ABSTRACT

In this review, we have explained the drug “Daridorexant” which is been used for the treatment of insomnia. Clinical research has shown, however, that individuals with insomnia have inconsistent reporting of subjective (i.e., self-reported diaries) and objective (i.e., polysomnography) estimations of their sleep characteristics. Idorsia Pharmaceuticals Ltd. is developing daridorexant (Quviviq™), an orally given dual orexin Type 1 and Type 2 (OX1 and OX2) receptor antagonist (DORA), for the treatment of insomnia. Daridorexant was chosen from a pool of medication candidates because it had estimated effect duration of 8 h at a dosage of 25 mg and a half-life designed to minimize residual effects that might impede daytime functioning. Symptoms have been self-reported by approximately 30% of the general population and can cause a wide range of daily impacts such as fatigue, decreased energy, mood changes, and cognitive impairments. We have explained the pharmacokinetics and pharmacodynamics profile of Daridorexant. It preferentially targets orexin neurons and inhibits downstream neuronal pathways that promote wakefulness; however, it does not affect neuronal pathways that induce adverse effects found with positive allosteric gamma-aminobutyric acid-A receptor modulators. In the context of arrestin-mediated pathways, the possibility of biased signaling is being investigated. The drugs used in the orexinergic system are also included in this review.

KEY WORDS: Allosteric gamma-aminobutyric acid-A receptor modulators, Arrestin-mediated pathway, Daridorexant, Insomnia, Orexinergic system

INTRODUCTION

Insomnia is a prevalent disorder that impairs a person’s sleep hygiene and, as a result, the quality of life for an unequal percentage of people. Patients frequently experience, having trouble getting to sleep staying asleep, or going back to sleep after early in the morning. These problems can impair daily activities and performance by resulting in tiredness, hypersomnia, mood disorders, impaired memory, and inattentiveness.[1] The multiple categories and subtypes for diagnosing insomnia have undergone numerous revisions, leading to uneven and unsatisfying approaches to therapy. To make diagnosis easier, the International Classification of Sleep Disorders (ICSD-3) committee reclassified insomnia subtypes as short-term, chronic, and other. The ICSD-3 and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V), need symptoms to appear at least 3 times/week and last for at least 3 months to diagnose chronic insomnia.[2-3] Cognitive-behavioral therapy is the first-line treatment for insomnia (CBT-I). Although demonstrated to be successful, the use of short-term medication in combination with CBT-I has also been recommended.[4-6] The inclination is generally diagnosed clinically based on self-reported symptoms rather than polysomnography (PSG) characteristics. Clinical research has shown, however, that individuals with insomnia have inconsistent reporting of subjective (i.e., self-reported diaries) and objective (i.e., PSG) estimations of their sleep characteristics.[7,8] Benzodiazepines, Z-drugs, melatonin receptor agonists, and sedating antidepressants are among the most often used pharmacological treatments for insomnia.[9] Idorsia Pharmaceuticals Ltd. is developing
Ongoing clinical trials

Insomnia symptoms have been self-reported by approximately 30% of the general population and can cause a wide range of daily impacts such as fatigue, decreased energy, mood changes, and cognitive impairments. Daridorexant is a usually safe and well-tolerated DORA that has been investigated to relieve insomnia symptoms and lessen the detrimental impact it may have on a patient’s daily life. Daridorexant’s possible adverse effects are regarded as minor and may include headache, gait instability, weariness, and nasopharyngitis. In Japan, two Phases III studies testing daridorexant as an insomnia medication are presently enrolling patients: A randomized, double-blind trial exploring effectiveness and safety (jRCT2031200452) and a randomized, open-label study investigating long-term safety (JapicCTI-205444).

Phase II

In a randomized, double-blind, and Phase II study, daridorexant 5–50 mg was linked with a dose-dependent decrease in waking time after sleep onset (WASO) in individuals (18–64 years of age) with insomnia condition (NCT02839200). In a randomized, double-blind trial exploring effectiveness and safety (jRCT2031200452) and a randomized, open-label study investigating long-term safety (JapicCTI-205444).

Phase III

Adult patients with insomnia were randomized to daridorexant 25 mg (n = 310) or 50 mg (n = 310), or placebo (n = 310) once a day for 3 months in study one. The primary objectives were changes in WASO and latency to persistent sleep (LPS) from baseline to month 1 and month 3 as evaluated by PSG in a sleep laboratory.

