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LEADING ARTICLE

Orexin Receptor Antagonists for the Prevention and Treatment of Alzheimer's Disease and Associated Sleep Disorders

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Abstract

Orexins/hypocretins are neuropeptides produced by the hypothalamic neurons, binding two G-protein coupled receptors (orexin 1 and orexin 2 receptors) and playing a critical role in regulating arousal, wakefulness, and various physiological functions. Given the high prevalence of sleep disturbances in Alzheimer's disease (AD) and their reported involvement in AD pathophysiology, the orexin system is hypothesized to contribute to the disease pathogenesis. Specifically, recent evidence suggests that orexin's influence may extend beyond sleep regulation, potentially affecting amyloid-β and tau pathologies. Dual orexin receptor antagonists (DORAs), namely suvorexant, lemborexant, and daridorexant, demonstrated efficacy in treating chronic insomnia disorder across diverse clinical populations. Considering their stabilizing effects on sleep parameters and emerging evidence of a possible neuroprotective role, these agents represent a promising strategy for AD management. This leading article reviews the potential use of orexin receptor antagonists in AD, particularly focusing on their effect in modulating disease-associated sleep disturbances and clinical outcomes. Overall, clinical studies support the use of DORAs to enhance sleep quality in patients with AD with comorbid sleep and circadian sleep–wake rhythm disorders. Preliminary results also suggest that these compounds might influence AD pathology, potentially affecting disease progression. Conversely, research on selective orexin receptor antagonists in AD is currently limited. Further investigation is needed to explore orexin antagonism not only as a symptomatic treatment for sleep disturbances, but also for its broader implications in modifying AD neurodegeneration, emphasizing mechanisms of action and long-term outcomes.

1 The Orexin System: Brain Structures, Pathways, and Role in Arousal and Sleep

Orexins/hypocretins are neuropeptides that exist in two isoforms derived from a common precursor (prepro-orexin) isolated independently in 1998 by two research groups [1, 2]. The orexin/hypocretin isoforms—orexin-A (hypocretin-1) and orexin-B (hypocretin-2)—are synthesized by a small group of neurons located in the lateral and dorsal areas of the hypothalamus and bind two G-protein coupled receptors, the orexin-A/hypocretin-1 receptor (OX1R) and the orexin-B/hypocretin-2 receptor (OX2R). OX2R has the same affinity for both orexin-A and orexin-B, whereas OX1R binds orexin-A with higher affinity [1–3].

The two orexin receptors are extensively distributed throughout the brain, supporting a diffuse network of projection fibers that target cortical, subcortical, and brainstem regions, establishing the orexin system [3–5]. Although this system is involved in a variety of behavioral and physiological functions (e.g., energy homeostasis, emotion regulation, and reward) [6–11], it predominantly projects to brain areas involved in the regulation of wakefulness and sleep, such as cholinergic neurons in the basal forebrain and noradrenergic neurons in the locus coeruleus [3–5, 12–14]. In short, in the sleep–wake flip-flop model, orexin neurons facilitate prolonged wakefulness by enhancing the activity of aminergic neurons, which in turn inhibit sleep-promoting GABAergic neurons in the ventrolateral preoptic area [5, 15–17]. Conversely, when orexin

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Key Points

Recent research highlights a potential role for orexin neurotransmission in counteracting Alzheimer's disease (AD).

Dual orexin receptor antagonists proved effective in the treatment of insomnia and circadian sleep–wake disorders associated with AD.

Further studies are needed to evaluate orexin antagonism as a preventive strategy against AD neurodegeneration.

neurons are switched to the OFF state, aminergic neurons are not activated and sleep is promoted by the GABAergic neurons [15, 18]. In line with these results, orexin neurons discharge has been shown to be more pronounced during wakefulness and almost absent during sleep [19, 20].

The importance of orexin neurotransmission has been recognized by studying narcolepsy type 1, a sleep disorder characterized by the autoimmune-mediated loss of orexin neurons, which has served as a pathological model of orexin suppression [21]. Consistent with the role of orexin in the sleep–wake cycle, patients with narcolepsy type 1 experience excessive daytime sleepiness with marked instability of both sleep and wake states, manifested by sleep attacks, cataplexy (a sudden loss of muscle tone—as in the REM sleep stage—triggered by strong positive or negative emotions), and sleep paralysis (a dissociated state with loss of muscle tone typical of REM sleep stage coupled with arousal from sleep). Selective agonism of OX2R has shown preliminary, but promising, results in reducing these symptoms [22]. Furthermore, chronic insomnia disorder (ID), which has been hypothesized to be related to overexpression/hyperactivation of the orexin system, is amenable to treatment with pharmacological antagonists targeting OX1R and OX2R [23–27]. Although direct and experimental evidence of orexin dysregulation in chronic ID has not yet been reported, the rationale for the use of dual orexin receptor antagonists (DORAs) in ID has been drawn from research documenting that sleep deprivation (either total or selective) is associated, in humans, with an increase in cerebrospinal fluid (CSF) orexin levels, and in animal model studies, with high orexin-A levels in rat brain tissues from the cerebral cortex, locus coeruleus, and posterior hypothalamus, likely reflecting the increased activation of orexin neurotransmission [28, 29].

