Review

Orexinergic Receptor Antagonists as a New Therapeutic Target to Overcome Limitations of Current Pharmacological Treatment of Insomnia Disorder

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Abstract

Insomnia disorder is a common condition that is considered a risk factor for multiple physical and mental disorders, contributing to reduced quality of life and increased healthcare expenditures. Although cognitive behavioral therapy (CBT) is typically recommended as the primary intervention, its accessibility is hindered by limited resources, prompting the prevalent use of pharmacological interventions as the primary treatment in clinical settings. This study reviews the benefits and risks of current pharmacological treatments for insomnia, with special reference to the orexinergic system as a novel therapeutic target for treatment. The prescription of GABAergic mechanism enhancers (benzodiazepine (BZD) and "Z drugs") has shown efficacy in short-term insomnia treatment (less than 4 weeks), however, concerns arise regarding their long-term effectiveness, unfavorable tolerability and safety profiles, including the potential for dependency. Drugs with antihistamine properties, including certain antidepressants and antipsychotics, exhibit short-term efficacy but have documented tolerability limitations, especially in the elderly. The use of melatonin, available in various formulations, lacks comprehensive long-term data. Dual orexin receptor antagonists (DORAs) such as daridorexant, lemborexant, and suvorexant, represent a novel approach to insomnia treatment by inhibiting wakefulness rather than enhancing sedation. As the only DORA approved for insomnia treatment by the European Medicines Agency (EMA) and Food and Drug Administration (FDA), daridorexant has demonstrated sustained efficacy over a 12-month period, improving nocturnal sleep parameters and daytime functionality, with a favorable safety and tolerability profile.

Keywords

insomnia; benzodiazepines; orexin; DORAs; daridorexant

Introduction

The Diagnostic and Statistical Manual of Mental Disorders (DSM-5) defines "insomnia disorder" as a persistent difficulty with sleep onset, duration, consolidation, or quality despite conducive sleep conditions. Additionally, this condition is necessarily accompanied by daytime repercussions within social, occupational, educational, academic, or behavioral domains. The consequences of insomnia have been related to a deteriorating quality of life, the appearance of depression, increased suicidal ideation, absenteeism, traffic and occupational accidents, disability, cardiovascular disease, increased healthcare utilization, and even increased mortality rates. Indeed, insomnia can coexist with diverse comorbidities such as spanning mental, neurological, cardiovascular, endocrinological, respiratory, gastrointestinal, and oncological conditions. Despite appropriate treatments for the aforementioned pathologies, insomnia disorder is considered a distinct entity and should be treated independently, rather than as a condition secondary to other comorbidities [1,2].

This paper reviewed the "pharmacological treatment of insomnia" using PubMed, Web of Science, Scopus, and Google Scholar as search engines to access the most rele-

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vant literature. Key phrases used to perform the literature search included "*insomnia*", "*sleep disorders*", "*sleep physiology*", "*insomnia pathophysiology*", and "*insomnia treatment*". Likewise, we have tested the various pharmacological groups with some relation to sleep or insomnia. The authors have reviewed and selected the most relevant articles written in Spanish, English, or French, published during the last four decades.

Approach to Insomnia Treatment. Benefit/Risk Ratio

Insomnia is a complex disorder that requires a multifactorial therapeutic approach. Guidelines from the European Sleep Research Society [3], and the American Academy of Sleep Medicine (AASM) [4] suggest a comprehensive insomnia treatment strategy including sleep hygiene, psychotherapy (cognitive behavioral therapy; CBT), and pharmacotherapy. Practically all clinical guidelines and consensus on the treatment of insomnia recommend CBT as the first line of treatment. While CBT is universally recommended as first-line treatment, practical limitations such as resource scarcity, lack of adherence and persistence on the part of patients, and cost constraints hinder its widespread adoption. In addition, recent studies have demonstrated that CBT is not always effective and it exhibits a lower efficacy on objective sleep parameters, improving normal sleep in less than half of those treated with CBT [5].

This article refers exclusively to pharmacological treatment through four drug groups according to their mechanism of action: benzodiazepine (BZD) receptor agonists, histaminergic H1 receptor antagonists (AH1), melatonin receptor agonists, and dual orexin receptor antagonists (DORAs) [5].

Pharmacological interventions for insomnia must demonstrate both short- and long-term safety and efficacy, addressing not only quantitative measures of sleep, such as Total Sleep Time (TST), wakefulness after sleep onset (WASO), and Latency to Persistent Sleep (LPS), but also qualitative measures such as sleep quality, improved daytime performance, and general health [6]. Ideally, insomnia disorder treatments should encompass a 24-hour period, ensuring effectiveness throughout the night while optimizing daytime functioning. However, many existing medications for insomnia fail to meet this criterion, offering relief for either maintenance or initial insomnia but rarely both. Moreover, many of these medications can diminish daytime function due to morning sedation and residual effects that interfere with work, family, and social relationships for many patients [7]. Therefore, an ideal hypnotic should enhance sleep quality while simultaneously improving daytime functioning.