CURRENT AND EMERGING THERAPIES FOR INSOMNIA

Orexin receptor antagonists

The orexin/hypocretin receptor plays an important role in the control of sleep-wake cycles, arousal, and hunger. A medicine that works as an orexin receptor antagonist may produce drowsiness and allow for extended durations of sleep, which may be beneficial in the treatment of insomnia. A very new class of drugs called DORAs includes daridorexant, which works on distinct brain pathways than other therapies now on the market. These medications were created as an alternate therapy to positive allosteric gamma-aminobutyric acid (GABA) Receptor modulators have historically been used to treat insomnia. The discovery of daridorexant was the outcome of a research program aimed at finding a medicine with sleep-promoting qualities that did not impair next-morning alertness, cognition, or memory. It accomplishes this by blocking the function of the neuropeptide orexin, which is principally produced in the lateral hypothalamus and exerts its effects by activating two G protein-coupled receptors, orexin.
Tyagi, et al.: Daridorexant: A drug to treat insomnia

receptors Type 1 and Type 2. Orexin promotes daytime alertness and is mostly inactive during sleep. According to the insomnia daytime symptoms and impacts questionnaire (IDSIQ), daridorexant improves and enhances daytime function.[23] Daridorexant is a usually safe and well-tolerated DORA that has been investigated to relieve insomnia symptoms and lessen the detrimental impact it may have on a patient’s daily life. Daridorexant’s possible adverse effects are regarded as minor and may include headache, gait instability, weariness, and nasopharyngitis.[18]

PHARMACOKINETICS/PHARMACODYNAMICS OF DARIDOREXANT

Pharmacokinetics

The drug’s pharmacokinetic profile is identical following multiple-dose and single-dose administration, and there is no build-up, with peak plasma concentrations reaching within 1-2 h (Tmax). A high-fat/high-calorie lunch delayed the tmax of daridorexant by 1.3 h and lowered Cmax by 16% in volunteers, but did not affect total exposure (AUC). The medication has a volume of distribution of 31 L and is bound to plasma proteins 99.7% of the time. The terminal half-life (t1/2) of daridorexant was 8 h in all experiments[13,24] February 14, 2022. In pharmacokinetic modeling studies, Daridorexant’s AUC increased by 240% and >400% when paired with the weak CYP3A4 inducer rifampin and the moderate CYP3A4 inducer Diltiazem, respectively. In contrast, the AUC was reduced by 30% and >50% when mixed with the strong CYP3A4 inducer diltiazem. There were no interactions or pharmacokinetic profile changes when daridorexant 50 mg was taken with Famotidine, Citalopram, or Rosuvastatin.[25] Contrarily, the simultaneous administration of ethanol and Daridorexant reduced psychomotor function and lengthened the tmax.[26]

Pharmacodynamics

The orexin receptors OX1R and OX2R are bound by and antagonistic to daridorexant (Ki = 0.47 and 0.93nm, respectively).[27] Daridorexant enhanced total sleep duration as stated by patients and sleep initiation and maintenance during clinical trial phases. Furthermore, diminished was patients’ perception of daytime fatigue.[28] Daridorexant (Quviviq™) was created particularly to act on orexin receptors OX1 and OX2, antagonizing their effects and inducing sleep.[13] The sleep-wake cycle is governed by intricate interactions between sleep-promoting systems and hormones, such as inhibitory GABA activity, and wake-promoting systems, such as orexin, acetylcholine, and monoaminergic systems.[29] There are two known orexin types (OXA and OXB) that bind to orexin Type 1 and 2 receptors (OX1R and OX2R), which are G-protein coupled receptors. OXA primarily binds to OX1R, whereas OX2R has a dual affinity for OXA and OXB.[19] Daridorexant prevents the wake-promoting neuropeptide OXA and OXB from binding to OX1R and OX2R, hence inhibiting the wake urge.[30] Daridorexant preferentially targets orexin neurons and inhibits downstream neuronal pathways that promote wakefulness; however, it does not affect neuronal pathways that induce adverse effects found with positive allosteric GABA-A receptor modulators.[32] According to a recent study, daridorexant crosses the blood-brain barrier and functions by competitively binding to the active sites of human OX1 and OX2 receptors, with Kî values of 0.52 nm at OX1R and 0.78 nm at OX2R, without affecting any GABA receptors or brain regions with abuse potential.[19] Although daridorexant was present in plasma at awakening, it did not have any sleep-related or cognitive effects (impairment in memory or attention), as is the case with benzodiazepines like diazepam and eszopiclone. However, daridorexant has been shown to help induce and promote sleep throughout 8 h, with the greatest advantages being seen when orexin neuronal activity is at its highest level.[19] According to the IDSIQ, it has recently been found to enhance daytime performance.[34] Receptor Orexin, often referred to as hypocretin, is a neuropeptide that stimulates wakefulness and is produced by a small number of neurons in the lateral hypothalamus. By stimulating orexin neurons, which are most active while you are awake and least active when you are asleep, orexin preserves awareness.[35] The histaminergic neurons in the tuberomammillary nucleus (TMN), the noradrenergic neurons in the locus coeruleus, the serotonergic neurons in the dorsal raphe, the dopaminergic neurons in the ventral tegmental area, and the cholinergic neurotransmitters in the basal forebrain, pedunculopontine, and alter odor are among the wake-promoting neurons to which orexin neurons project.[31]