Indeed, both OX1R and OX2R play a role in the maintenance of vigilance and wakefulness [30]. However, while OX2R is mainly responsible for sleep–wake rhythm regulation [31, 32], OX1R is significantly involved in reward modulation and emotional regulation [9], in line with its high expression in the locus coeruleus [33, 34]. Consistently, co-administration of OX1R and OX2R antagonists showed attenuated sleep-promoting effects compared with a single OX2R antagonist in rats [32], suggesting that sleep-promoting effects could be efficiently achieved by selectively antagonizing OX2R [35].

In light of this evidence, supported by the growing body of clinical research supporting the efficacy of DORAs [36–38], the modulation of the orexin system by targeting OX2R or both orexin receptors has been hypothesized as a promising pharmacological approach for managing ID and circadian sleep–wake cycle disorders. Nonetheless, given the complex interactions between orexin and other neurotransmitters [39–41], and considering previous evidence achieved in Alzheimer's disease (AD) and showing the correlation of high CSF orexin levels with a more marked sleep impairment, the clinical potential of the orexin antagonism has been investigated [42–44]. Consistently, an association between orexin activity, amyloid-β pathology, and circadian sleep–wake rhythm disruptions has been reported, and sleep promotion has been hypothesized as a therapeutic approach for counteracting the deposition of amyloid-β and the formation of amyloid plaques in the brain [43, 45–48].

This review summarizes the emerging findings on the role of orexin in the pathophysiology of AD and examines the current evidence for the efficacy of orexin antagonism in the treatment of sleep disorders and other behavioral disturbances in AD.

2 Alzheimer's Disease and the Sleep–Wake Cycle

AD presents as a complex disorder characterized by diffuse neurodegeneration starting in the hippocampus and spreading to the cerebral cortex, and is clinically characterized by cognitive decline accompanied by behavioral symptoms manifesting over the course of the disease. According to current research frameworks and guidelines, the pathophysiological hallmarks of AD include extracellular aggregation of misfolded amyloid-β proteins (amyloid plaques), intracellular deposition of twisted strands of tau proteins (neurofibrillary tangles), and evidence of neuronal damage and cell death in the brain [49, 50]. These physiological signs may precede the development of clinical symptoms by several years, primarily affecting memory and other cognitive domains and progressing along a continuum from subjective cognitive complaints to mild cognitive impairment and manifest dementia.

Currently, up to 60–80% of dementia cases are attributable to AD, and the increasing prevalence of the disease combined with the lack of effective treatments makes it a prominent public health and societal problem [50–52]. Moreover, considering that AD is a common neurological disease affecting the elderly, the increase in the mean age of the population may be associated with the progressive increase in the incidence of the disease [53].

In this context, great emphasis has been placed on identifying feasible biomarkers and treatment targets to alleviate symptoms and slow the progression of AD, with increasing evidence highlighting the critical role of sleep disturbances [45, 54–56].

Sleep and circadian sleep–wake cycle disruptions are highly prevalent in patients with AD, with up to 40% experiencing conditions such as sleep-disordered breathing, insomnia, sleep–wake rhythm disorders, excessive daytime sleepiness, and restless legs syndrome [57–63]. More than just an epiphenomenal manifestation of disease-related neurodegeneration, sleep disturbances may be involved in the long-term, complex, pathophysiological mechanisms leading to AD [45, 64, 65]. In particular, sleep disturbances may affect patients with AD from the early stages of the disease, and sleep problems have been associated with a worse prognosis of AD and an increased risk of institutionalization [66]. Moreover, a fragmentation of the circadian rest–activity rhythm has been shown in cognitively unimpaired adults with evidence of preclinical amyloid pathology [67]. Sleep disturbances might even be considered as prospective risk factors triggering AD pathology, and several longitudinal population-based studies have shown that sleep disturbances and circadian sleep–wake cycle disorders, such as sleep fragmentation, reduction of REM sleep, dysregulation of non-REM sleep, altered slow-wave activity, phase advance of the circadian sleep–wake cycle, and sleep-disordered breathing might predict or accelerate the onset of dementia and cognitive decline by several years [68–73]. In line with this evidence, sleep pathological changes have been proposed as candidate biomarkers for early identification of patients with AD, although further evidence is needed [70].

In addition to robust evidence for the role of slow-wave sleep and REM sleep in cognitive function and memory consolidation [74–77], ongoing preclinical and clinical research has demonstrated how chronic sleep disruption may directly contribute to the pathophysiology of AD by impairing glymphatic clearance, leading to increased accumulation of amyloid-β [45, 78–81].

