Orexants, Orexin Receptor Antagonists: Novel Therapeutic Agents For Insomnia Disorder

ABSTRACT

Insomnia is when a person feels difficulty falling asleep or staying asleep, often associated with complications, such as fatigue, sleepiness, etc. Insomnia may cause disruptions in daytime physical and mental abilities. Orexins or hypocretins are the neuropeptides secreted from the lateral hypothalamus and play a major role in the sleep-wake cycle through a complex interplay between wake-promoting and sleep-promoting neuronal systems. Orexin receptor antagonists (Orexants) are the new treatment options for insomnia disorder, narcolepsy, and other sleep disturbances. There are two classes of Orexants, namely those that bind selectively to a specific orexin receptor are selective orexin receptor antagonists (SORA), and the others that bind to both the orexin receptors are dual orexin receptor antagonists (DORA). The first DORA was almorexant but restricted in use and the other three approved DORAs, such as suvorexant, lemborexant, and daridorexant were approved by the FDA, and several other DORAs and SORAs are under various stages of discovery and clinical investigation. Among the labeled limitations, the currently approved Orexants are contraindicated in people with narcolepsy and are controlled substances owing to their misuse liability. The present review discussed the sleep-wake cycle, phases of a sleep cycle, orexins, and Orexants, and summarized the pharmacology of the three approved DORAs, a type of Orexants and their potential advantages and limitations of their use in pharmacotherapy of insomnia disorder.

Keywords: Almorexant, Daridorexant, DORA, Insomnia, Lemborexant, Narcolepsy, Orexants, Orexins, Sleepiness, SORA, Suvorexant

1. INTRODUCTION

“Sleep is an altered state of consciousness wherein humans show diminished mental, physical, and motor activity, and inhibit the ability to respond to certain sensory stimuli” [1,2]. “It is a highly conserved behavior and the most significant biological process for preserving physical and mental health” [1-3]. “Essentially, sleep is impacted by age and/or concomitant health issues, rendering all age groups of humans predominantly susceptible to sleep deprivation, sleep loss, and dysregulation” [3,4]. “Importantly, the amount and/or quality of sleep in modern human society is reducing resulting in various sleep disorders that are associated with functional decline in vital organ systems and a wide array of undesired health outcomes, such as cognition, immune status, wound healing, neuronal repair, endocrine regulation, and more” [1-4].

1.1 Sleep Stages

“There are two basic phases of sleep, rapid eye movement (REM) sleep and non-REM (NREM) sleep. Sleep functions in a relatively predictable cyclical pattern between these two major phases. Each phase and stage are linked to specific brain waves and neuronal activity, offer unique characteristics in the brain wave, muscle tones, and eye movement patterns, and represent the relative depth of sleep. NREM sleep comprises approximately 75% to 80% of total sleep whereas REM comprises the remaining 20% to 25% of sleep. A healthy person cycles through NREM and REM sleep several times during a typical night's sleep, with progressively longer, deeper REM periods occurring later in the sleep session. A total of 4 to 5 sleep cycles are completed in a night” [1,3,4].

1.1.1 NREM Sleep Phase

As the name indicates, NREM is characterized by an absence of eye movements and rapid eye movements characterize REM. NREM sleep is subdivided into the three stages numbered 1 to 3 [1,3]. Stage 1 NREM sleep is the changeover from wakefulness to sleep. During this short period of relatively light sleep, a gradual decrease in heartbeat, breathing, eye movements, and relaxation of skeletal muscles with occasional twitches [1,3]. Particularly, brain waves begin to slow from their daytime wakefulness patterns. It is the shallow stage of sleep where a person is still easily awoken. This stage usually lasts 1 to 7 minutes. Rhythmical alpha waves characterize electroencephalogram (EEG) at a frequency of 8 to 13 cycles per second [1,3,4]. Stage 2 NREM sleep is a period of light sleep stage before a person enters deeper sleep. It is characterized by slowing of heartbeat and breathing, and muscles relax even further. Core body temperature drops and eye movements stop. Stage 2 is a much deeper sleep state than stage 1, however, individuals are still awoken with heavy stimulation. Brain wave activity slows but is marked by brief bursts of electrical activity and records low voltage "sleep spindles and K-complexes" EEG [1,2]. "Current theories suggest that memory consolidation occurs primarily during this stage. This stage lasts for about 30–60 minutes. A person spends more repeated sleep cycles in stage 2 sleep than in other sleep stages and progresses to consume 50% of the total sleep cycle later in the night" [1,3,4]. "Stage 3 NREM sleep is the period of deep sleep that one needs to feel refreshed in the morning. It occurs in longer periods during the first half of the night. There is a slowing of heartbeat and breathing to their lowest levels during this stage of sleep [3]. Skeletal muscles are relaxed more and it may be difficult to awaken any person in this stage. This NREM stage 3 lasts about 20 to 40 minutes, initially. EEG is characterized by high-voltage and slow-wave frequency" [1,3,4].

