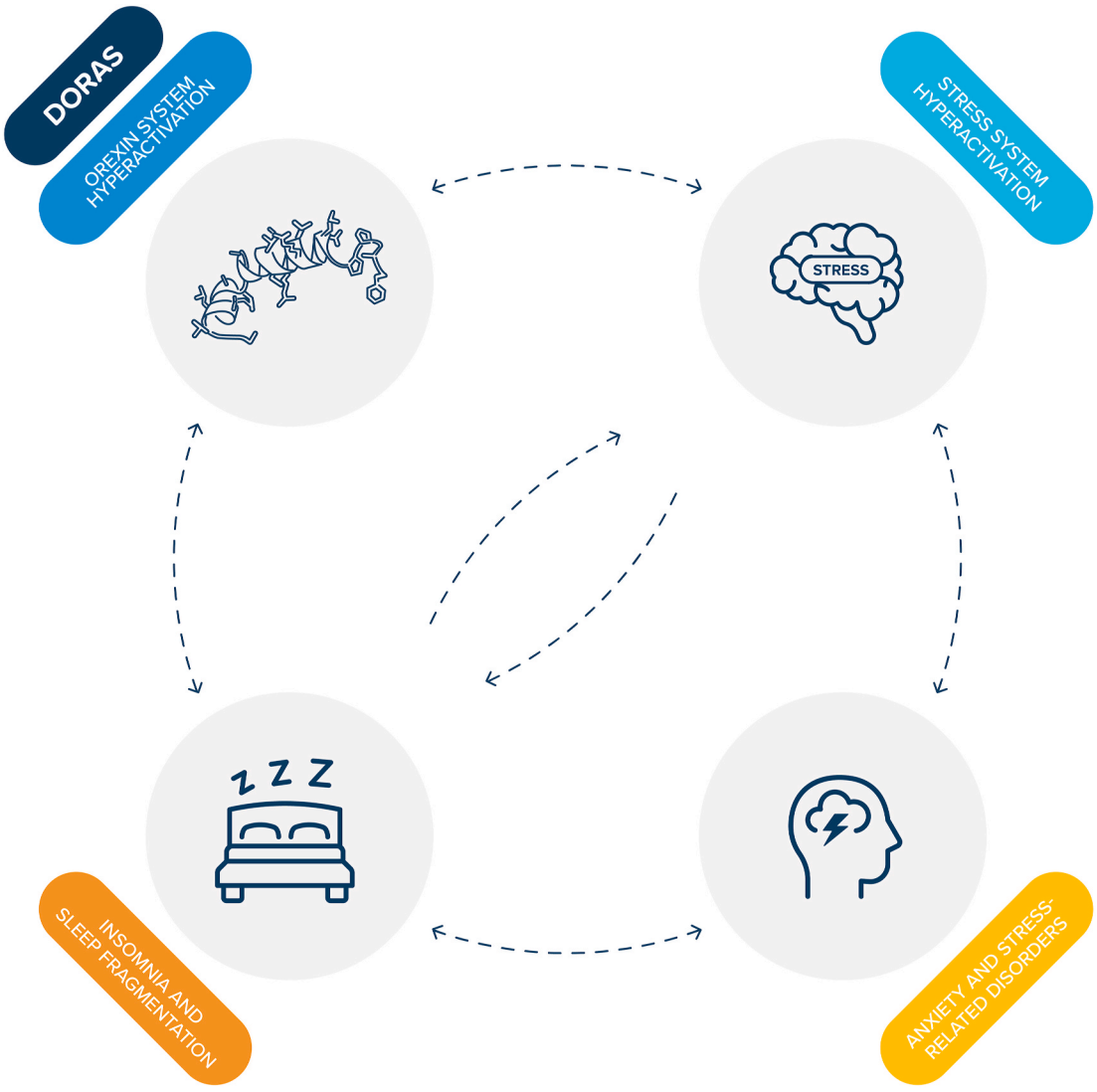

Fig. 3. Insomnia and sleep fragmentation increases the psychological burden in anxiety and stress-related disorders, which in turn are fueled by the hyperactivation of the stress system. Orexin system dysregulation may participate to sleep impairment and can represent a target for DORAs.

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Declaration of competing interest

Laura Palagini serves as a scientific advisor to Idorsia Pharmaceuticals. Claudio Liguori serves as a scientific advisor to and has received scientific support from Idorsia Pharmaceuticals. The remaining authors declare no competing interests.

Data availability

Data will be made available on request.

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