This mechanism may be responsible for a recursive pathway in which sleep disruption leads to increase cerebral amyloid-β deposition, which in turn impairs sleep continuity and ultimately evolves into AD. Consistently, the local decrease in slow-wave activity associated with reduced hippocampal activation during sleep has been shown to fully mediate the relationship between amyloid-β burden and memory consolidation [82].

Taken together, these findings support the central role of sleep in the pathogenesis of AD and highlight the importance of treating comorbid sleep disorders and enhancing sleep quality as a strategic approach to managing disease progression. A precise understanding of the role of orexin in the interplay between AD and sleep may help to tailor current treatment strategies to the specific clinical features of the disease.

3 Orexin in Alzheimer's Disease

The neurobiological mechanisms underlying sleep disruption in AD are complex and likely involve different neurotransmitter systems, including GABAergic neurons, cholinergic neurons of the basal forebrain, and widespread aminergic regions [15, 42, 83, 84]. Orexinergic projections play a balancing role in these mechanisms by facilitating the wake-promoting activities of cholinergic and aminergic neurons. Like other neuronal populations, orexin neurons may undergo progressive degeneration driven by AD. Post mortem studies have indeed revealed a significant loss of hypothalamic orexinergic neurons in patients with AD [85–87]. However, despite these findings in late-stage AD, conflicting evidence has emerged from studies investigating CSF orexin levels in patients with both mild cognitive impairment and dementia due to AD, conditions in which increased orexin levels have been detected [88–91]. This increase, observed across both early and symptomatic stages of the disease, may reflect a dysregulation due to a compensatory mechanism countering AD-induced neurodegeneration [43]. A comprehensive meta-analysis has shown that, although on the one hand patients with AD can present with higher CSF orexin levels when compared with controls, on the other hand different studies showed that CSF orexin levels of patients with AD are similar to that of controls, highlighting significant methodological heterogeneity across studies [92].

However, the high CSF orexin levels documented in AD have been associated with sleep impairment, since the increase of CSF orexin levels significantly correlated with the reduction of sleep efficiency, the increase of wakefulness after sleep onset, and the fragmentation of REM sleep [88, 89]. Further evidence documented that patients with obstructive sleep apnea (OSA) presented higher CSF orexin levels than patients with AD, who in turn showed higher CSF orexin concentrations than controls. Notably, patients with OSA also presented low CSF levels of amyloid-β_{42} than controls, although these levels were higher than those of patients with AD [93]. Given these findings and the hypothesized link between sleep

disturbances and amyloid-β accumulation, orexinergic signaling might specifically influence the pathophysiology of AD through its impact on the sleep–wake cycle. Correlations between CSF orexin levels and AD biomarkers, namely amyloid-β and tau-proteins, have been reported in both patients with AD and the healthy elderly [94–96]. Murine models have shown that interstitial fluid (ISF) amyloid-β levels are associated with wakefulness, and they increase following acute sleep deprivation and intraventricular orexin infusion. Conversely, infusion of a DORA, almorexant, decreased amyloid-β in the ISF and reduced amyloid-β plaque formation in amyloid precursor protein (APP) transgenic mice [46]. In addition, reduced amyloid-β pathology and increased sleep duration were observed in APP transgenic mice with knocked-out orexin gene [47]. The rescue of orexinergic neurons in the hypothalamus resulted in augmented amyloid-β pathology in the same model, while focal overexpression of orexin in the hippocampus did not alter the amount of wakefulness or amyloid-β levels.

Interestingly, an inverse process has been hypothesized to occur in narcolepsy type 1, characterized by chronic orexin deficiency, where reduced amyloid burden has been observed in elderly patients, and can be also related to the absence of orexinergic neurotransmission [97].

These findings align with recent evidence linking sleep deprivation with acute increases in CSF amyloid-β and tau proteins in humans [98, 99], and suggest that orexin hyperactivity contributes to increased cerebral amyloid burden through its impact on the sleep–wake cycle (see Fig. 1). This supports a potential bidirectional mechanism where orexin dysregulation disrupts sleep, thereby increasing amyloid-β formation, which in turn detrimentally affects sleep, further impacting orexin transmission. Therefore, in the long-term, countering orexin dysregulation and addressing sleep disruptions could potentially result in a reduction in amyloid-β accumulation, as evidenced by preclinical studies showing that chronic administration of the DORA suvorexant reduces amyloid-β pathology and mitigates cognitive impairment as measured by behavioral tests in APP mice [100]. In addition, a human study documented that use of suvorexant, the first approved DORA, acutely reduced tau phosphorylation and amyloid-β levels in the central nervous system [101].

Overall, this expanding research base encourages further investigation into drugs targeting the orexin systems in AD to explore their effects both on sleep disturbances and other clinical manifestations of the disorder.