GABAergic functionalism enhancers commonly used as hypnotics include BZDs and "Z drugs", which are the most prescribed hypnotics in Spain according to the Spanish Agency of Medicines and Health Products (AEMPS) (2023) [8]. Specifically, lormetazepam (70%) and flurazepam (3%) are commonly prescribed BZDs whereas zolpidem (22%) stands out among "Z drugs". According to the "United Nations International Narcotics Control Board" (2022) [9], Spain is the world leader in BZD prescription. BZDs are positive allosteric modulators of gamma aminobutyric acid A (GABA-A) receptors and, generally reduce sleep onset time and increase total sleep time. However, BZDs often fail to enhance daytime functioning and may exacerbate it, possibly due to their nonspecific pharmacodynamics and prolonged half-lives (T1/2) (T1/2: flurazepam from 51 to 100 hours; quazepam from 25 to 41 hours). On the contrary, zolpidem, the primary "Z" hypnotic, has a short T1/2 (2 to 5 hours), which may contribute to early awakenings, and the occurrence of complex behaviors (sleepwalking and hallucinations), and a rebound effect. The European guideline for the diagnosis and treatment of insomnia [3] indicates that BZDs are effective for short-term insomnia treatment ($\leq$4 weeks), decreasing sleep onset latency, reducing the number of nocturnal awakenings, and increasing total sleep time. However, BZDs may disrupt sleep architecture and worsen daytime functioning, leading to cognitive and memory impairment and an increased risk of traffic accidents. A systematic review and network meta-analysis concludes that BZDs are effective for short-term insomnia treatment, with significant improvements in subjective sleep quality, albeit with lower safety compared to placebo due to the risk of dependence, next-day withdrawal, and hangover [10].

A potential link between BZDs and mild cognitive impairment and dementia remains a controversial concern. Ferreira *et al*. [11] (2022) carried out a systematic review of reviews on the possible association of the use of benzodiazepines and related substances with dementia in older adults, suggesting an association between BZDs and "Z drugs" usage with an increased risk of dementia in older adults. However, other studies note that both BZDs and anxiety disorders are associated with an increased risk of dementia, but the use of BZDs did not pose an additional risk [12]. These findings propose that BZDs would facilitate the detection of subclinical symptoms, as both anxiety disorders and insomnia could be prodromal symptoms of dementia [13]. In addition, prolonged use of BZDs has been associated with a modest increase in the risk of overall mortality, especially when used in conjunction with opi-

oids [14]. Overall, the benefit-risk ratio of this combination is negative, although in certain clinical settings, e.g., palliative care, the benefits of combining opioids with BZDs may outweigh the risks [15].

Furthermore, it is noteworthy that, according to the screening tool of older person's prescriptions (STOPP)/screening tool to alert doctors to right treatment (START) criteria, BZDs are the most inappropriately prescribed medications for the elderly in Spain. This use is concerning considering the risk of prolonged sedation, confusion, falls, bone fractures, traffic accidents, and aggravation of pre-existing respiratory insufficiency, as well as dependence and withdrawal syndrome [16]. Moreover, factors such as a history of substance abuse, prolonged treatment, high doses, short T1/2 BZD, and high potency increase the risk of dependence. Withdrawal should always be gradual to avoid rebound effects or withdrawal syndrome [17].

On the other hand, according to the meta-analysis by Khong *et al*. [18] (2012), BZD use has been associated with an increased risk of hip fractures that varies between 1.8% in Germany, 2.0% in the United Kingdom, 5.2% in Italy, 7.4% in France, 8.0% in the United States, and 8.2% in Spain [18]. This traumatic record is associated with the very high use of BZD in Spain (93.304 DDD/1000 inhab/day in 2021) which demonstrated a higher increase than reported in other European countries according to the AEMPS [8].

In the recent network meta-analysis by Yue *et al*. [10] (2023), "Z drugs", especially zolpidem, were objectively more effective than placebo on several sleep parameters such as Sleep latency (SL), wakefulness after sleep onset (WASO). However, these "Z drugs" caused the highest number of dropouts and adverse events (headaches, dizziness, hallucinations, memory impairment). In general, a minimum effective dose of BZDs and "Z drugs" should be used only when essential and for less than four weeks, especially in subjects over 60 years of age [3], due to their low benefit/risk ratio and their ability to produce dependence [19].

