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REVIEW ARTICLE

Daridorexant: A drug to treat insomnia

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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, Oxinergic 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 CBTI-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

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daridorexant (Quviviq™), an orally given dual orexin Type 1 and Type 2 (OX1 and OX2) receptor antagonist (DORA), for the treatment of insomnia. OX1 and OX2 are G protein-coupled receptors found throughout the brain. The hypothalamic endogenous ligands orexin A and orexin B (also known as hypocretin-1 and -2) enhance alertness through interactions with OX1 and OX2.[5,10] In the United States, the suggested dosage of daridorexant is 25–50 mg once each night, taken within 30 min of going to bed, with at least 7 h left until anticipated wakeup.[11] The prevalence of insomnia symptoms rises with age, reaching up to 50% in persons over the age of 65.[12] Daridorexant is a novel powerful, selective DORA that has been licensed to treat insomnia in individuals over the age of 18.[13] The daridorexant Phase III testing program in adult patients (aged 18 years) with insomnia disorder included two 12-week studies, one of which assessed both authorized doses of daridorexant, 50 and 25 mg, in combination with placebo (ClinicalTrials.gov identifier NCT03545191), and the other analyzed lower doses of daridorexant (ClinicalTrials.gov identifier NCT03575104), as well as a 40-week long-term extension study Daridorexant 50 mg and 25 mg enhanced sleep start, sleep maintenance, and the patient's subjective estimate of sleep amount in 12-week research (Trial 1), and at the highest dose of 50 mg also enhanced many aspects of daily performance (sleepiness, mood, and alert/cognition).[14] Daridorexant inhibits the binding of orexin, which are wake-promoting neuropeptides and natural ligands to these receptors, on orexin receptors OX1R and OX2R. Daridorexant lowers hyperactive wakefulness; in clinical studies, daridorexant enhanced sleep and daytime performance in insomnia patients.[15]

Drug profile

Actelion Pharmaceuticals Ltd., developed Daridorexant. Actelion split off its drug research activities and early-stage clinical development assets into a newly formed Swiss biopharmaceutical business, Idorsia Pharmaceuticals Ltd., in connection with the acquisition of Actelion by Johnson and Johnson in June 2017.[7] Daridorexant was approved for the first time in the United States on January 7, 2022, for the treatment of adult patients with insomnia characterized by troubles with sleep onset and/or sleep maintenance.[11] Daridorexant was chosen from a pool of medication candidates because it had an 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. The medicine is U.S. government approval and has gotten a favorable opinion from the European Union's Committee for Medicinal Products for Human Use, with regulatory evaluation in Switzerland and Canada continuing.[15] Daridorexant (ACT-541468) is a DORA that has had multiple Phases I and II studies published as well as Phase III trials completed, in which daridorexant was well tolerated with good effects on sleep metrics and no next-morning residual effects.[16]

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.[17] 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] 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).[19]

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.[20]

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.[21] 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.[22] 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

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 (t12) 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]

MECHANISM OF ACTION OF DARIDOREXANT

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.[30] Daridorexant prevents the wake-promoting neuropeptide OXA and OXB from binding to OX1R and OX2R, hence inhibiting the wake urge.[31] 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 Kb values of 0.52 nm at OX1R and 0.78 nm at OX2R, without affecting any GABA receptors or brain regions with abuse potential.[33] 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.[15] 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 serotoninergic 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.[10] 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 (HCRTR1 and HCRTR2) (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:

1. Suvorexant: FDA-approved (2014)
2. Lemborexant: FDA-approved (2019)
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,

zolpidem, and zaleplon) GABA-A subunit alpha 1 receptor modulators, the most commonly used hypnotics, induce sleep by the inhibiting central nervous system (CNS) activity broadly.[44] 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.[45] 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[46]. 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 fingdings 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.[51,52]

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

1. Van Someren EJ. Brain mechanisms of insomnia: New perspectives on causes and consequences. Physiol Rev 2021;101:995-1046.
2. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. Vol. 21. United States: American Psychiatric Association; 2013. p. 591-643.
3. Guan NC, Abousheishaa AA. Commentary: Validation of the somatic symptom Disorder-B criteria scale for adults in South Korea. Alpha Psychiatry 2022;23:235-6.
4. Riemann D, Benz F, Dressle RJ, Espie CA, Johann AF, Blanken TF, *et al*. Insomnia disorder: State of the science and challenges for the future. J Sleep Res 2022;31:e13604.
5. Herring WJ, Roth T, Krystal AD, Michelson D. Orexin receptor antagonists for the treatment of insomnia and potential treatment of other neuropsychiatric indications. J Sleep Res 2019;28:e12782.
6. Huang W, Li Z, Wu S, Hong J, Wen G. Small-world network of patients with primary insomnia: A resting-state functional magnetic resonance imaging study. Nan Fang Yi Ke Da Xue Xue Bao 2021;41:424-9.
7. Harvey AG, Tang NK. (Mis) perception of sleep in insomnia: A puzzle and a resolution. Psychol Bull 2012;138:77-101.
8. Wilson SJ, Nutt D, Alford C, Argyropoulos S, Baldwin DS, Bateson A, *et al*. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias, and circadian rhythm disorders. J Psychopharmacol 2010;24:1577-601.
9. Sateia MJ, Buysse DJ, Krystal AD, Neubauer DN, Heald JL. Clinical practice guideline for the pharmacologic treatment of chronic insomnia in adults: An American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med 2017;13:307-49.
10. Scammell TE, Winrow CJ. Orexin receptors: Pharmacology and therapeutic opportunities. Annu Rev Pharmacol Toxicol 2011;51:243-66.
11. Markham A. Correction to daridorexant: First approval. Drugs 2022;82:841.
12. Ortega G. Iconicity and sign lexical acquisition: A review. Front Psychol 2017;8:1280.