OREXIN RECEPTORS

Daridorexant specifically targets orexin neurons and inhibits downstream neuronal pathways that promote wakefulness; however, it does not affect neuronal pathways that induce adverse effects that are frequent in positive allosteric GABA-A receptor modulators.[19] Orexin binds to the G-protein coupled receptors orexin-1 receptor (OX1R) and orexin-2 receptor (OX2R), also known as Hypocretin receptor Types 1 and 2 (HCRT1 and HCRT2) (seven-transmembrane domain). Orexin A binds to both OX1R and OX2R, whereas orexin B binds primarily to OX2R. Orexin receptors have been identified to raise calcium levels and activate protein kinase C, both of which are essential adenyl cyclase regulators. In numerous in vitro investigations, OX1R demonstrated an affinity for coupling to Gi and Gs family proteins.[36] Gs activation occurred at greater orexin concentrations, and Gi signaling pathways were 100-fold.
more potently activated. The activities of OX1R and OX2R are heavily reliant on calcium influx caused by GQ subtype activation. In the context of arrestin-mediated pathways, the possibility of biased signaling is being investigated.

Sleep-related disorders
Because orexins have been identified to enhance arousal by modulating sleep alertness pathways, orexin antagonists are being investigated as a possible alternative due to their favorable adverse effect profile.[37] Single orexin receptor antagonists (SORAs) and dual orexin receptor antagonists are used as a treatment for insomnia (DORAs). For their possible role in narcolepsy, orexin agonists are now being researched. Following extensive research, it was shown that DORAs block OX1R and OX2R, promoting non-rapid eye movement (NREM) and rapid eye movement (REM) sleep, lengthening REM sleep, and reducing the delay until REM sleep DORAs are especially beneficial in insomnia associated with comorbidities such as schizophrenia and Parkinson’s disease.[38]

Mood disorders
Because orexinergic neurons participate in conditioned fear, they may be examined as a potential target for anxiety disorders. Orexin levels were shown to be elevated in cases of anxiety, and activation of orexin was connected with panic states in mouse models. Seltorexant, Almorexant, and Filorexant are several of the compounds examined in mouse research for serious depression with sleeplessness.[39]

Neurodegenerative disorders
Many degenerative illnesses, including Alzheimer’s disease, multiple sclerosis, Parkinson’s disease, and amyotrophic lateral sclerosis, have been researched for the function of a receptor for orexin. Among them, the involvement of the Orexinergic system in Alzheimer’s disease is being extensively researched.[40]

DRUGS IN THE OREXINERGIC SYSTEM

Agonists
TAK-925 is a recently studied agonist that mimicked the action of the peptide. TAK-925 activated OX2R on multiple nuclei in an electrophysiological investigation.[27] Agonists have been extensively researched for their function in narcolepsy, cataplexy, and hypophagia.[41]

Antagonists
Single opposing orexin receptors
During orexin production, neurons are activated the day and silent during the night. Orexin A levels in various species’ cerebral fluid change according to circadian cycles, peaking during active waking periods.[42]

OX1R
SB-334867 was the first SORA created to treat insomnia, although it was unable to enhance sleep characteristics such as sleep latency and time spent in the sleep state. One issue with OX1R antagonism was non-selective binding to other receptors such as adenosine and serotonin. There have been very few trials employing these medicines, and their usefulness when attempting to treat obesity, addiction, panic disorder, and anxiety, and epilepsy are being investigated.[38]