Drugs with antihistamine properties can induce sedation and sleep. Histaminergic H1 receptor antagonists (AH1), such as diphenhydramine and doxylamine, exert sedative effects by blocking H1 receptors in the histaminergic pathway originating from the tuberomammillary nucleus (TMN) of the hypothalamus, thereby promoting sleep. Although both drugs are approved as over-the-counter drugs in Spain, they are associated with reduced driving ability and are recommended on for occasional insomnia in young adults due to rapid tolerance development [3]. Beyond sedation and daytime somnolence [20], AH1 can also cause weight gain and anticholinergic side effects like delirium, cognitive alterations, urinary retention, and constipation, making them unsuitable for the elderly [19,21]. The AASM Clinical Practice Guideline does not recommend the use of doxylamine or diphenhydramine due to their low efficacy relative to safety concerns [5].

Some sedative antidepressants such as amitriptyline, doxepin, mirtazapine, trazodone, and trimipramine, possessing AH1 activity, can induce sleep. In general, their use should be limited to insomnia co-occurring with depression and/or anxiety. Trazodone at a dose of 50 mg did not demonstrate significant efficacy on sleep parameters (SL, TST and WASO). Despite an unfavorable benefit-risk ratio, most patients prefer trazodone to no treatment [5,21]. Despite not being approved by the Food and Drug Administration (FDA) for this indication, trazodone is extensively prescribed in North America as a hypnotic, following restrictions akin to those applied to BZDs. In Spain, the AEMPS has recorded a sustained increase in its consumption, from 0.23 dose per 1000 inhabitants per day (DHD) in 2000 to 2.39 DHD in 2013, even though its official indication is limited to mixed states of depression and anxiety with or without secondary insomnia. However, in primary insomnia, the efficacy of trazodone (50 mg), which disappears after one week of treatment, is lower than that of BZDs with higher dropout rates. Moreover, it is difficult to justify its widespread use as a hypnotic, especially in the elderly [5,21]. In fact, the AASM Clinical Practice Guideline does not recommend the use of trazodone due to the paucity of evidence on its efficacy as a hypnotic [4].

Doxepin (3 and 6 mg) behaves as a specific H1 receptor antagonist without anticholinergic, antiadrenergic, or anti-serotonergic effects, and has been approved by the FDA for the treatment of insomnia as it slightly improves the duration and maintenance of sleep, although not the induction of sleep [22]. In Spain, the lowest dose of doxepin marketed is 25 mg, a dose much higher than that recommended as a hypnotic, and resultantly associated with adverse effects like those observed with other tricyclic antidepressants [19,21]. Both doxepin and trazodone found effective in the short-term treatment of insomnia, but less than that of BZDs [3].

Mirtazapine is a sedative antidepressant that exhibits a potent antagonistic ability against H1 receptors, as well as 5-HT2A, 5-HT2C, and alpha-2 adrenergic receptors. For more than a decade, low doses of mirtazapine have been prescribed off-label for the treatment of insomnia. How-

ever, there are no controlled studies on insomnia with this antidepressant [23]. Its T1/2 is 20–40 hours, thus increasing the likelihood of daytime sedation. The use of mirtazapine could be useful in patients with depression and insomnia who may benefit from weight gain [19,21].

Antipsychotics with antihistamine properties, especially quetiapine and olanzapine, are prescribed as "off-label" medication for sleep induction and maintenance. However, outside of psychiatric disorders, their adverse effects, including weight gain, extrapyramidal symptoms, and the potential risk of sudden death in the elderly, do not warrant their use as hypnotics [21,24].

Gabapentinoids, including gabapentin and pregabalin, are drugs that block the alpha2delta subunits of voltage-dependent calcium channels. While originally indicated as anticonvulsants and therapeutic agents for neuropathic pain, they are now widely used for off-label conditions like insomnia. The meta-analysis by Hong *et al*. [25] (2022) indicates that gabapentinoids can improve sleep in patients with generalized anxiety disorder and neuropathic pain. However, gabapentinoids carry risks of central depression, drowsiness, and dizziness, heightening the chances of falls and traffic incidents. Classified as a category V narcotic in the US, pregabalin warrants concern due to its addictive potential, as well as increased toxicity when used concomitantly with opioids [25].

Melatonin is a neurohormone that aids in sleep initiation by acting on MT1 receptors and regulates the sleep-wake cycle and circadian rhythms through MT2 receptors. In general, the presentations of melatonin marketed are very heterogeneous, such as immediate release (IR), prolonged release (ER), and food supplements, and resultantly their compositions, quality, purity, dosage, and formulations vary greatly (capsules, sublingual tablets, patches, and preparations for intravenous administration), making it difficult to evaluate them as hypnotics [19]. Since 2007, melatonin LP 2 mg has been authorized as a prescription drug for insomnia treatment in patients over 55 years old. Studies suggest it improves sleep onset latency, quality of life, morning alertness, and psychomotor performance [21,26], leading to its recommendation by the British Association of Psychopharmacology for older patients [27]. Similarly, an umbrella review of 14 systematic reviews detected statistically significant improvements in sleep latency and total sleep time associated with the use of melatonin [28]. However, the AASM suggests that, given the widespread use and apparently benign adverse effect profiles, patients may use it even when data do not clearly support its efficacy. Furthermore, the AASM indicates that there is no evidence for the use of melatonin in chronic insomnia, and clinicians should not use melatonin as a treatment for sleep-onset or sleep maintenance insomnia in adults [4].