13. Markham A. Daridorexant: First approval. Drugs 2022;82:601-7.
14. Mignot E, Mayleben D, Fietze I, Leger D, Zammit G, Bassetti CL, *et al*. Safety and efficacy of daridorexant in patients with insomnia disorder: Results from two multicentre, randomized, double-blind, placebo-controlled, phase 3 trials. Lancet Neurol 2022;21:125-39.
15. Roch C, Bergamini G, Steiner MA, Clozel M. Nonclinical pharmacology of daridorexant: A new dual orexin receptor antagonist for the treatment of insomnia. Psychopharmacology (Berl) 2021;238:2693-708.
16. Muehlan C, Boehler M, Brooks S, Zuiker R, van Gerven J, Dingemanse J. Clinical pharmacology of the dual orexin receptor antagonist ACT-541468 in elderly subjects: An exploration of pharmacokinetics, pharmacodynamics, and tolerability following single-dose morning and repeated-dose evening administration. J Psychopharmacol 2020;34:326-35.
17. Ersoy A, Waller M. Drilling detritus and the operating parameters of thermally stable PDC core bits. Int J Rock Mech Min Sci 1997;34:1109-23.
18. Zammit G, Dauvilliers Y, Pain S, Kinter DS, Mansour Y, Kunz D. Daridorexant, a new dual orexin receptor antagonist, in elderly subjects with insomnia disorder. Neurology 2020;94:e2222-32.
19. Dauvilliers Y, Zammit G, Fietze I, Mayleben D, Kinter DS, Pain S, *et al*. Daridorexant, a new dual orexin receptor antagonist to treat insomnia disorder. Ann Neurol 2020;87:347-56.
20. Carney CE, Edinger JD, Kuchibhatla M, Lachowski AM, Bogouslavsky O, Krystal AD, *et al*. Cognitive behavioral insomnia therapy for those with insomnia and depression: A randomized controlled clinical trial. Sleep 2017;40:zsx019.
21. Kukkonen JP, Leonard C. Orexin/hypocretin receptor signaling cascades. Br J Pharmacol 2014;171:314-31.
22. Janto K, Prichard JR, Pusalavidyasagar S. An update on dual orexin receptor antagonists and their potential role in insomnia therapeutics. J Clin Sleep Med 2018;14:1399-408.
23. Hudgens S, Phillips-Beyer A, Newton L, Kinter DS, Benes H. Development and validation of the insomnia daytime symptoms and impacts questionnaire (IDSIQ). Patient 2021;14:249-68.
24. Muehlan C, Brooks S, Zuiker R, van Gerven J, Dingemanse J. Multiple-dose clinical pharmacology of ACT-541468, a novel dual orexin receptor antagonist, following repeated-dose morning and evening administration. Eur Neuropsychopharmacol 2019;29:847-57.
25. Gehin M, Wierdak J, Sabattini G, Sidharta PN, Dingemanse J. Effect of gastric pH and a moderate CYP3A4 inducer on the pharmacokinetics of daridorexant, a dual orexin receptor antagonist. Br J Clin Pharmacol 2022;88:810-9.
26. Berger B, Brooks S, Zuiker R, Richard M, Muehlan C, Dingemanse J. Pharmacological interactions between the dual orexin receptor antagonist daridorexant and ethanol in a double-blind, randomized, placebo-controlled, double-dummy, four-way crossover phase I study in healthy subjects. CNS Drugs 2020;34:1253-66.
27. Bovin MJ, Marx BP, Weathers FW, Gallagher MW, Rodriguez P, Schnurr PP, *et al*. Psychometric properties of the PTSD checklist for diagnostic and statistical manual of mental disorders-fifth edition (PCL-5) in veterans. Psychol Assess 2016;28:1379-91.
28. Benca RM, Cirelli C, Rattenborg NC, Tononi G. Basic Science of Sleep. In: Comprehensive Textbook of Psychiatry. Philadelphia, PA: Lippincott, Williams, and Williams; 2004, p. 280-94.
29. Boutrel B, Koob GF. What keeps us awake: The neuropharmacology of stimulants and wakefulness-promoting medications. Sleep 2004;27:1181-94.
30. Xu TR, Yang Y, Ward R, Gao L, Liu Y. Orexin receptors: Multi-functional therapeutic targets for sleeping disorders, eating disorders, drug addiction, cancers, and other physiological disorders. Cell Signal 2013;25:2413-23.
31. Baumann CR, Bassetti CL. Hypocretins (orexins) and sleep-wake disorders. Lancet Neurol 2005;4:673-82.
32. Hahn B, Robinson B, Geng J, Bansal S, Luck S, Gold J. ACNP 60th Annual Meeting: Poster Abstracts P551–P830. Biochem Biophys Res Commun 2018;503:1973-9.
33. Treiber A, de Kanter R, Roch C, Gatfield J, Boss C, von Raumer M, *et al*. The use of physiology-based pharmacokinetic and pharmacodynamic modeling in the discovery of the dual orexin receptor antagonist ACT-541468. J Pharmacol Exp Ther 2017;362:489-503.
34. Kunz D, Dauvilliers Y, Benes H, García-Borreguero D, Plazzi G, Kinter DS, *et al*. Long-term safety and tolerability of daridorexant in patients with insomnia disorder. CNS Drugs 2023;37:93-106.
35. Ohno K, Sakurai T. Orexin neuronal circuitry: Role in the regulation of sleep and wakefulness. Front Neuroendocrinol 2008;29:70-87.
36. Sun Y, Tisdale RK, Kilduff TS. Hypocretin/orexin receptor pharmacology and sleep phases. Front Neurol Neurosci 2021;45:22-37.
37. Kumar A, Chanana P, Choudhary S. Emerging role of orexin antagonists in insomnia therapeutics: An update on SORAs and DORAs. Pharmacol Rep 2016;68:231-42.
38. Equihua AC, De La Herrán-Arita AK, Drucker-Colin R. Orexin receptor antagonists as therapeutic agents for insomnia. Front Pharmacol 2013;4:163.
39. Al-Kuraishy HM, Abdulhadi MH, Hussien NR, Al-Niemi MS, Rasheed HA, Al-Gareeb AI. Involvement of orexinergic system in psychiatric and neurodegenerative disorders: A scoping review. Brain Circ 2020;6:70-80.
40. Al-Kuraishy H, Abdulhadi M, Hussien N, Al-Niemi M, Rasheed H, Al-Gareeb A. Involvement of an orexinergic system in psychiatric and neurodegenerative disorders: A scoping review. Brain Circ 2020;6:70-80.
41. Kimura H, Ishikawa T. 0142 TAK-925, an orexin 2 receptor-selective agonist, enhanced cortical arousal in a narcolepsy mouse model different from effects of modafinil. Sleep 2020;43:A56.
42. Desarnaud F, Murillo-Rodriguez E, Lin L, Xu M, Gerashchenko D, Shiromani SN, *et al*. The diurnal rhythm of hypocretin in young and old F344 rats. Sleep 2004;27:851-6.

