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REVIEW ARTICLE

A comprehensive review of Dual Orexin Receptor Antagonist (DORA), Daridorexant: Novel drug for sleep and related disorders

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ABSTRACT
Sleep disorders are increasing at an alarming rate with insomnia affecting nearly one third of the world population. The mechanisms of wakefulness and sleep are intricate. The main pathophysiology involves the interplay of inhibitory neurotransmitters especially GABA. Another neuroransmitter orexin which was earlier considered to be responsible for the satiety control was also found to be responsible for maintaining arousal. With the efforts of numerous researchers, two types of orexin receptors were discovered. This led to development of Dual Orexin Receptor Antagonist (DORA),Daridorexant which was recently approved by the FDA for sleep related disorders and to improve the overall sleep quality. This review elucidates the currently available information regarding Daridorexant.
Keywords: Daridorexant, Dual Orexin Receptor Antagonist, Sleep disorder, Insomnia

INTRODUCTION

Daridorexant, an oral Dual Orexin Receptor Antagonist(DORA), for OX1 and OX2 receptors to treat insomnia has been recently approved by US FDA. It has been shown to be effective in reducing the effects of insomnia, improving everyday performance, and improving overall sleep quality. It provides reliefto patients from their sleeplessness without the negative side effects or addiction issues associated with more traditional drugs like benzodiazepines and sedatives. Orexin-containing neurons in the lateral hypothalamus are largely responsible for producing a pair of neuropeptides known as hypocretins. The brain has a high level of expression for orexin receptors. They can be divided into two types: OX-1 and OX-2,. Both are G protein coupled receptors. The endogenous ligands orexin A and orexin B, also known as hypocretin-1 and -2, are produced by the hypothalamus, and they interact with OX-1 and OX-2 to induce wakefulness. [1,2]Originally ascribed as feeding regulators in the brain, orexins have been demonstrated to stimulate food intake on intra-cereberoventricular administration.[3] Besides the aforesaid role these peptides play a variety of other vital physiological functions including the control of the sleep-wake cycle, energy balance, neuroendocrine functions, glucose metabolism, stress-adaptive responses, reward-seeking, and drug addiction. [4] The understanding of orexin's role in the maintenance of alertness has made the orexin system a possible target for new drug development. [5] If the binding of orexin to either of the orexin receptors is a contributing factor to alertness, an exogenous medicine created to act as an agonist to the orexin receptors could promote wakefulness, which could be helpful in narcolepsy patients. An orexin receptor antagonist, on the other hand, would have the opposite effect, increasing sleep, which might be helpful for treating insomnia. The treatment with this drug is predicated on the notion that by permanently blocking the orexin receptor through antagonistic action, the orexin system's typical wake-promoting activities will be diminished, resulting in ensuing fatigue and longer

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sustained periods of sleep.[6] The pathological processes of neurological illnesses like narcolepsy, insomnia, depression, ischemic stroke, drug addiction, and Alzheimer's disease (AD) also involve orexin/receptor pathways.[7]The mechanism of action of DORAs is entirely different from conventional sleep-inducing drug. When humans are awake, orexin neurons are most active, and when they are asleep, they are essentially silent. They are connected to a number of wake-promoting neuronal populations, including the histaminergic neurons of the tuberomammillary nucleus, which primarily express OX-2, the noradrenergic neurons of the locus coeruleus, which primarily express OX-1, the serotoninergic neurons of the dorsal raphe, which primarily express OX-1 and OX-2, the dopaminergic neurons of the ventraltegmetal (expressing both OX-1 and OX-2).Orexins control wakefulness by activating these wake-promoting areas. By inhibiting OX-1 and OX-2, DORAs helps in falling asleep. Positive GABA-A receptor modulators on the other hand have the ability to prevent the more ubiquitous neural pathway inhibition and associated negative consequencesbyselectively targeting and inhibiting the activity of wake-promoting neurons.[7]