Therefore, currently available pharmacological treatments are based on generalized and nonspecific potentiation of GABA-A receptor-mediated mechanisms, as is the case with BZD and their "Z drugs". While these drugs offer short-term efficacy, long-term uses pose the risk of dependence and other adverse effects. Other drugs used to treat insomnia target H1 histaminergic receptors, such as AH1, certain antidepressants, and antipsychotics, may also worsen daytime performance as seen in BZDs [21,29]. Melatonergic agents, including melatonin receptor agonists such as ramelteon, are not widely available in Europe; melatonin, due to its heterogeneous nature, has not lived up to expectations. Therefore, if the limitations inherent to these mechanisms are to be avoided, it seems reasonable to explore alternative mechanisms, among which orexinergic mechanisms stand out [21,30].

Physiological Role in Orexinergic System

The orexinergic system consists of a central network composed of a restricted group of 10,000 to 20,000 neurons in rodents and between 50,000 and 80,000 in humans. These neurons are located exclusively in cells of the lateral, dorsomedial, and perifornical hypothalamus. These neurons receive a series of input signals and resultantly release neurohormones (orexins/hypocretins) through an extensive network of output connections that excite different encephalic structures [30] (Fig. 1). The figure was original and generated using PowerPoint (Microsoft 365 PowerPoint Slide Presentation Software).

Neurons in the orexinergic nuclei of the hypothalamus produce an excitatory neuropeptide that was discovered by two independent research groups in 1998. One group named it "orexin" because of its ability to increase food intake [31] while the other group named it "hypocretin" because it is secreted by the hypothalamus [32]. The International Union of Basic and Clinical Pharmacology recommended in 2012 to designate the peptides and their receptors with the term orexin (abbreviated as OX) and to name their respective genes and mRNA as hypocretin (abbreviated as HCRT). Orexins are derived from a hypothalamic precursor called preproorexin, which has a 131 amino acid structure in humans. This precursor generates two polypeptides, orexin A (OXA), consisting of 33 amino acids and identical in humans, rodents, pigs, and cows, and orexin B (OXB), which has 28 amino acids in humans and differs by two amino acids in rodents. Both orexin A and orexin B have a structural homology of 46%. Orexins bind