43. Tobaldini E, Nobili L, Strada S, Casali KR, Braghiroli A, Montano N. Heart rate variability in normal and pathological sleep. Front Physiol 2013;4:294.
44. Bruni O, Ferini-Strambi L, Giacomoni E, Pellegrino P. Herbal remedies and their possible effect on the GABAergic system and sleep. Nutrients 2021;13:530.
45. Glaum P, Simao MC, Vaidya C, Fitch G, Iulinao B. Big city Bombus: Using natural history and land-use history to find significant environmental drivers in bumble-bee declines in urban development. R Soc Open Sci 2017;4:170156.
46. Chai F, Johnson KS, Claustre H, Xing X, Wang Y, Boss E, *et al*. Monitoring ocean biogeochemistry with autonomous platforms. Nat Rev Earth Environ 2020;1:315-26.
47. Tomczyk S, Muehlan H, Freitag S, Stolzenburg S, Schomerus G, Schmidt S. Is knowledge "half the battle"? The role of depression literacy in help-seeking among a non-clinical sample of adults with currently untreated mental health problems. J Affect Disord 2018;238:289-96.
48. Ziemichód W, Grabowska K, Kurowska A, Biała G. A comprehensive review of daridorexant, a dual-orexin receptor antagonist as a new approach for the treatment of insomnia. Molecules 2022;27:6041.
49. Edinger JD, Means MK. Cognitive-behavioral therapy for primary insomnia. Clin Psychol Rev 2005;25:539-58.
50. Wilson S, Anderson K, Baldwin D, Dijk DJ, Espie A, Espie C, *et al*. British Association for Psychopharmacology consensus statement on evidence-based treatment of insomnia, parasomnias, and circadian rhythm disorders: An update. J Psychopharmacol 2019;33:923-47.
51. Zammit G, Erman M, Wang-Weigand S, Sainati S, Zhang J, Roth T. Evaluation of the efficacy and safety of ramelteon in subjects with chronic insomnia. J Clin Sleep Med 2007;3:495-504.
52. Rybarczyk B, Lund HG, Garroway AM, Mack L. Cognitive behavioral therapy for insomnia in older adults: background, evidence, and overview of the treatment protocol. Clin Gerontol 2013;36:70-93.