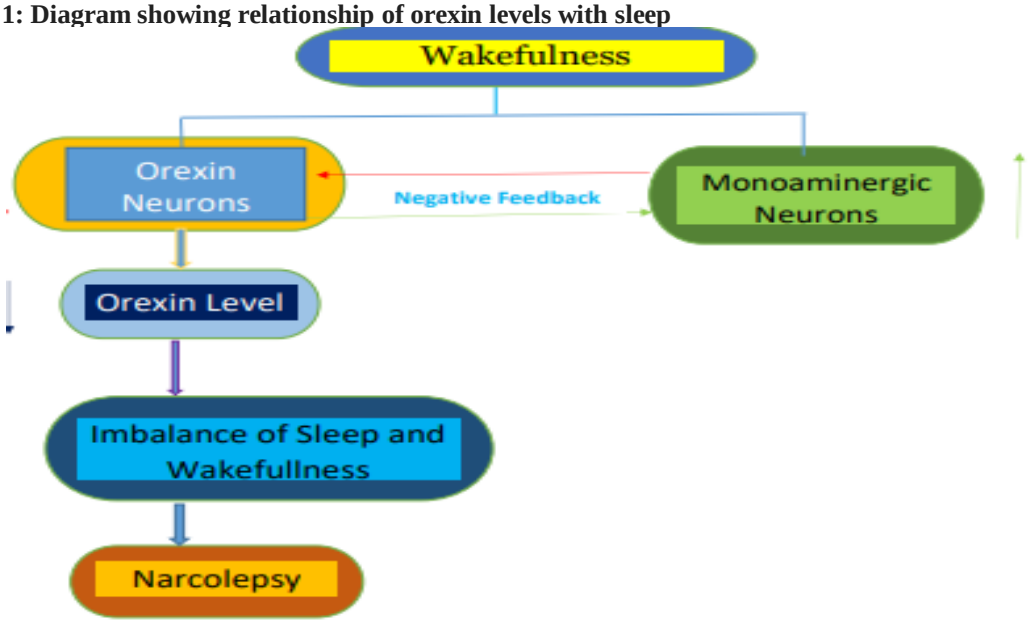
INSOMNIA

Insomnia is a very common disorder that negatively affects quality of life. Patients frequently struggle to get asleep, stay asleep, or fall back asleep after waking up early in the morning. Weariness, hypersomnolence, mood swings, memory loss, and in-attentiveness are just a few of the problems that may have a significant impact on everyday activities and performance. The International Classification of Sleep Disorders (ICSD) reclassified the categories of insomnia as short-term, chronic, and other in order to facilitate diagnosis. According to the ICSD-3 and Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth Edition, patients must have symptoms like recurrent poor sleep quality or quantity that causes distress or impairment in important areas of functioning to be diagnosed as insomnia. Other symptoms are lying awake for long periods of time, waking several times during the night, waking up early unable to get back to sleep, not feeling refreshed after sleeping or feeling fatigued or sleepy during the day and difficultly focusing on a task. As a complex issue that commonly co-occurs with other illnesses, insomnia calls for a multimodal approach to therapy.[1,8]

EPIDEMIOLOGY

Insomnia is considered to afflict 30–35% population worldwide, with a 5% annual incidence. [9-14] Insomnia is more common in older individuals, women, people with impairments, and those whose jobs require irregular shifts. [9] The number of individuals with age 65 years or more in the world has already surpassed 700 million, and by 2050, that figure is anticipated to triple to 1.5 billion. The likelihood of experiencing insomnia symptoms increases with age and can approach 50% in people over 65yrs.[15] The treatment options are restricted in the aged population. [8] Some other factors that causesleep related disorders are unemployment, marital status (such as widowed, divorced, or separated), and poor socioeconomic status.[16] Nearly half of all the cases of insomnia are associated with a comorbid psychiatric issue. Majority of insomnia sufferers also have a coexisting physical illness. [10-19] Over 80% of people with major depressive disorder also had sleeplessness, and nearly half of all cases of insomnia preceded a mood disorder.[20] Diabetes, depression, and hypertension are long-term sequalae of insomnia.[7]

Figure 1: Diagram showing relationship of orexin levels with sleep



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PATHOPHYSIOLOGY OF INSOMNIA

The pathophysiology of insomnia is intricate to describe.[21] This can be partially explained by the heterogenic nature of insomnia and its incidence in coexisting diseases. [21,22] The symptoms of insomnia are described in the present literature using a variety of approaches, including the neurobiological, cognitive, behavioural, and emotional models. [23-26] Regardless of the hypothesis, there is universal agreement that insomnia results from a disruption of brain areas that regulate the circadian rhythm and homeostatic systems that control sleep and wakefulness. The ascending reticular activation system (ARAS) promotes alertness whereas the ventrolateral preoptic region (VLPR) promotes sleep. The orexin system (hypocretin/orexin-containing neurons), which suppresses the VLPR to maintain awake, is one of the brain regions that is triggered by ARAS. The flip-flop switch is produced when the VLPR suppresses the ARAS through two neurotransmitters, Gamma-aminobutyric acid (GABA) and galanin, to show how sleep and awake are mutually incompatible events. [21,25,26] Sleeplessness is currently thought to be a hyperarousal illness with cognitive, emotional, and somatic symptoms. High-frequency electroencephalographic activity when sleeping, racing thoughts, elevated cortisol levels, rising blood pressure, and increased concern are all symptoms of this condition. [27,28]