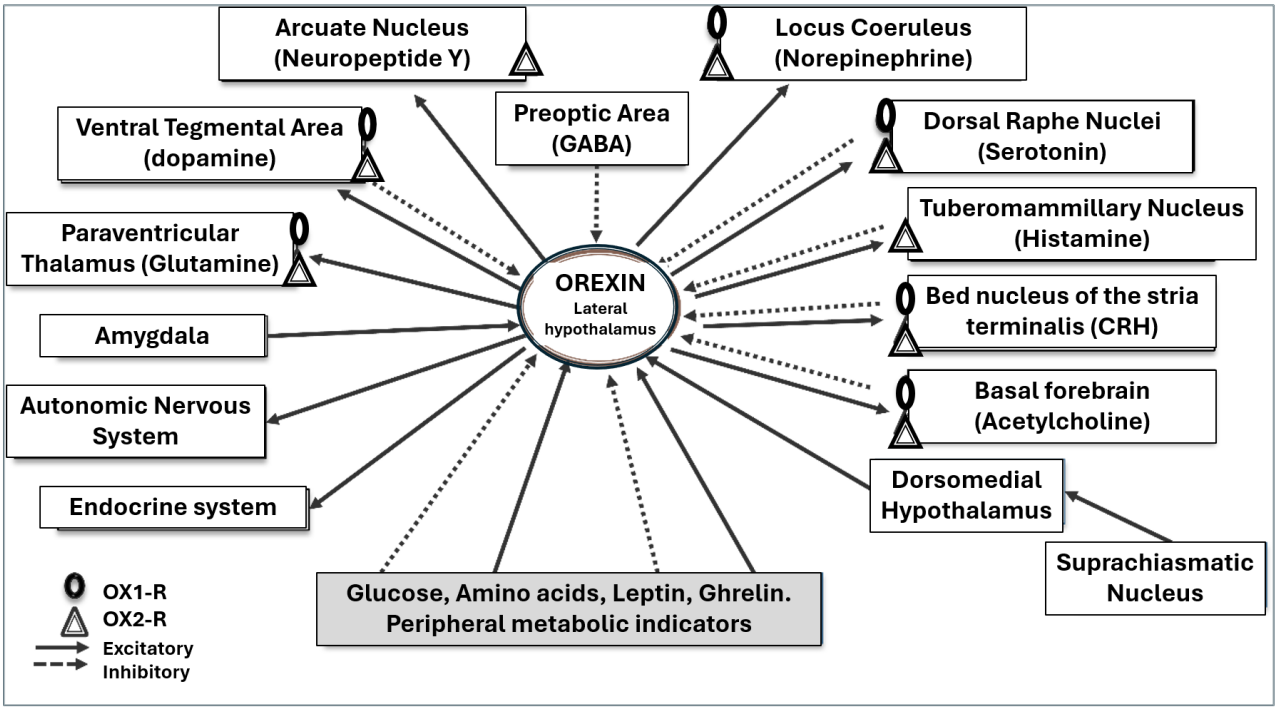

Fig. 1. Schematic representation of the orexinergic system. Excitatory and inhibitory signals related to the orexinergic center of the lateral hypothalamus are included, as well as its connections with different areas of the central nervous system (CNS). The orexin receptors (OX1-R and OX2-R) are mainly involved in each nucleus and the neurotransmitters controlled by these receptors in each nerve area (Cecilio Álamo).

to two orexinergic receptors (OX1-R and OX2-R) coupled to G proteins. Specifically, OXA binds to OX1-R, activating the sodium/calcium exchange channel, thereby depolarizing the postsynaptic membrane. In contrast, both OXA and OXB bind to OX2-R increasing the expression of glutamatergic N-methyl-D-aspartate receptors (R-NMDA), though OXB has a higher affinity for this reaction. R-NMDA upregulation exhibits excitatory effects while inactivating G-protein-regulated inward-rectifier potassium channels (GIRK) [33].

Hypothalamic orexinergic neurons are well-informed as they receive inputs from several areas of the brain. For example, inputs from the hypothalamic ventrolateral preoptic nucleus (VLPO) are key for sleep control by releasing GABA, resultantly inhibiting orexin secretion. Additionally, inputs from the suprachiasmatic nucleus, the central biological clock, are fundamental in the control of the circadian sleep/wake rhythm. Moreover, connections from the limbic system provide positive emotional information, while the amygdala provides fear-related information. In addition, orexinergic neurons receive peripheral metabolic inhibitory signals mediated by glucose or ghrelin, and excitatory signals including non-essential amino acids, acidification, increased CO_2 concentration, and leptin. Upon processing this diverse information, the orexinergic centers respond through a series of output projections by controlling endogenous orexin levels to prepare the individual for wakefulness in various environmental and emotional contexts [34,35].

The wide network of excitatory outputs of the hypothalamic orexinergic neurons are directed to different neuronal areas and nuclei, which have the function of maintaining wakefulness under appropriate conditions. For this purpose, the hypothalamic orexinergic nuclei contact the VLPO and tuberomammillary nucleus (TMN) of the hypothalamus, with the locus coeruleus (LC) in the pons, all of which are implicated in sleep regulation. Similarly, connections are made with the arcuate nucleus of the hypothalamus which is involved in feeding control and the ventral tegmental area (VTA) of the midbrain, which is important for feeding control and motivation and reward. The orexinergic projections are distributed through the serotonergic raphe nuclei and the reticular formation, key areas for regulating sleep and motor activity. In addition, they project widely to structures of the central autonomic nervous system network involved in sympathetic and parasympathetic

control, including the rostral ventrolateral medulla (RVLM) and the paraventricular nucleus of the hypothalamus. During wakefulness, orexin-induced activation regulates blood pressure, heart rate, intake, energy homeostasis, reward systems, cognition, and mood, all of which are critical for survival [35].

These outputs release orexin, which stimulates the two OX-R subtypes. Thus, neurons of the histaminergic tuberomammillary nucleus (NTM) express mainly OX2-R, whereas, in the LC, which has the largest endowment of noradrenergic neurons in the CNS, OX1-R predominates. Similarly, orexin acts on both OX1-R and OX2-R receptors in the serotonergic nuclei of the dorsal raphe, the dopaminergic neurons of the ventral tegmental area, and the cholinergic neuronal nuclei of the basal forebrain and the pons, including the laterodorsal tegmental nuclei [33]. Through these receptors, orexin stimulates the release of noradrenergic, histaminergic, serotonergic, and cholinergic neurotransmitters to modulate the sleep/wake cycle. Some of these nuclei are components of the ascending activating reticular system, which projects to the basal forebrain, thus generating cortical activation. In fact, an increase in orexin levels leads to elevated release of noradrenaline by the LC or dopamine, triggering sleep disturbances and nocturnal sleep loss. Orexin's primary role is to initiate wakefulness, favoring the transition to Rapid Eye Movement (REM) sleep, which facilitates awakening and entry into the waking phase, as well as sustaining wakefulness [34,35]. This function is mediated by cholinergic neurons of the basal forebrain, which produce the characteristic waves of the electroencephalogram (EEG) associated with wakefulness and REM sleep. The role of serotonin is more complex since its actions on sleep/wakefulness depend on the different serotonergic receptors it activates. Similarly, histamine also plays a crucial role in regulating the sleep/wake cycle; stimulation of H1 histamine receptors by orexin enhances wakefulness, while activation of the H3 receptor promotes sleep by retroactively decreasing histamine levels [30].