1.1.2 REM Sleep Phase

"REM sleep is the final phase of sleep before a new cycle begins and initially occurs about 90 minutes after falling asleep. In this phase, eyes move rapidly from side to side behind closed eyelids. Most of the dreaming occurs during REM sleep, although some can also occur in non-REM sleep. There is a significant reduction in blood flow and metabolism" [1-3]. "Growth hormone secretion usually occurs during the first few hours after sleep onset while thyroid hormone secretion increases later. Breathing becomes faster and irregular, and heart rate and blood pressure increase to near waking levels. Further, arm and leg muscles become temporarily paralyzed, which prevents one from acting out of dreams. Mixed-frequency brain wave activity becomes closer to that seen in wakefulness" [1,3]. "REM is characterized by "Sawtooth waveforms," theta waves, and slow, alpha waves in a desynchronized pattern on EEG. As one age, a person spends less time in REM sleep. Memory consolidation most likely requires both non-REM and REM sleep" [1,3,4].

1.2 Insomnia

"Insomnia is a common sleep disorder characterized by difficulty falling or staying asleep and the inability to get back into sleep occurring at least 3 times a week for at least three months and with a positive response to questions, such as Do you experience difficulty in falling asleep or staying asleep" [5-7] "Mostly, insomnia disorders are underdiagnosed or undertreated resulting in a significant healthcare burden owing to increased morbidity and mortality and leading to poorer quality of life for those who experience it" [6-8]. Despite adequate sleep opportunities, insomnia frequently presents daytime symptoms [5,7,8]. "The Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, (DSM-5) and the 10th revision of the International Classification of Diseases (ICD-10), a medical classification list by the World Health Organization (WHO) have proposed similar criteria" [5-9]. "Insomnia affects 9 to 15% of the general population and of those one-third of adults (30–36%) report at least one nocturnal insomnia symptom" [10,11]. Indeed, the prevalence of chronic insomnia disorder is estimated between 6 and 10% [7]. "Insomnia disorder is frequently accompanied by comorbid conditions, such as depression and other neurological disorders, cardiovascular disease, diabetes, and disturbances in the respiratory and gastrointestinal systems" [12]. "Besides, any type of cancer should be treated as a separate clinical condition, but not as a secondary issue to other comorbidities [9,13]. Insomnia was previously divided into primary and secondary types but now includes short-term, chronic, and other subtypes. The recently released third edition of the International Classification of Sleep Disorders (ICSD-3) removed the previously used subtypes of sleep disorders, such as paradoxical, idiopathic, psychophysiological, and inadequate sleep hygiene, thereby ensuring a more comprehensive understanding of insomnia" [14]. "Acute insomnia is also known as adjustment insomnia, stress-related insomnia, transient

psychophysiological insomnia, symptomatic insomnia, sub-acute insomnia, and sub-chronic insomnia. The ICSD-3 defined chronic insomnia as having one of the following problems for at least 3 months: having difficulty in sleep initiation, having difficulty in maintaining sleep, early awakening, and difficulty sleeping without a caregiver. Indeed, short-term insomnia also has the same problems but for less than 3 months" [15]. "Short-term insomnia is a complex condition influenced by environmental, genetic, psychological, and behavioral factors, leading to hyperarousal and a state of indifference" [14,15]. "Indeed, neurobiology of sleep and neurochemistry of wakefulness and sleep states are highly complex processes that are neurophysiologically facilitated by fine-tuned neurochemical changes, including several neurotransmitters and neuromodulators, viz. serotonin, acetylcholine, γ-amino-butyric acid (GABA), glutamate, norepinephrine, dopamine, histamine, adenosine, melatonin, hypocretin, and melanin-concentrating hormone" [16,17]. Nevertheless, the role of a single neurotransmitter or neuromodulator, rather than their complex interactions within organized neuronal systems and neurochemicals regulates the sleep and wake cycle and drives their switches. Dysregulation of these neuronal systems and medications interfering with these neurochemical systems leads to numerous sleep-wake disorders characterized by functional changes in alert promotion, wakefulness, and sleep [17]. Among these neuronal and neurochemical systems, the orexin system is potentially highly significant and has been associated with wakefulness and alert promotion prompting the discovery of several lead molecules [12-16]. "Of particular note, small-molecule dual orexin receptor antagonists (DORAs) that include suvorexant, lemborexant, and daridorexant are recently approved for the pharmacological management of insomnia disorder" [17-23].

2. OREXINS AND HYPOCRETINS

2.1 Discovery

Orexins were identified independently by two research groups in 1998. These two research groups identified that the two orexins A and B are structurally similar and are ligands for G-protein coupled receptors (GPCRs). One group named them as orexins and the other group as hypocretin. Both orexins were produced by the common precursor peptide, prepro-orexin. In Greek, orexins mean appetite. Orexin neurons are found in the lateral hypothalamus but project throughout the CNS [18,19]. The orexin system consists of two peptides, orexin-A and orexin-B, derived from prepro-orexin. These peptides are produced by lateral hypothalamic (LH) neurons and interact with two G protein-coupled receptors: orexin receptors 1 and 2 (OX1R, Hcrtr1) and 2 (OX2R, Hcrtr2) [4,20,21]. Orexinergic innervation extends across the brain, including monoaminergic areas, the thalamus, and the cortex [4,20]. "The orexin system is essential for staying awake and controlling attentiveness in physiological processes. Orexin-A levels in the brain and cerebral spinal fluid follow a diurnal cycle, increasing during wakefulness and rapidly decreasing during sleep" [18]. "Orexin projections can lengthen or disrupt sleep periods by exciting wake-promoting regions such as the locus coeruleus, dorsal raphe, tuberomammillary histamine, and basal forebrain/brainstem acetylcholine secreting neurons" [22,23].