4 Orexin Antagonism in AD: Current Clinical Evidence and Ongoing Trials

Building on the basic understanding developed in the previous sections, this part of the review summarizes the current clinical evidence regarding the use of orexin antagonists

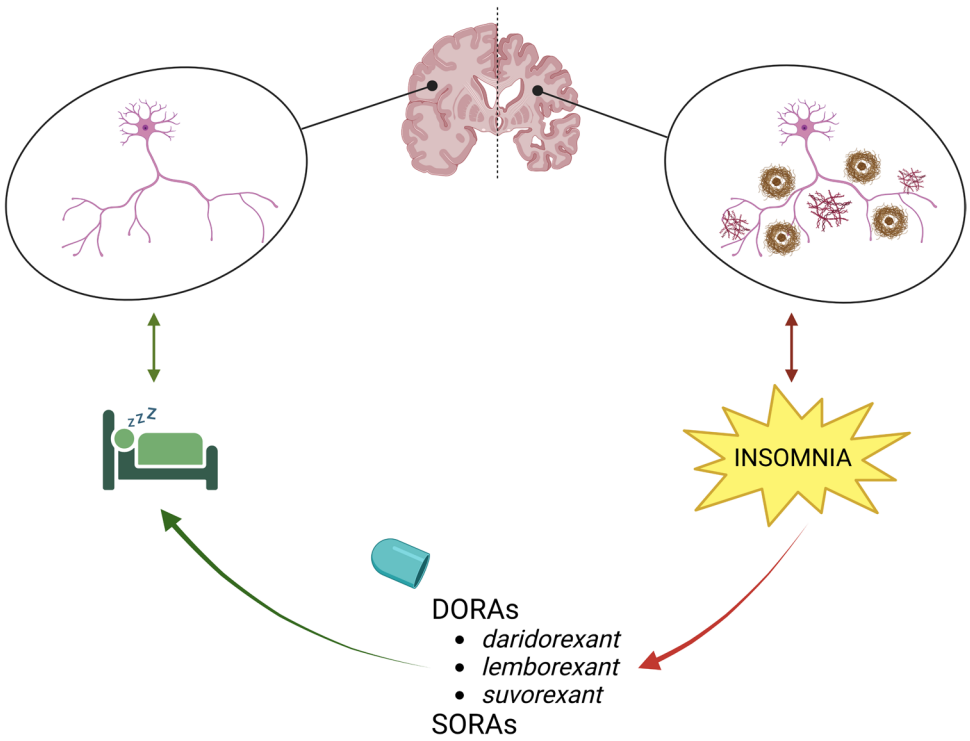

Fig. 1 Schematic representation of the hypothesized mechanism linking sleep and the accumulation of amyloid-β and tau proteins. Sleep disruption due to insomnia and sleep fragmentation contribute to the increase in neuropathology leading to clinical Alzheimer's disease and neurodegeneration. Conversely, targeting insomnia with orexin antagonism may restore sleep and subsequently prevent or slow the deposition of toxic proteins in the brain. *DORAs* dual orexin receptor antagonists, *SORAs* selective orexin receptor antagonists

in patients with AD and outlines ongoing studies aimed at evaluating the efficacy of DORAs and selective OX2R antagonists (2-SORAs) in targeting sleep disorders as well as disease-specific pathophysiological processes within the AD continuum.

For this purpose, we have updated and expanded a recent review we conducted on the utility of DORAs for sleep disturbances comorbid with neurological and psychiatric disorders [102]. To focus on clinically relevant results, we limited our research to human studies and trials with already approved and currently under-review DORAs including suvorexant [103], lemborexant [104], and daridorexant [105], and the 2-SORAs [37] seltorexant (JNJ-42847922) [106] and JNJ-48816274 [107]. In particular, suvorexant, Lemborexant, and daridorexant have shown specific efficacy in treating insomnia in older adults, encouraging their use in AD and other neurodegenerative diseases [108–111].

Since the mechanism of action of orexin antagonists on AD manifestations is thought to be mediated by their effects on sleep, we chose to focus on 2-SORAs, which have shown preliminary promising sleep-promoting and antidepressant effects in patients with major depressive disorder [112, 113], and to exclude selective OX1R antagonists (1-SORAs). As we noted above, OX1R appears to be predominantly involved in motivational and emotional processes, and 1-SORAs are not expected to have pronounced sleep-promoting effects [32]; they are primarily being studied in preclinical models for the treatment of psychiatric disorders within the anxiety spectrum and substance use [114, 115]. Furthermore, research on 1-SORAs is currently limited, with only one molecule in clinical development [116].

To select research papers easily accessible to clinicians and practitioners, target searches were performed on PubMed/MEDLINE database with dedicated search queries (e.g., ["Alzheimer's disease" AND "dual orexin receptor antagonist*"] or ["Alzheimer's disease" AND "suvorexant"]) for the period from January 2014 (year of approval of suvorexant) to the present (May 2024). The reference lists of relevant reviews were also screened, and all types of papers (clinical trial reports, case series, case reports) presenting results on the effects of DORAs or 2-SORA in patients with AD, as well as on AD biomarkers in cognitively unimpaired participants, were considered. In addition, the clinicaltrials.gov database was searched for ongoing clinical trials involving DORAs and 2-SORAs in the context of AD, and trials of interest for this review were recorded and summarized.