Orexin serves as a prime example of a neuropeptide with widespread innervation, controls the function of numerous neuronal groups, and influences various functions. However, inadequate orexin levels are related to certain clinical disorders. For example, most patients with narcolepsy exhibit nearly undetectable orexin levels in the cerebrospinal fluid, and post-mortem studies of these patients demonstrate a specific loss of orexinergic neurons in the brain. In fact, low OXA levels are one of the criteria currently used for the diagnosis of narcolepsy. In contrast, a significant increase in plasma OXA levels has been related to the course and severity of insomnia in relation to normal sleepers [36].

It could be said that the orexins behave like the conductor of an orchestra of neurotransmitters, noradrenaline, serotonin, dopamine, histamine, and acetylcholine, jointly in charge of interpreting the "symphony of wakefulness". Controlling the conductor seems more effective than controlling each of the performers separately.

Orexin Receptors (OX1-R and OX2-R) a New Target for the Pharmacological Approach to Insomnia

Considering the important role of orexins in stimulating orexinergic receptors to promote and maintain wakefulness, it is logical to think that the antagonism of orexin receptors (OX1-R and OX2-R) may improve sleep parameters. Indeed, orexin receptor antagonism constitutes a new and differential approach in the treatment of insomnia that goes beyond the gabaergic, histaminergic, or melatoninergic mechanisms employed to date by most hypnotic agents. Agents with an affinity for OX1-R and OX2-R are considered dual orexin receptor antagonists (DORAs) [34].

In 2007, Brisbare-Roch and colleagues [37] demonstrated the efficacy of almorexant, the first dual antagonist of OX1-R and OX2-R receptors, in promoting sleep in rats, dogs, and healthy subjects. However, despite these initial positive effects in the treatment of insomnia symptoms, the clinical development of almorexant was discontinued due to hepatic safety concerns. The first DORA approved in the USA was suvorexant, granted in 2014 for primary insomnia. However, the presence of residual morning sleepiness forced a reduction of the optimal daily dose from 40 mg to 20 mg. The reported daytime sleepiness was caused by suvorexant's long T1/2, with a range of 10 to 22 hours, resulting in elevated plasma levels that continue to block orexin receptors into the following morning, disrupting the normal capacity to complete important tasks after awakening. Suvorexant is approved in the USA, Japan, and Australia, but has not been licensed in Europe [38,39].

Lemborexant is a DORA with a T1/2 of 17 to 19 hours, with the maximum recommended dose being 10 mg/day. It was approved in 2019 in the USA and is also approved in Canada, Japan, Australia, and other Asian countries, but remains unavailable in Europe or the UK [40]. A recent addition to the DORA group, as well as to the field of hypnotics overall, is daridorexant, which has recently received approval in North America. It stands out as the sole DORA approved in the European Union and was recently introduced to the market in Spain in September 2023. As such, we will conduct a more comprehensive analysis of daridorexant.

Daridorexant is the First and Only Dora Approved in Europe for the Treatment of Chronic Insomnia

Daridorexant (Quviviq®) is a selective dual OX1-R and OX2-R antagonist developed by Idorsia Pharmaceuticals Ltd. for the treatment of chronic insomnia. Daridorexant was selected from a group of drug candidates, with the aim of achieving a hypnotic drug possessing suitable pharmacokinetic and pharmacodynamic profile characteristics for the treatment of both onset and maintenance insomnia [41,42]. Importantly, it was designed to not affect alertness, cognition, or memory the following morning. The results of this program have allowed daridorexant to be approved in 2022 by both the US FDA for the treatment of adults experiencing insomnia characterized by difficulties initiating or maintaining sleep and by the European Medicines Agency (EMA), for adult patients with insomnia symptoms persisting for at least 3 months and significantly impacting daytime activity. Daridorexant is the first DORA available in Europe [41,42].

Most Relevant Pharmacokinetic Aspects of Daridorexant

From a pharmacokinetic point of view, daridorexant is quickly absorbed, reaching its maximum plasma concentrations (Cmax) in a period of 1 to 2 hours (Tmax), ensuring a rapid onset of action to treat sleep onset or reconciliation insomnia. In addition, daridorexant has a T1/2 elimination time of approximately 8 hours, so its residence in the body is adequate for the treatment of sleep onset and maintenance without inciting residual effects the following morning, thus improving daytime functioning [41]. The pharmacokinetics of daridorexant addresses a need unmet by other DORA medications with a longer T1/2, such as lemborexant (17–19 hours) and suvorexant (12 hours). In addition, the pharmacokinetics of daridorexant are dose-proportional (25 and 50 mg), with no accumulation following single or multiple dose administration. Daridorexant is 99.7% bound to plasma proteins and has a volume of distribution of 31 L, indicating that it effectively crosses the blood-brain barrier [38].