CURRENT TREATMENT

Due to the complex aetiology of insomnia and the numerous causative factors, a variety of treatment approaches are required for patients to obtain a higher quality of life and improved daytime alertness and performance. Treatments are based on the underlying cause, which depends upon patients and the healthcare provider. [1] Due to its lack of pharmacological involvement and negligible side effects, cognitive behavioural therapy (CBT) is currently advised as the first-line therapy for insomnia as opposed to other forms of treatment. For most cases of insomnia, even those that are refractory to medicine, CBT should be considered a low-risk and effective therapy option. [29] The goal of CBT, a structured treatment offered by behavioural sleep specialists, is to reconstruct the patient's harmful patterns and attitudes about sleep. It eliminates arousal triggers that hinder sleep, employ relaxation techniques, and more. It also aims to educate the patient about circadian cycles. Pharmacological treatments for insomnia include benzodiazepines receptors agonist (BZRA), histamine receptor antagonists, melatonin receptor agonists, and DORA. Although the short-term efficacy of these drugsare well demonstrated, but once a drug is withdrawn, the efficacy diminishes rapidly.[30,31] Long term pharmacological therapies for insomnia, are now being discouraged due to the likelihood of abuse and a variety of other side effects.[32,33]Benzodiazepines and other hypnotics are known to develop physical dependence in patients receiving long-term care, and ceasing medication can result in withdrawal symptoms that last for months. [34] New treatment alternatives like DORAs can be used for insomnia without the negative side effects and drug dependence that were the main issues with traditional drugs like benzodiazepines and other sedatives.[1,35]As a result of the discoveries that led to the conclusion that day time sleepiness is linked to the loss of orexin-producing neurons and that blocking both OX1 and OX2 improves sleep parameters, orexin antagonists have been targeted upon as a newer treatment option for the sleep related disorders.[36]

MECHANISM OF ACTION

DORAs inhibit both OX1R and OX2R and allow sleep to occur. It is possible to prevent the more pervasive neural pathway inhibition and related adverse effects that are inherent to positive GABA-A receptor modulators by selectively concentrating on and suppressing the activity of wake-promoting neurons.[7].Determined in intracellular Ca2+ release assays, daridorexant functions as a competitive, orthosteric antagonist with apparent partition coefficient (K_b) as mentioned in Table -1

Table 1 –Values of apparent partition coefficient (K_b) in different species at OX1R and OX2R receptors

Receptor	Species		
Apparent partition coefficient (K_b)	Rat	Dog	Human
OX1R (nM)	1.1	0.3	0.5
OX2R(nM)	1.7	0.7	0.8

Daridorexant is thus equipotent in antagonizing both OX1R and OX2R.[40] A study conducted on rats and Beagle dogs found that daridorexant reduces wakefulness while lengthening non-REM and REM periods. However, it had no impact on the overall length of time spent in these cycles, showing that normal sleep architecture (i.e., the ratio of REM to non-REM sleep and vice versa) was maintained. [38,39]It has been demonstrated to induce and promote sleep over a period of 8 hrs, with the greatest benefits occurring when orexin neuronal activity is at its highest. Although daridorexant was found in plasma upon awakening, it had no effect on sleep or cognition (impairment in memory or attention), as is the case with benzodiazepines like diazepam and eszopiclone.[7,40-43] It has also been shown that it preserves muscle strength and coordination as well as the natural ability to wake up and respond to auditory, unpleasant, visual, and threat signals, in contrast to GABA-A receptor modulators that diminish

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psychomotor responses. [7,39,44-47]Unlike benzodiazepines or other sleep-inducing drugs, has no effect on cognition, learning, attention, memory, or any of these functions.[48-51] The Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ)and the Insomnia Daytime Performance test both indicate that daridorexant improves daytime performance.[52] Most importantly, DORAs have not been shown to have any abuse/additive potentials or withdrawal symptoms, in contrast to benzodiazepines or other sleep-inducing drugs like zolpidem, which works via GABA-A or GABA-B. [7, 38,57-59]Treiber et al. determined daridorexant brain penetration in rats, 3 hours after oral administration of daridorexant at doses of 30 and 100 mg/kg. Daridorexant concentration increased to 665 nMafter the 30 mg/kg dose administration,whereas total brain concentration increased to 2247–12,000 nMafter 100 mg/kgof dose administered. [40]