Current evidence and ongoing trials are discussed in the two separate subsections below for DORAs and 2-SORAs, respectively. The results of the published studies that were reviewed are summarized in Table 1, while active clinical trials retrieved from clinicaltrials.gov are reported and described in Table 2.

4.1 *DORAs* in Alzheimer's Disease

Several studies have investigated the efficacy of DORAs in patients diagnosed with AD. One significant study by Herring et al. described a large double-blind, randomized clinical trial (RCT) that explored the effect of 10 mg suvorexant (scalable to 20 mg after 2 weeks of treatment) compared with placebo on polysomnography-assessed sleep parameters in patients with mild-to-moderate probable AD dementia and comorbid insomnia ($n = 285$ randomized patients; $n = 142$ suvorexant, $n = 143$ placebo) [117]. Eligible age ranged from 50 to 90 years, and 71% ($n = 202$) of enrolled patients were older than 65 years old. After 4 weeks of treatment, a greater increase in total sleep time (TST; mean change from baseline: +73 minutes for suvorexant versus +45 minutes for placebo) along with a greater decrease in wakefulness after sleep onset (WASO; mean change from baseline: −45 min for suvorexant versus −29 min for placebo) were observed in patients treated with suvorexant. Higher post-treatment sleep efficiency was also found in the suvorexant group, while no differences were observed in sleep latency or sleep architecture (i.e., portion of TST spent in different REM and non-REM sleep stages). The improvement in TST and reduction in WASO were particularly pronounced toward the end of the night, with these changes unaffected by covariates (i.e., age, sex, Mini Mental State Examination score, apolipoprotein E genotype, and number of apnea/hypopnea events). Adverse events were reported in 22.5% of participants in the suvorexant group versus 16.1% of participants in the placebo group, with no treatment-emergent serious adverse events. The most common adverse event was mild-to-moderate somnolence (4.2% of treated patients versus 1.4% of placebo patients).

Another study by Moline et al. investigated the effect of various dosages of lemborexant (2.5 mg, 5 mg, 10 mg, 15 mg) compared with placebo in a phase 2 multicenter, double-blind, RCT involving patients with mild-to-moderate AD dementia and irregular sleep-wake rhythm disorder (ISWRD; $n = 62$ randomized patients; $n = 12$ lemborexant 2.5 mg; $n = 13$ lemborexant 5 mg; $n = 13$ lemborexant 10 mg; $n = 12$ lemborexant 15 mg; $n = 12$ placebo) [118]. Patients' age was between 60 and 90 years ($n = 59$, i.e. 94% ≥ 65 years). All patients underwent actigraphy monitoring for 2 weeks prior to randomization and then during 4 weeks of treatment and 2 weeks of follow-up. Actigraphy-derived circadian (including least active 5 h, L5; most active 10 h, M10; relative amplitude of the rest–activity rhythm, RA; interdaily stability; and intradaily variability), wake, and sleep parameters (wake efficiency, wake fragmentation, sleep efficiency, sleep fragmentation, and daytime and nighttime TST) were considered as clinical endpoints. After 4 weeks of treatment, a significantly greater decrease in mean L5 activity was observed in the lemborexant 2.5 mg, 5 mg, and 15

Table 1 Reviewed studies investigating the use of dual orexin receptor antagonists (DORAs) in the treatment or prevention of Alzheimer's disease

References	Country	Study design	Condition	Treatment	Sample	Outcomes	Main findings	Adverse events	Clinicaltrials.gov identifier
Herring et al., 2020 [110]	USA	RCT	AD with insomnia	Suvorexant (SUV) 10 mg (up to 20 mg) for 4 weeks versus placebo	$n = 285$ randomized patients; $n = 142$ SUV; $n = 143$ placebo	PSG-assessed sleep parameters	Reduced WASO, increased TST, and higher sleep efficiency in patients receiving SUV after 4 weeks of treatment. No significant alterations in sleep stages	Somnolence, headache, fall, dry mouth	NCT02750306
Moline et al., 2020 [111]	USA, Japan, UK	RCT	AD with ISWRD	Lemborexant (LEM) 2.5, 5, 10, or 15 mg for 4 weeks versus placebo	$n = 62$ randomized patients; $n = 12$ 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-assessed circadian-rhythm, nighttime sleep, and daytime wakefulness	Reduced actigraphy-measured least active 5 h and more stable rest-activity rhythm in patients receiving LEM after 4 weeks of treatment. LEM 5 mg appeared to be the most favorable dose	Constipation, somnolence, arthralgia, headache, nightmares (most common, not reported in LEM 2.5 mg and LEM 5 mg groups)	NCT03001557
Lucey et al., 2023 [98]	USA	RCT	Healthy volunteers	Suvorexant (SUV) 10 mg or 20 mg acute administration (two doses over 36 hours) versus placebo	$n = 38$ randomized participants; $n = 13$ SUV 10 mg; $n = 12$ SUV 20 mg; $n = 13$ placebo	CSF amyloid-β and tau levels; PSG-assessed sleep parameters	Rapid reduction in amyloid-β in participants receiving SUV 10 mg or 20 mg and reduction in the ratio of phosphorylated tau-threonine-181 to unphosphorylated tau-threonine-181in participants receiving SUV 20 mg. No differences between SUV and placebo in PSG-assessed sleep parameters	Not reported	NCT03077620
Hamuro, Honda, and Wakaura, 2018 [112]	Japan	Prospective trial (single arm)	AD with insomnia (difficulty in sleeping continuously for more than 4 h)	Suvorexant (SUV) 15 mg up to 20 mg for 4 weeks	$n = 6$ consecutive patients	Clinical evaluation, reported sleep duration	All patients able to sleep continuously for 6 h per night after treatment	None	–
Hanazawa and Kamijo, 2019 [113]	Japan	Case series	AD with nocturnal delirium	Suvorexant (SUV) 15 mg	$n = 4$ hospitalized elderly patients (≥ 82 years)	Clinical evaluation	Rapid sleep improvement in all cases after SUV administration	Not reported	–