Daridorexant is metabolized almost entirely (89%) by CYPP450 isoenzymes 3A4, being excreted as inactive metabolites (M1; M3; M10) in the feces (approx. 57%) and secondarily in the urine (approx. 28%). Metabolization does not show significant variations by age, sex, race, or body mass. However, daridorexant absorption may be delayed by high-calorie, high-fat meals and alcohol, although this delay does not affect other pharmacokinetic parameters. The use of potent CYP3A4 inhibitors, such as clarithromycin, itraconazole, and ritonavir, can increase daridorexant plasma levels, so concurrent use with these agents is contraindicated. With moderate inhibitors of this isoenzyme, the use of daridorexant at a dose of 25 mg/day is recommended [42]. Daridorexant is not recommended for use in patients with severe hepatic impairment, while in those with moderate impairment, a reduced dosage of 25 mg/day is advised. No dose adjustment is necessary for mild hepatic impairment or renal insufficiency. In patients over 65 years of age, optimal efficacy is achieved with a dose of 50 mg/day, so this is the recommended dose [43].

Most Relevant Pharmacodynamic Aspects of Daridorexant

From a pharmacodynamic point of view, the most important action of daridorexant is its ability to antagonize, equipotently, the two orexinergic receptors, OX1-R and OX2-R. While inhibiting OX2-R alone is adequate to induce sleep in individuals, the additional antagonism of OX1-R reduces patients' anxiety about their ability to sleep sufficiently. Consequently, the simultaneous antagonism of both receptors provides added benefits in the management of insomnia [38].

Daridorexant decreases wakefulness and preserves sleep architecture by proportionally increasing both REM and non-REM sleep phases. This feature is not observed with BZDs or "Z drugs", which can alter the normal sleep architecture [38]. Daridorexant's dual equipotent antagonism of OX1-R and OX2-R ensures equal inhibition of arousal- and wake-promoting stimuli [44]. Moreover, daridorexant is a highly selective orexinergic antagonist, as demonstrated by studies on more than 130 pharmacological targets, including receptors potentially related to dependency development, such as GABAergic or opioid receptors. Thus, studies on neurotransmitter transporters, ion channels, and various enzymes demonstrated that neither daridorexant, nor any of its metabolites, were able to bind, activate, or inhibit any of these targets [45]. Furthermore, daridorexant has not been linked to any targets implicated in substance abuse, and animals chronically treated with daridorexant did not show any withdrawal symptoms. These findings suggest that daridorexant does not cause physical dependence, even when used long-term [46]. Thus, the molecular profile of daridorexant is highly selective, exclusively antagonizing the action of orexins on OX1-R and OX2-R, which predicts favorable tolerability and safety [46].

Clinical Development and Efficacy of Daridorexant

The clinical evidence for the efficacy and safety of daridorexant in the treatment of patients with insomnia is primarily supported by an extensive clinical development program, which included eighteen Phase 1 studies [45], three Phase 2 studies [46,47], and two additional Phase 3 studies [48]. These were supported by complementary double-blind phase 3 extension studies and targeted analyses to obtain further information on short- and long-term efficacy and safety [47]. These studies are of high quality and low risk according to the Cochrane risk of bias assessment criteria [48].

This clinical development has shown that daridorexant, at doses of 50 and 25 mg/day, significantly improves sleep parameters according to DSM-5 insomnia disorder criteria. In this regard, the objective primary endpoints, measured by polysomnography, including LPS and the WASO, are improved with daridorexant compared to the placebo group over one month and three months of treatment. In addition, subjective secondary endpoints improved compared to placebo, such as patient-recorded subjective total sleep time (sTST). Similarly, there was an improvement in patients' daytime activity and functionality using the self-reported IDSIQ ("Insomnia Daytime Symptoms and Impacts Questionnaire") scale, approved by the FDA to assess daytime symptoms in people with insomnia disorder [49]. This daytime parameter is central to the DSM-5 diagnosis of insomnia disorders and was considered by patients to be the most important benefit provided by daridorexant [50].

In a large network meta-analysis of 20 hypnotics, daridorexant was found to be more effective than placebo on LPS, WASO, and TST. The WASO analysis showed that daridorexant was superior to the "Z drugs" such as zaleplon and eszopiclone, as well as the melatoninergic agonists such as ramelteon and tasimelteon [10].