2.2 Chemistry

Orexin-A consists of a 33-amino acid peptide and also with an N-terminal pyro glutamyl residue with two interchain disulfide bonds and also consists of C-terminal amidation. Orexin B consists of 28-amino acid with C-terminally amidated linear peptide [19,22,23].

2.3 Orexin receptors

Two types of receptors orexin type 1 receptor (OX1R/HCRTR1) and orexin/hypocretin type 2 receptors (OX2R/HCRTR2). OX1Rs are found selectively in the locus coeruleus (LC) and cingulate cortex. OX2Rs are found selectively in the tuberomammillary nucleus (TMN), nucleus accumbens, and paraventricular nucleus (PAN) [4,20,22]. The contribution of OXRs to sleep-wake regulation is studied using orexin receptor knockout mice. OX1R has a higher affinity for orexin-A than orexin-B, while OX2R shows a similar affinity for orexin-A and orexin-B. OX2R plays a larger role than OX1R [4,20,22,24].

3. OREXIN RECEPTOR ANTAGONISTS

Two classes of orexin/hypocretin receptor antagonists were present. These agents are commonly referred to as 'Orexants'. Firstly, which are selective for a specific orexin receptor are known to be selective orexin receptor antagonists (SORAs), which are selective for OX1Rs or OX2Rs. Next is the dual orexin receptor antagonist which has an affinity for both OX1Rs and OX2Rs (DORAs) [4,18-20,23]. The orexin signaling system consists of orexin A and B and its G-protein coupled receptors, orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R). Orexins by binding to their corresponding receptors can regulate sleep, thus, blocking orexin receptors is a pathophysiological approach to key pharmacotherapy for insomnia disorder [18,21,25]. The role of Orexants is to promote wakefulness and the treatment of sleep disturbances by inhibiting the effects of orexin. Dual orexin receptor antagonists (DORAs) are medications that prevent wakefulness by blocking the binding of wake-promoting orexin neuropeptides. They improve sleep onset and maintenance of insomnia with reduced next-day impairment. DORAs have no rebound insomnia or withdrawal effects and have minimal abuse potential [4,18-20].

3.1 Clinical development of orexin receptor antagonists (SORAs and DORAs)

As of now, three Orexants, particularly DORAs, viz. suvorexant (MK-4305), lemborexant (E2006), and daridorexant (ACT-541468) are approved for marketing by the US Food Drug Administration (FDA) and several others are undergoing clinical development [4,20,23-26]. The first Orexant (DORA) was almorexant [ACT-078573, a tetrahydroisoquinolone] but clinical development was restricted due to its hepatotoxicity. Almorexant was the first DORA to proceed to phase 2 studies in 2007. During phase 3 studies of almorexant conducted by Actelion and GlaxoSmithKline, in January 2011, they reported few adverse effects irrelevant to the orexin system's function [4,20,23,27]. The first Orexant as well as the advanced DORA is suvorexant [MK-4305, a diazepane] approved by the FDA in 2014. The second Orexant, lemborexant (a DORA), was approved for insomnia by the US FDA in 2019. The third Orexant, daridorexant (a DORA), was approved for the treatment of insomnia in the USA for sleep maintenance in 2022. Several Orexants are in various phases of clinical development. Fazamorexant (YZJ-1139) is a DORA under development for insomnia and progressed to phase 3 [28]. Seltorexant (MIN-202, JNJ-42847922, JNJ-922) is a selective OX2 antagonist (2-SORA) that facilitates prolonged sleep duration and improved sleep quality upon oral administration. It crosses the blood-brain barrier and occupies OX2R in the brain in rats. It is under development for major depressive disorder, insomnia, and sleep apnea, and progressed to phase 3 [29]. Nivasorexant (ACT-539313) is a selective OX1 antagonist (1-SORA) under development for binge eating disorder and previously for anxiety disorders, up to phase 2 [30,31]. Vornorexant (ORN-0829, TS-142), a DORA undergoing clinical development for insomnia and sleep apnea, progressed up to phase 3 [32,33]. Another DORA, GSK-649868 (SB-649868) was under investigation in phase 2 and showed significant improvement in total sleep time and REM sleep duration without adverse effects [34]. Tebideutorexant (JNJ-61393215, JNJ-3215), a 1-SORA is under development for major depressive disorder, however, no development was reported for anxiety disorders and panic disorder in phase 2 [35]. As of now, clinical development of ACT-335827, a 1-SORA, and almorexant (ACT-078573), a DORA was abandoned in 2011 [28]. Further, the clinical development of EMPA, a 2-SORA and filorexant (MK-6096), a DORA was discontinued in 2015 [23,36]. Furthermore, GSK-649868 (SB-649868; DORA), JNJ-10397049, a selective OX2 antagonist (2-SORA), RTIOX-276, a 1-SORA, SB-334867, the first non-peptide 1-SORA, SB-408124, a 1-SORA, and TCS-OX2-29, the first non-peptide 2-SORA were in the early stages of development for potential use in sleep disorders [23,28]. The first 1-SORA SB-334867 and JNJ-48816274 were shown to decrease reward-seeking behavior that is present with drug addiction and intake of high-fat foods [21,26]. SB-334867 increases both NREM and REM sleep and reverses the sleep-modulating effects of OX1R (HCRT1). JNJ-54717793 was another 1-SORA decreased panic behavior and anxiety [21,25,26,37]. The list of Orexants (1-SORAs, 2-SORAs, DORAs) in various stages of clinical development is presented in Table 1 and the overview of the pharmacology of the approved Orexants (three DORAs) is summarized in Table 2.