AD Alzheimer's disease, *CSF* cerebrospinal fluid, *ISWRD* irregular sleep-wake rhythm disorder, *PSG* polysomnography, *RCT* randomized clinical trial, *TST* total sleep time, *WASO* wakefulness after sleep onset

mg groups compared with placebo, but not in the lemborexant 10 mg group. Patients receiving lemborexant 5 mg and 15 mg also showed a significant increase in RA, indicating an improvement in the robustness of the circadian rhythm. In addition, a significant decrease in the median percentage of mean daytime sleep bouts was observed in the lemborexant 5 mg and 15 mg groups, and a significant decrease in the mean number of nighttime wake bouts from baseline to week 4 was observed in the two low-dose lemborexant 2.5 mg and 5 mg groups compared with the placebo group. No significant treatment-related changes in sleep duration or sleep efficiency were reported, and the study does not provide an explanation for the lack of effect of the intermediate 10 mg dosage, which does not appear to be due to significant differences in demographic or clinical variables between the treatment arms. Regarding safety, the incidence of adverse events was higher in the highest-dose group (lemborexant 15 mg) compared with placebo (50.0% versus 33.3%), but treatment-related adverse events occurred only in the lemborexant 5 mg, 10 mg, and 15 mg groups. Constipation, somnolence, arthralgia, headache, and nightmares were the most common adverse events and were not reported for placebo, lemborexant 2.5 mg, or lemborexant 5 mg. No worsening of cognitive function was observed after the treatment period. Overall, this study, which is the first to report the effects of a DORA in AD patients with circadian sleep–wake cycle disruption, supports the efficacy and safety of lemborexant in improving circadian-related parameters in ISWRD, suggesting that lemborexant 5 mg may be the most effective and safe dose in this frail population of patients.

Two smaller reports also investigated suvorexant's effectiveness in treating sleep-related symptoms of AD. Although less reliable in terms of the results obtained, these case series were included in the review list as a possible basis for future investigations in real clinical settings. A prospective trial conducted in Japan assessed suvorexant (15 mg starting dose, up to 20 mg as needed) over 4 weeks in six elderly patients (mean age, 87.5 ± 7.1 years) with dementia due to AD and insomnia (defined as difficulty in sleeping continuously for more than 4 h per night for more than 3 nights a week) [119]. Post-treatment, all patients managed to sleep continuously 6 six h per night. The suvorexant dose was increased to 20 mg at the end of treatment in five of six patients, and no adverse effects among those monitored (i.e., somnolence, headache, and weakness) were observed. Moving to another sleep-related clinical manifestation, a case series described the effectiveness of acute administration of suvorexant 15 mg for 3 nights to treat nocturnal delirium in four hospitalized patients with AD [120]. Two cases were refractory to antipsychotics, one case was contraindicated for antipsychotics, and the last case was given suvorexant as a first-line treatment. In all cases, immediate improvement in sleep was observed, with one case of symptom recurrence after discontinuation, which was reversed by restarting suvorexant. Despite the very small sample size and the lack of a rigorous study design, it is noteworthy that in these two reports, suvorexant was successfully administered to patients older than 80 and up to 98 years of age. Furthermore, these preliminary results in delirium associated with AD are consistent with previous studies showing the clinical potential of suvorexant and lemborexant in the prevention and treatment of delirium in intensive care units [121, 122] and encourage further longitudinal research in this area, as delirium is recognized as a risk factor for dementia, which may share pathophysiological mechanisms with AD [123, 124].