The recommended initial and maintenance dose of daridorexant is 50 mg/day, which improves nocturnal sleep parameters and daytime function in patients with chronic insomnia, including those over 65 years of age. Its efficacy remains stable after 3 months of treatment, with an increase in total sleep time of approximately 1.5 hours and average sleep duration of 6.5 hours [48], in line with the proposed targets for chronic insomnia treatment [51]. The subjective estimation of sleep time coincides with the objective one determined by polysomnography, which could be due to the preservation of sleep architecture, unlike the findings reported with other hypnotics, such as BZDs [52].

In an extension study with a one-year duration of treatment, daridorexant (50 mg/day) maintained the nocturnal and diurnal improvements observed in the first 3 months of treatment, with no signs of physical dependence, tolerance, dose adaptation, and without rebound effect. These data speak in favor of the possible long-term use of daridorexant [6].

Regarding safety and tolerability, all doses of daridorexant (25 and 50 mg) in the two Phase 3 studies exhibited similar rates of adverse effects compared to placebo, with the most common being nasopharyngitis, headache, drowsiness, and tiredness. There were no cases of cataplexy or other complex sleep behaviors, suggesting that daridorexant is unlikely to induce narcolepsy-like symptoms [48].

Two patients treated with daridorexant (10 and 25 mg) presented suicidal ideation, although their pre-existing conditions (schizophrenia and depression) could have contributed to this effect. Moreover, abrupt discontinuation of daridorexant treatment was not associated with rebound insomnia or signs of withdrawal [48]. Ufer *et al*. [53] (2022) conducted a trial to evaluate the abuse potential of daridorexant (50, 100, and 150 mg) in recreational narcotic drug users without insomnia, in which daridorexant (50 mg) was found to induce less interest or craving than zolpidem (30 mg), which served as a reference. However, at supratherapeutic doses (100 and 150 mg), the appetite for daridorexant was similar to that of zolpidem (30 mg) [53,54]. Given that subjects with a history of alcohol or other substance abuse or addiction may be at increased risk for substance abuse, the AEMPS recommends that these patients be closely monitored.

The usual dosage of daridorexant is 50 mg/day, which is the maximum recommended daily dose for both initial and maintenance treatment in adults, including those over 65 years of age. In certain clinical circumstances, such as moderate hepatic insufficiency or concurrent use of moderate inhibitors of the 3A4 isoenzymes of cytochrome P-450, a reduced dose of 25 mg may be appropriate. Lower doses of daridorexant (5 and 10 mg) have not been marketed because of their suboptimal effectiveness.

Conclusions

Insomnia disorder is a highly prevalent condition associated with significant morbidity, reduced quality of life, and substantial socioeconomic burdens. Most clinical practice guidelines and expert consensus recommend CBT as the primary treatment. However, challenges in accessing

CBT, its associated costs, variable patient response, and the widespread impact of insomnia have led to increased reliance on pharmacotherapy.

Pharmacotherapy for insomnia is common and hypnotic agents are among the most prescribed drugs. For more than half a century, GABAergic mechanism enhancers (BZD and "Z drugs") have dominated the insomnia treatment market. The short-term efficacy of these medications in inducing or maintaining sleep must be weighed against the risks associated with their regular long-term use, including cognitive dysfunction, falls, fractures, tolerance, and dependence. On the other hand, some medications with antihistamine properties, including some antidepressants and antipsychotics, are used for insomnia without an authorized indication generally. Importantly, these medications exhibit tolerability and long-term efficacy limitations, especially in the elderly. The use of melatonin is very common, yet the heterogeneity of its presentations make it difficult to demonstrate its efficacy in insomnia [21,55].

Against this background, the exploration of new pharmacological targets, such as the orexinergic system, has yielded promising results in the development of a new class of medications, providing better alternatives for patients. These medications, known as DORAs, include daridorexant, lemborexant, and suvorexant. Unlike other pharmacological agents, DORAs promote sleep by inhibiting wakefulness rather than enhancing sedation.

Daridorexant is the only DORA approved for the treatment of chronic adult insomnia by the EMA and FDA. With its ideal T1/2 of 8 hours, daridorexant ensured enhanced sleep induction and maintenance, leading to improved daytime functionality without affecting morning activity. This agent has demonstrated continuous efficacy over a 12-month period, with a favorable safety and tolerability profile without risk of withdrawal or rebound effects [56].

Availability of Data and Materials

All data generated or analyzed during this study are included in this published article.

Author Contributions

CÁ: Conceptualization, Methodology, Formal analysis, Supervision, Writing original draft, Writing–review and Editing; JSR: Conceptualization, Methodology, Formal analysis, Supervision, Writing original draft, Writing–review and Editing; CZA: Methodology, Formal analysis, Writing–review and Editing, Supervision. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Ethics Approval and Consent to Participate

Not applicable.

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Conflict of Interest

The authors declare no conflict of interest.

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