3.2 Suvorexant

“Suvorexant (Belsomra®) (MK-4305) was the first Orexant and a DORA approved by the US FDA in August 2014 for the treatment of adult patients with insomnia presented with difficulty in sleep onset or sleep maintenance [38,39]. The dose recommended was 10 mg orally, once per night within 30 minutes of going to bed. Suvorexant was also approved in Japan in 2014. In phase 3 studies, suvorexant improved total sleep time (TST), latency to onset of persistent sleep (LSP), objective and subjective wake time after sleep onset (WASO), and insomnia severity index [19]. If the 10 mg dose was well tolerated but not effective then the dose can be increased to 20 mg once daily. The FDA stated that patients taking 20 mg doses should be advised against conducting activities like driving requires full mental alertness” [23,25,37,41].

Table 1. The list of Orexants, the orexin receptor antagonists in clinical development [4,20,23,24,28,62]

OREXANTS (Orexin Receptor Antagonists)			
Type	1-SORA (a selective OX1 receptor antagonist)	2-SORA (a selective OX2 receptor antagonist)	DORA (Dual orexin OX1 and OX2 receptor antagonist)
Receptor specificity	OX1 receptor	OX2 receptor	Both OX1 and OX2 receptors
Compounds	ACT-335827	EMPA	Almorexant (ACT-078573)
	SB-334867	Seltorexant (MIN-202, JNJ-42847922, JNJ-922)	Filorexant (MK-6096)
	SB-408124	GSK-649868 (SB-649868	Suvorexant (MK-4305)
	SB-674042	JNJ-10397049	Lemborexant (E2006)
	Nivasorexant (ACT-539313)	TCS-OX2-29	Daridorexant (ACT-541468)
	Tebideutorexant (JNJ-61393215, JNJ-3215)		Fazamorexant (YZJ-1139)
	RTIOX-276		Vornorexant (ORN-0829, TS-142)
	SB-334867		GSK-649868 (SB-649868)
	SB-408124		

3.2.1 Pharmacodynamics

It has a high affinity for both orexin-1 and orexin-2 receptors. In most of the animal studies, suvorexant showed an increase in both non-rapid eye movement and rapid eye movement sleep [41,42].

3.2.2 Pharmacokinetics

Suvorexant dose of 10 mg oral administration is 82% bioavailable. Plasma clearance was 2.9 L/h and the volume of distribution was 49 L, the elimination half-life (t1/2) was 12 h, metabolized by CYP3A4, CYP2C19, and M9 was the circulating metabolite which was not active pharmacologically [41-43]. Excretion is 66% through feces and 23% through urine. No dose adjustment is required for renal impairment. The dose should be reduced when used with CYP3A4 inhibitors. Clearance was 2-3 times lower in men. Pharmacokinetics was performed in open-label, single-dose studies in renal impairment, but not performed in hepatic impairment. Suvorexant when administered with high-fat meal had no clinically significant effects but lowered tmax by 1.5 hours. Suvorexant can be taken with or without food but can be taken on an empty stomach for patients desiring faster sleep onset [42,43].

3.2.3 Clinical trials

First, the efficiency was evaluated in 254 primary insomnia patients in a phase 2 study of 4 weeks duration. While 10 mg, 20 mg, 40 mg, and 80 mg suvorexant vs placebo were given in a crossover fashion and significant effects on WASO were achieved at all doses while the effects of LPS were observed at 80 mg. In phase 3 about 2041 subjects were there and in which 839 elderlies with insomnia were given 20 mg and 40 mg for 8 months duration. In both studies, WASO and LPS were reduced [42-45].