OX2R
OX2R is expressed in nuclei involved in arousal, such as the paraventricular nucleus and TMN. Inhibiting these nuclei will enhance sleep induction and can therefore investigate as a target in insomnia. EMPA has the lowest propensity to induce sleep among OX2R antagonists. When compared to DORA, the sleep-promoting OX2R antagonist effects are less potent but more selective.[22]

Dual orexin receptor antagonists
Although the therapeutic significance of the various sleep phases has not been conclusively shown, an increase in both NREM and REM sleep is likely desired to maintain the ratio in physiological proportions. Furthermore, the orexin system engages several brain regions, targeting wake-promoting areas that express either both receptors or only one subtype.[43] The major indication is to enhance sleep latency and maintenance of sleep in people along with primary insomnia due to a unique method of action. Narcolepsy, impaired daytime wakefulness, complicated sleep habits, hepatic/renal impairment, respiratory depression, and suicidal thoughts are all potential contraindications and side effects of DORA. It should be taken with caution when combined with CYP3A4 inhibitors.[19, 22]

Antagonists of dual orexin receptors:
3. Filorexant: Preclinical
4. Almorexant: Discontinued
5. MK-6096: Phase II
6. Daridorexant: Phase III
7. Seltorexant: Phase III.

PHARMACOLOGY AND NON-PHARMACOLOGY TREATMENT

Pharmacological treatment of insomnia
Insomnia medications target the gamma-aminobutyric acid Type-A (GABA-A), serotonin, histamine, or melatonin receptors. Positive allosteric z-drugs (zopiclone,
Daridorexant is therefore equally effective in inhibiting OX1R and OX2R. In a panel screen of more than 130 central and peripheral pharmacological targets other than orexin receptors, including GABA receptors and other brain targets linked with addiction risk, daridorexant showed no meaningful *in vitro* activity.[40] Two Phases 3 clinical investigations of the new DORA daridorexant (ACT-541468) for insomnia were completed in 2020. This chemical was found as part of a comprehensive drug discovery effort focusing on opposing orexin receptors[40]. A biosimilar is a biological medicine that has equivalent quality, safety, and effectiveness to an already approved biotechnology-applied product, in conformity with non-clinical findings and its adequate pharmacokinetic profile.[47] According to clinical studies, the drug daridorexant helps patients with insomnia sleep better and has no negative effects the next morning.[48]

Non-pharmacological treatment of insomnia

The objective of treating insomnia is to enhance sleep quality and quantity, in addition to daytime functioning, while avoiding negative occurrences and lingering consequences the next morning. In patients with chronic medical diseases and concomitant mental problems, including mood, anxiety, drug use, and stress- and trauma-related disorders, the prevalence of insomnia is significantly greater. The American Academy of Sleep Medicine (AASM) recommends Cognitive-Behavioral Therapy for Insomnia (CBT-I) as the best suitable evidence-based therapy for people with insomnia.[34,49,50] CBT-I consists of sleep hygiene education, cognitive therapy, relaxation methods, environmental stimuli control, and sleep restriction application. However, despite adhering to the elements of CBT-I, a lot of people with primary insomnia experience continuing sleep disturbance, and other patients are simply unable to practice the tenets of CBT-I consistently enough to achieve clinically noticeable effects, requiring adjunctive pharmacological interventions.[31,32]

CONCLUSION

The current pharmaceutical solutions for chronic insomnia therapy do not satisfy the demands of all individuals. Daridorexant, a DORA, was found as a result of an intensive drug discovery effort targeted at enhancing a sleep-promoting agent’s effectiveness and pharmacokinetic profile. Chronic sleeplessness is more common in women and the elderly. Treatment should be adjusted to the patient’s specific needs, and individuals may need to alter drugs to discover the one that best relieves their complaints. At present, the orexin receptor role is recognized to the point of drug development, with further targets being explored primarily in highly specific illness conditions such as insomnia and addiction. Chronic insomnia is quite common, affecting around 30% of the general population. Insomnia reduces cognitive and physical functioning and is linked to a variety of poor daily functions in emotional, social, and physical domains. Older age, female gender, and concomitant medical and mental problems are all risk factors for an increased prevalence of chronic insomnia. Accurate neurobehavioral and neurobiological knowledge is required for effective pharmaceutical and behavioral therapies to treat insomnia. At present, four types of drugs are approved: DORAs, BZRAs, histamine receptor antagonists, and melatonin receptor agonists. Daridorexant is a DORA that was recently licensed by the US FDA for the treatment of insomnia in adults.

REFERENCES

11. Markham A. Correction to daridorexant: First approval. Drugs 2022;82:841.