Finally, as mentioned above, a recent study explored the putative preventive role of suvorexant in AD-related neurodegeneration [101]. Building on the reviewed literature on the relationship between orexin dysregulation, and cerebral amyloid-β accumulation and tau pathology, Lucey et al. examined the effects of the acute administration of two suvorexant dosages (10 mg and 20 mg) versus placebo on CSF concentrations of different isoforms of amyloid-β and tau proteins in a small RCT involving 38 healthy and cognitively unimpaired adults aged 45–65 years without self-reported or diagnosed sleep disorders ($n = 13$ suvorexant 10 mg, $n = 12$ suvorexant 20 mg, $n = 13$ placebo). Different forms of amyloid-β (Aβ38, Aβ40, and Aβ42), tau and phosphorylated-tau (T181, pT181, S202, pS202, T217, and pT217) were measured in CSF samples collected continuously over 36 h. Starting 5 h after administration, both suvorexant dosages reduced all amyloid-β isoforms (Aβ38, Aβ40, and Aβ42) compared with placebo (10–20% decrease), and a reduction in phosphorylated-tau-threonine-181 (10–15% decrease in the ratio of phosphorylated tau-threonine-181 - pT181 - to unphosphorylated tau-threonine-181 - T181) was observed in participants receiving suvorexant 20 mg, while no changes were observed in phosphorylated-tau-serine-202 - pS202 - and phosphorylated-tau-threonine-217 - pT217. Notably, suvorexant had no effect on sleep parameters, with no significant differences in sleep architecture between the three groups. The authors speculate that this finding may support a direct, sleep-independent mechanism of action of orexin antagonism on AD pathophysiology. However, larger studies investigating the long-term effects of suvorexant and other DORAs on AD-related biomarkers in clinical samples are needed to test whether relevant differences in sleep macrostructure were masked by the small sample size and to clarify whether the observed acute effects are maintained over time under sustained treatment conditions. Indeed, two registered clinical trials currently enrolling participants aim to investigate the potential preventive long-term use of DORAs in AD. Specifically, the SToP-AD trial (clinicaltrials.gov identifier: NCT04629547) is evaluating whether 24 months of daily suvorexant treatment can slow brain amyloid-β accumulation as measured by plasma biomarkers

Table 2 Ongoing trials registered on clinicaltrials.gov investigating treatment or preventive use of dual orexin receptor antagonists (DORAs) or selective orexin receptor 2 antagonists (2-SORAs) in Alzheimer's disease (list updated 14 May 2024)

Trial title	Country	Eligible participants	Treatment	Main outcomes	Status	Phase	Clinicaltrials.gov identifier
Sleep Trial to Prevent Alzheimer's Disease (SToP-AD)	USA	Healthy elderly (≥ 65 years)	Suvorexant 20 for 24 months mg versus placebo	CSF and plasma AD-related biomarkers (amyloid-β and tau)	Recruiting	2	NCT04629547
DORA and LP in Alzheimer's Disease Biomarkers	USA	Healthy elderly (≥ 65 years)	Lemborexant 10 mg or 20 mg for 6 months versus placebo	CSF AD-related biomarkers (tau and amyloid-β)	Recruiting	2	NCT06274528
Lemborexant for Insomnia in a Patient With Dementia: An N-of-1 Trial	Canada	Patients with early onset dementia (unspecified) and insomnia	Lemborexant 5 mg to 10 mg for 8 weeks (single arm, alternating with placebo)	Patient-reported quantity (daily) and quality (weekly) of sleep	Recruiting	4	NCT06093126
Daridorexant to Treat Insomnia in Patients With Mild Cognitive Impairment and Mild to Moderate Alzheimer Disease (DARIDOR-ALZ)	France	Outpatients aged 60–85 years with MCI or mild-to-moderate early stage AD	Daridorexant 50 mg for 1 month versus placebo	PSG-assessed sleep parameters	Recruiting	4	NCT05924425
A Study of Seltorexant in Participants With Probable Alzheimer's Disease	USA	Adults/older adults aged 55–85 years with probable AD and manifest agitation	Seltorexant 20 mg for 42 days versus placebo	Clinician-rated agitation and aggression and caregiver-rated sleep disturbances	Completed	2	NCT05307692

AD Alzheimer's disease, *CSF* cerebrospinal fluid, *MCI* mild cognitive impairment, *PSG* polysomnography

in cognitively intact elderly patients. Another study (clinicaltrials.gov identifier: NCT06274528) is also recruiting older adults without significant cognitive impairment to evaluate whether 6 months of treatment with lemborexant can reduce amyloid-β (Aβ38, Aβ40, Aβ42 isoforms) and tau proteins (pT181/T181 ratio) in the CSF.

Two other clinical trials are recruiting patients with dementia due to AD or mild cognitive impairment to further evaluate the efficacy and safety of lemborexant and daridorexant in the treatment of comorbid insomnia (clinicaltrials.gov identifiers: NCT06093126 and NCT05924425), while a phase II study evaluating the acute effect of lemborexant 25 mg on CSF tau (pT181/T181 ratio) and amyloid-β was withdrawn prior to completion of enrollment in late 2023 due to enrollment and supply difficulties (clinicaltrials.gov identifier: NCT05728736).