3.2.4 Safety studies

It is conducted in healthy and non-elderly and elderly subjects to assess next-morning driving performance with the same doses given in phase 3. The outcomes are below the clinically significant threshold of 2.4 cm indicating that suvorexant is not causing clinically meaningful driving impairment. Another safety study was performed to assess psychomotor performance in healthy elderly subjects during the middle of the night awakening after bedtime administration of a supratherapeutic dose of 30 mg. The impairment of psychomotor performance was reported at 1.5 h post-administration. The safety of suvorexant was not known in pregnancy and lactation and is contraindicated in narcolepsy [42,46].

Table 2. Overview of the pharmacology of the approved Orexants: Dual Orexin Receptor antagonists (DORAs) [4,20,23,28,41,42,48,49,53,57,59,62]

Properties	Suvorexant	Lemborexant	Daridorexant
Alternative names	Belsomra®, MK4305	Dayvigo®, E2006	QuviviQ®, ACT 541468, Nemorexant
WHO ATC code	N05C (hypnotics and sedatives)	N05C (hypnotic and sedatives)	N05C (hypnotic and sedatives)
Dose; Route of administration	5 - 20 mg; Oral	5 mg, 10 mg; Oral	25 mg, 50 mg; Oral
Pharmacodynamics	Acts as a selective dual antagonist of the orexin OX1 and OX2 receptors.	Acts as a selective dual antagonist of the orexin OX1 and OX2 receptors.	Acts as a selective dual antagonist of the orexin OX1 and OX2 receptors.
Pharmacokinetics	Bioavailability: 82% Metabolism: CYP3A4 Elimination: Feces $T_{1/2}$: 12 h; T_{max}: 2-3 h Vd 49 L Protein binding >99%	Bioavailability: 87% Metabolism: CYP3A4 Elimination: Feces $T_{1/2}$: 17-19 h; T_{max}: 1-3 h Vd 1970 L Protein binding >94%	Bioavailability: 62% Metabolism: CYP3A4 Elimination: Feces $T_{1/2}$: 8 h; T_{max}: 1-2 h Vd 31 L Protein binding >99.7%
Indications	Treatment of sleep-onset and sleep-maintenance insomnia in adults	Treatment of sleep-onset and sleep-maintenance insomnia in adults	Treatment of sleep-onset and sleep-maintenance insomnia in adults
Adverse effects	Somnolence, fatigue, daytime sleepiness, dizziness, headache, dry mouth, impaired next-day driving ability	Somnolence, fatigue, nightmares, and palpitations	Nasopharyngitis, headache, fatigue, dizziness, nausea, sleepiness, somnolence
Advantages	Increases total sleep time; Increases REM sleep; No effect on NREM sleep; Does not disrupt sleep architecture; Does not cause respiratory depression; Does not cause tolerance, dependence, withdrawal, and rebound effects; No anticholinergic effects; No	Increases total sleep time; Increases REM sleep; No effect on NREM sleep; Does not disrupt sleep architecture; Does not cause respiratory depression; Does not cause tolerance, dependence, withdrawal, and rebound effects; No anticholinergic effects; No	Increases total sleep time; Increases REM sleep; No effect on NREM sleep; Does not disrupt sleep architecture; Does not cause respiratory depression; Does not cause tolerance, dependence, withdrawal, and rebound effects; No

	effect on body weight; Can be prescribed to the elderly	effect on body weight; Can be prescribed to the elderly; NO driving impairment	anticholinergic effects; No effect on body weight; Can be prescribed to the elderly
Limitations	Contraindicated in people with narcolepsy; Concomitant use with strong CYP3A4 inhibitors is not recommended; Risk of suicidal ideation; Misuse liability; Driving impairment; Schedule IV controlled substance in the US	Contraindicated in people with narcolepsy; Concomitant use with strong CYP3A4 inhibitors is not recommended; Risk of suicidal ideation; Misuse liability; Schedule IV controlled substance in the US	Contraindicated in people with narcolepsy; Concomitant use with strong CYP3A4 inhibitors is not recommended; Risk of suicidal ideation; Misuse liability; Driving impairment; Schedule IV controlled substance in the US

3.3 Lemborexant

Lemborexant (E2006; DAYVIGO™) is the second Orexant approved by the USA FDA on 20 December 2019. It is an opening receptor antagonist (DORA) developed by Eisai Inc. for the treatment of adults with insomnia and subsequently approved on 23 January 2020 in Japan [13,48]. Lemborexant is being investigated for the treatment of Irregular Sleep-Wake Rhythm Disorder (ISWRD) associated with Alzheimer's disease [23,49]. Lemborexant was approved in several countries, including the United States, Canada, Australia, and several Asian countries, for the treatment of insomnia in adults [50]. The dose recommended was 5 mg orally, once per night immediately before going to bed with at least 7 hours remaining before the planned time of awakening. The dosage may be increased to 10 mg per night based on tolerability and effectiveness [51,52]. Lemborexant was not recommended for people with narcolepsy and severe hepatic impairment [48,53].

3.3.1 Pharmacodynamics

It has high selectivity for both OXR1ss and OXR2 receptors. Its mechanism of action is via dual orexin receptors. In *in vitro* studies, lemborexant acts as a competitive antagonist for both the orexin receptors which interferes with orexin neurotransmission to facilitate sleep [15,42,53,54].

3.3.2 Pharmacokinetics

Lemborexant, when taken orally, is absorbed rapidly [42,55]. Still, absorption was altered when absorbed with a high-fat, high-calorie meal, and sleep onset, may be delayed if administered with or soon after a meal [42,53]. Plasma protein binding was approximately 94%, and the volume of distribution was 1970 L. It is metabolized by CYP3A4 and with CYP3A5 the circulation metabolite is M10. Lemborexant is eliminated in feces 57.4% and 29.1% in urine, and <1% is eliminated in unchanged form. Half-life is 17 hours for a 5 mg dose and 19 hours for a 10 mg dose [42,49,56]. Moderate or strong CYP3A inhibitors or inducers should be avoided with lemborexant. Lemborexant should be avoided in patients with severe hepatic impairment and people with narcolepsy [42,49].

3.3.3 Clinical trials

Lemborexant vs placebo for chronic insomnia phase 2 completed in the USA and also for circadian rhythm sleep disorders and mild to moderate Alzheimer's disease phase 2 trials were ongoing in Japan, USA, and UK. Another multinational study, lemborexant vs placebo for insomnia disorder was completed. A multicentre pilot study evaluated the effectiveness of immediate or extended-release zolpidem taken frequently or infrequently to lemborexant 5 mg or 10 mg which was known at 2 weeks of treatment for people with insomnia and the expected date of completion was July 2020 [49].

3.3.4 Adverse effects

Somnolence, nightmares, and palpitations in lemborexant 5 mg or 10 mg vs placebo and patients discontinued after first 30 days of administration. More than 2% of subjects who took lemborexant 5 mg or 10 mg vs placebo showed somnolence, fatigue, headache, and abnormal dreams [42,49]. Sleep paralysis 1.3%, hypnogogic hallucinations with lemborexant 5 mg or 10mg vs 0% placebo, complex sleep behavior

like sleep-walking and sleep-driving if occurred then treatment should be discontinued immediately, night postural instability, rebound insomnia if treatment stopped [42,49,56].

3.4 Daridorexant

Daridorexant (QUVIVIQTM; ACT-541468), a DORA patented in 2013, was developed by Idorsia Pharmaceuticals Ltd and is the third Orexant that received its first approval by the US FDA on 7 January 2022 for the treatment of insomnia [57-59]. It is the first Orexant approved for the management of insomnia in the European Union [23,37]. It is indicated for treating adults with insomnia for at least 3 months and has a considerable impact on how they function during the day [57,60]. The dose recommended in the USA is 25 mg to 50 mg once per night taken within 30 minutes before bedtime, with at least 7 hours remaining prior to planned awakening [57-59]. When compared to a placebo, daridorexant was shown to help patients fall asleep more quickly and stay asleep longer. Dosages of 50 mg of the drug were also found to be more effective and to have longer-lasting effects than 25 mg doses [61]. Few warnings regarding CNS depressant effects, worsening of depression, sleep paralysis, hallucinations, and cataplexy-like symptoms were included in US prescribing information [23,57-59,62]. No information was available for administration of daridorexant during breastfeeding.

3.4.1 Pharmacodynamics

Daridorexant is a DORA for OXR1 and OXR2. The inhibition constant kb values for human OX1 and OX2 receptors are 0.52 nm and 0.7 nm, respectively [57,59].

3.4.2 Pharmacokinetics

The pharmacokinetic profile for a single dose and multiple dose administration of daridorexant was the same and no accumulation. The peak plasma concentration (Tmax) is within 1-2 hours and a half-life of 8 hours. When administered with a high-fat, high-calorie meal Cmax was reduced by 16% and Tmax was within 1.3 hours (increased). Highly bound to plasma proteins 99.7% and the volume of distribution was 31 L [57-59]. It is metabolized by CYP3A4 (89%) in the liver and excreted through feces (~57%) and also through urine (~28%) [61]. AUC may increase rapidly by 240% and >400% when concomitantly administered with moderate CYP3A4 inhibitors diltiazem and strong CYP3A4 inhibitors itraconazole [57,58]. Also, AUC may decrease by ~30% and >50% when concomitantly administered with moderate CYP3A4 inducers efavirenz and strong CYP3A4 inducer rifampin. When administered along with ethanol then Tmax may be prolonged and may inhibit psychomotor functioning [57,58,61]

3.4.3 Clinical trials

Two different trials were conducted (NCT03545191 and NCT03575104), which reported that doses of 25 mg and 50 mg of daridorexant improved sleep outcomes and daytime functioning with 50 mg dose in patients with insomnia disorder in two pivotal phase 3 clinical trials. In a randomized double-blind, phase 2 trial, the dose of 5 mg – 50 mg of daridorexant has been associated with a dose-dependent reduction in WASO in patients 18 - 64 years of age with insomnia [58,59,63]. Moreover, two phase 3 trials evaluating daridorexant for insomnia are recruiting patients in Japan. A randomized open-label study investigating long-term safety (JapicCTI-205444) [58].