4.2 2-SORAs in Alzheimer's Disease

As previously mentioned, 2-SORAs are currently under investigation for the treatment of depression [125, 126], considering the hypothesized sleep-promoting and antidepressant effects of seltorexant [112, 113, 127, 128]. Given the frequent co-occurrence of depression and AD and its potential direct association with AD-related neuropathology [59, 129–131], exploring treatments that simultaneously target both sleep impairment and depression could be valuable.

To date, no study has been published on the efficacy of 2-SORAs in AD. However, there is an ongoing interest in this area, as indicated by a registered clinical trial that has recently been completed (clinicaltrials.gov identifier: NCT05307692). This trial investigated the effects of seltorexant on the behavioral and psychological symptoms of patients with AD presenting with clinically significant agitation and aggression, although results have yet to be published.

5 Conclusions and Future Directions

This review has provided a succinct summary of the current evidence on the clinical potential of orexin antagonism in the treatment of sleep disturbances in patients with AD, and has also discussed the possibility of impeding neurodegenerative processes by counteracting amyloid-β and tau pathology through antagonism to orexin neurotransmission and thereby improving sleep.

Overall, two main lines of evidence emerged from this review. First, orexin antagonism by DORAs appears to be an effective treatment for sleep and circadian sleep–wake cycle disorders in AD with an acceptable safety profile. Specifically, in two well-designed RCT involving patients with AD, suvorexant effectively increased polysomnography

(PSG)-measured sleep duration and restored sleep continuity in participants concurrently diagnosed with insomnia, while lemborexant improved the robustness of the circadian cycle assessed by actigraphy throughout the study in patients with comorbid ISWRD. Although similar studies have not yet been completed with the other approved DORA, daridorexant, or with the 2-SORAs, these results are promising, especially in light of longstanding concerns about therapeutic options for the treatment of insomnia and other sleep disorders in patients with AD [132–136]. Nevertheless, the current findings should be considered preliminary, and further studies with long-term follow-up and a wider range of outcomes (e.g., neuropsychiatric symptoms, cognitive function, patients' and caregivers' health-related quality of life) are warranted to confirm the clinical effectiveness of DORAs in sleep disorders comorbid with neurodegeneration. The heterogeneity of sleep assessment methods (i.e., PSG, actigraphy, clinical judgment, self- or caregiver-reported sleep quality) should also be addressed, possibly encompassing the full spectrum of sleep medicine assessment tools and combining their respective advantages. In this context, the thorough evaluation of OSA is critical, given its well-established role as a modifiable risk factor for cognitive decline in AD [73, 137]. A comprehensive multimethod assessment protocol, such as that outlined in the ongoing Sleep Impairment in Subjects at Risk of Developing Alzheimer's Disease (WAVE-APOE4; clinicaltrials.gov identifier: NCT05649514) clinical study, could be pursued.

Furthermore, regarding the hypotheses linking AD with orexin dysregulation—specifically, the potential role of orexin in AD onset, which might be exerted both indirectly and directly through sleep and wake disturbances—evidence on the impact of orexin receptor antagonists on AD pathophysiology and core clinical features remains limited. The pivotal study by Lucey et al. [101] demonstrated an acute decrease in CSF AD-related biomarkers following administration of suvorexant in healthy adults, but further data are needed to confirm these findings and assess their significance. Notably, ongoing research and trials aim to investigate these effects over the long term and may soon enrich our understanding.

Future studies should build on these foundations to directly explore whether orexin antagonism can act as a preventive treatment for AD beyond being a symptomatic therapy for comorbid sleep disturbances. Such efforts should capitalize on the potential of multimethod sleep assessment, complementing the benefits of full PSG and quantitative EEG analysis with the prolonged measures of circadian rest–activity rhythms achievable with actigraphy and the home-based assessment of sleep stages and respiratory events with portable devices [70, 138], especially considering that PSG-based assessment may not be clinically feasible in severely impaired patients. Dedicated trials, such as the ongoing SToP-AD study, could be designed to include elderly individuals at risk of AD with and without sleep disturbances to investigate the longitudinal effects of prolonged treatment with DORAs or 2-SORAs on a comprehensive set of outcomes that include recognized features of AD. Along with detailed sleep measurements and biomarkers, cognitive and functional assessments should be considered as endpoints in these studies to effectively evaluate the extent to which targeting the orexin system can slow AD progression both pathophysiologically and clinically.

Declarations

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Ethics approval An ethics statement is not applicable as this study is based exclusively on published literature and publicly available information on registered clinical trials.

Consent to participate Not applicable.

Consent for publication Not applicable.

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

Code availability Not applicable.

Author contributions All authors contributed to the conception and design of the study. Matteo Carpi and Claudio Liguori performed the literature search and review. Nicola Biagio Mercuri provided critical supervision. The first draft of the manuscript was written by Matteo Carpi and Claudio Liguori, and all authors commented on earlier versions of the manuscript. All authors read and approved the final version of the manuscript and agreed to be accountable for the work.

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