3.4.4 Adverse effects

The most commonly reported adverse effects of daridorexant are nasopharyngitis, headache, fatigue, dizziness, nausea, somnolence, sleep paralysis, and hallucinations [57-60,63]. Daridorexant, a central nervous system depressant, is contraindicated for narcolepsy patients and should not be used with other depressants to avoid exacerbated effects [57,61].

4. ADVANTAGES OF OREXANTS: DUAL OREXIN RECEPTOR ANTAGONISTS AS CURRENT THERAPEUTIC OPTIONS

(1) In the short-term treatment of insomnia, benzodiazepines, non-benzodiazepine receptor agonists (“Z-drugs”; zopiclone, zaleplon, zolpidem), and sedating antidepressants are effective when used for ≤ 4 weeks [60]. (2) On the other hand, antihistamines, melatonin, antipsychotics, and herbal medicines are not generally recommended for the treatment of insomnia owing to poor outcomes [60,64]. (3) Moreover,

the potential benefits of light therapy, exercise, non-invasive brain stimulation techniques (eg., repetitive transcranial magnetic stimulation, transcranial direct current stimulation), and complementary and alternative treatments (eg., homeopathy, acupuncture, acupressure) are needed to be systematically investigated to justify their usefulness in the treatment of insomnia disorders [65-67]. (4) Furthermore, unlike benzodiazepines and Z-drugs, DORAs do not interact with GABA receptors, however, they have a distinct mechanism of action and exert antagonist effects by binding to orexin receptors [4,11-19,23,37,62]. (5) DORAs increase total sleep time predominantly by increasing REM sleep while they do not affect or even decrease NREM sleep [11-16;37]. This is potentially important that most hypnotics do not affect REM sleep [60,62]. (6) Unlike certain other hypnotics like benzodiazepines and Z-drugs, DORAs do not disrupt sleep architecture, and this might provide more restful sleep [11-17]. (7) The 2019 American Geriatrics Society Beers Criteria recommended that benzodiazepines and Z-drugs should be avoided in the elderly owing to adverse effects [4,20,68]. Recent studies have shown that DORAs have a positive benefit-risk profile in the elderly population generally consistent with younger patients, and no dose adjustments based on age are required [4,20,62,69-72]. (8) In addition, the use of benzodiazepines and or Z-drugs is associated with respiratory depression and is of particular concern in patients with compromised respiratory function [4,23,37,37,73]. “Indeed, the use of DORAs is not associated with any respiratory-related adverse effect when administered in subjects with mild-moderate obstructive sleep apnoea or moderate chronic obstructive pulmonary disorder” [4,23,74-76].

(9) Antihistamines, such as diphenhydramine and doxylamine, induce sedation by blocking H1 receptors in the histaminergic pathway, thereby promoting sleep. Although both drugs are approved as over-the-counter drugs in several countries, they are associated with daytime somnolence leading to reduced driving ability, therefore, they are recommended only for occasional insomnia in young adults due to rapid tolerance development [60,62,73,77]. (10) Further, these antihistamines can also cause weight gain and anticholinergic side effects, such as blurred vision, dry mouth, delirium, cognitive alterations, urinary retention, and constipation, rendering them unsuitable for the elderly [62,73,78]. (11) A few sedative antidepressants, such as doxepin, mirtazapine, amitriptyline, trazodone, and trimipramine, possessing antihistaminic (H1R) activity, can induce sleep [73]. On the whole, their use should be limited to insomnia with comorbid conditions, such as depression and/or anxiety [9,64]. (12) Trazodone is not approved by the US FDA but is used as a hypnotic following restrictions similar to those applied to benzodiazepines. Moreover, its sleep induction effect disappears after one week of treatment, and sleep induction is lower than that of benzodiazepine with higher dropout rates [9,64,79]. (13) Doxepin is a selective H1 receptor antagonist without anticholinergic, antiadrenergic, or anti-serotonergic effects, and has been approved by the FDA for the treatment of insomnia, in particular, this drug improves the duration and maintenance of sleep but had no effect on the induction of sleep [79]. It is associated with adverse effects similar to those observed with other tricyclic antidepressants [73,78]. (14) Mirtazapine, a sedative antidepressant, has potent antagonistic activity against H1 receptors, 5-HT2A, 5-HT2C, and alpha-2 adrenergic receptors. It has been prescribed off-label for the treatment of insomnia; however, daytime sedation is a limitation due to a prolonged half-life of 20–40 hours [79]. (15) Antipsychotics with antihistamine activities, particularly quetiapine and olanzapine, are prescribed as “off-label” drugs for induction and maintenance of sleep. Nevertheless, these agents are associated with adverse effects, such as weight gain, extrapyramidal symptoms, and the potential risk of sudden death in the elderly, therefore, these agents do not warrant their use as hypnotics [73,78,80]. (16) Gabapentin and pregabalin are gabapentinoids that block the $\alpha 2\delta$ subunits of voltage-dependent calcium channels but are associated with potential risks of central depression, drowsiness, and dizziness, increasing heightening the odds of falls and traffic incidents. (17) Adding to this, pregabalin is classified as a category V narcotic in the US owing to its addictive potential and increased toxicity when used concomitantly with opioids [81]. (18) “Melatonin is a neurohormone that helps in sleep induction by acting on MT1 receptors and regulates the sleep-wake cycle and circadian rhythms by acting on MT2 receptors. Melatonin and ramelteon are widely used for acute insomnia but not for chronic insomnia, treatment for sleep-onset, and/or sleep maintenance insomnia in adults” [82,83].

(19) Adding to this, the 2017 European Sleep Research Society therapeutic guidelines did not generally recommend benzodiazepines, benzodiazepine receptor agonists, or sedating antidepressants for the long-term treatment of insomnia [60]. (20) On the other hand, the 2017 guidelines of the American Academy of Sleep Medicine, weakly recommend a range of drugs for the treatment of chronic insomnia,

including benzodiazepines (triazolam, temazepam), benzodiazepine receptor agonists, Z-drugs, melatonin receptor agonist (ramelteon), a tricyclic antidepressant (doxepin), and a DORA (suvorexant). (21) Moreover, discontinuation of the approved Orexants (DORAs) does not show withdrawal symptoms which is unlikely with the use of other hypnotic agents, such as Z-drugs, melatonin agonists, sleep-promoting antidepressants, or benzodiazepines [20,23,62,64]. Of particular significance, the approved Orexants do not cause rebound effects on insomnia (i.e., an exacerbation of insomnia to a level worse than baseline) even after sudden interruption of treatment [4,20,62,64,73]. (22) Overall, the use of DORAs does not induce and show tolerance, dependence, withdrawal, and rebound effects [4,11-20;23,37,62,79].

5. LIMITATIONS OF DUAL OREXIN RECEPTOR ANTAGONISTS

The only absolute limitation of DORAs, the approved Orexants is that these drugs are contraindicated in people with narcolepsy as it may worsen their symptoms [4,11-20,23,62]. Their use is in people with severe hepatic impairment and is not recommended in these patients due to the possibility of risk of drug exposure. In contrast, DORAs may be used in subjects with mild-to-moderate hepatic or renal impairment, and dose adjustment is not necessary in these situations [4,11-17,20,23]. However, concomitant use of the approved Orexants (DORAs) with strong CYP3A4 inhibitors is not recommended owing to the potential for increased drug exposure while concomitant use of DORAs with strong CYP3A4 inducers may result in loss of drug effectiveness [4,11-17,20,23,78]. In addition, DORAs should be recommended carefully due to their drug-liking effects and possible misuse potential at doses higher than those approved for therapeutic use in patients with a history of drug misuse or alcoholism [4,13-18,20,23]. Other limitations about safety warnings and precautions as per prescribing information of the DORAs include CNS-depressant effects and daytime impairment including reduced motor coordination functions, mechanical work, and car driving. Similarly, DORAs should be used carefully in individuals with a history of depression or suicidality as they may rarely increase suicidal ideation [11-20,23,37,62,79]. These drugs are indicated for use in adults and the elderly but have not been studied in children and adolescents and hence their use is not recommended for and extended to these individuals [4,20,37,62,79]. Suvorexant has shown teratogenic effects in animals at doses much higher than the equivalents of those approved for therapeutic use in humans [41-43]. There is no data on the use of these drugs in pregnant women to inform a drug-related risk, including the risk of fetal harm or reproductive effects. Suvorexant is pregnancy category C in the US [39,41-43]. “The other two drugs, lemborexant and daridorexant, should not be used during pregnancy unless the benefit outweighs the risk to the fetus as the US FDA pregnancy category is not assigned. It is unknown whether a significant amount of any of these three DORAs is present in breast milk, whether affects lactation in breastfeeding women, or whether affects breastfed infants” [13-20,42,43,62]. “If any DORAs are necessarily required by the mother, it is not a purposeful reason to discontinue breastfeeding. However, monitor sedation in infants, particularly when nursing a newborn or preterm baby until more data become available for significant harm to paediatrics” [19,42,48,57,62].

6. CONCLUSIONS

Understanding the neurobiology of sleep, complex neurochemical interactions that regulate the sleep-wake cycle, and identification of druggable orexin receptors (OX1R and OX2R) targets is significant in drug discovery. In particular, Orexants, both SORAs and DORAs, are undergoing a series of clinical developments. Specifically, DORAs showed the first successful and beneficial effects in the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance and became important breakthrough therapeutics in sleep medicine. As of now, three Orexants (all are DORAs) have been approved, namely suvorexant, lemborexant, and daridorexant, and have the advantage of lack of tolerance, dependence, addiction, and rebound effects as a superior potency in sleep disorders. Indeed, DORAs are undergoing investigation to explore their therapeutic potential in other sleep disorders including those associated with neurological and neuropsychiatric disorders. Indeed, the use of approved Orexants (DORAs) is not associated with respiratory depression and is safely given to the elderly as well.

DISCLAIMER (Artificial intelligence)

Author(s) hereby declares that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc) and text-to-image generators have been used during the writing or editing of manuscripts.

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