PHARMACOKINETICS

At doses of 25–50 mg, daridorexant exhibits dose-dependent plasma concentration. Peak plasma concentrations are achieved within 1-2 hour and both single dose and several doses of the drugs have identical pharmacokinetic profiles. There is no sign of accumulation (tmax). A high-fat/high-calorie lunch had no impact on the overall exposure, but it delayed the tmax of daridorexant in volunteers by 1.3 hours and decreased Cmax by 16%. The drug has a 31 L volume of distribution and is 99.7% bound to plasma proteins.[56] In all studies [57, 58], daridorexant's terminal half-life ($t_{1/2}$) was less than 8 hours. It is metabolised by CYP3A4 (89%) and is primarily eliminated in the urine (57%) and faeces (28%) respectively. Age, sex, race, body size, and mild to severe renal impairment (Cockcroft-Gault 30 ml/min, not on dialysis) have no clinically significant effects on drug's pharmacokinetic properties. [59] Moderate (Child-Pugh B) but not mild (Child-Pugh A) hepatic impairment has been shown to increase the half-life of daridorexant. [57, 60] Due to the paucity of studies on the effects of severe hepatic impairment (Child-Pugh C) on the pharmacokinetics of the drug, daridorexant use is not advised in this patient population. [57] Without modifying the dosage, 50 mg of famotidine, the histamine 2 receptor inhibitor and daridorexant can be administered concurrently. [61]Coadministration of the SSRI citalopramand daridorexant 50 mg did not result in any clinically relevant changes in pharmacokinetic parameters. [62] According to physiologically based pharmacokinetic modelling, daridorexant AUC rose by 240% when administered with the moderate CYP3A4 inhibitor diltiazem and is expected to increase by > 400% when provided with the strong CYP3A4 inhibitor itraconazole. [22]On the other hand, coadministration of daridorexant with the moderate CYP3A4 inducer efavirenz decreased daridorexant AUC by 35% [20] while coadministration of daridorexant with the weak CYP3A4 inducer rifampin is projected to reduce daridorexant AUC by more than 50% [63]. So daridorexant should not be taken concurrently with a CYP3A4 inhibitor and strong CYP3A4 inducer. [57] The maximum dosage of daridorexant that is advised is 25 mg when used along with a moderate CYP3A4 inhibitor. The drugtmax was raised when alcohol was also administered, and this had cumulative effects on psychomotor performance. Due to this, patients are advised not to consume alcohol while using daridorexant [57, 64]. With other CNS depressants, daridorexantshould be used with caution and with dose adjustments. [57]

PRECLINICAL STUDIES

Maehara S et al. conducted a study to describe the pharmacological effects of daridorexant/SDM-878 both in vitro and in vivo condition. The in vitro potency and selectivity of drug were examined in Chinese hamster ovary (CHO) cells that exhibit stable expression of human orexin 1 (OX-1), human orexin 2 (OX-2), rat OX-1, and rat OX-2receptors. With IC_{50} values of 10.6 and 8.8 nmol/L for the human and rat OX2 receptors, respectively,drug demonstrated strong inhibitory effects. Neither the OX-1 receptor nor any other pharmacological targets, such as neurotransmitter receptors, ion channels, or transporters, were significantly affected by drug's off-target effects. Additionally, it showed positive pharmacokinetic characteristics, including a short plasma half-life, high oral bioavailability, and effective brain penetration in rats. These findings suggest that drug is a potent pharmaceutical tool for studying the function of the OX2 receptor both in vitro and in vivo.[65]

Smith et al. in their study investigated the role of orexin receptor in orexin-A-induced paradoxical sleep (PS) alteration using the OX-1 antagonist SB-334867-A. Orexin-A, a neuropeptide, alters the sleep-wake cycle in rats by increasing alertness, decreasing slow-wave sleep (SWS), paradoxical sleep (PS), and delaying the onset of PS. During the first hour following theintracerebroventricular (ICV) injection of SB-334867-A, orexin antagonist, the level of arousal, SWS-1 and 2 and PS were measured, together with the latency to initiation of the first 10-second PS epoch. By administering orexin-A, PS was less prevalent and appeared later. The drug, SB-334867-A counteracted orexin-action in this way. So this study showed that the OX1 is involved in modulating orexinergic sleep as well.[66]

CLINICAL STUDIES

A single oral dose of 5-200 mg of a 14 C-labeledmicrotracer was provided to healthy male individuals in one of the first studies conducted on humans to evaluate safety, tolerability, pharmacokinetics (PK), pharmacodynamics (PD), mass balance, metabolism, and absolute bioavailability. The drug was well tolerated and safe.

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Its pharmacokinetics profile showed rapid absorption and elimination, with geometric mean terminal half-life (t1/2) of 5.9–8.8 hrs and median time to reach maximum concentration (tmax) of 0.8–2.8 h. A acceptable PK-PD profile for a medication that promotes sleep was evident at doses of less than 25 mg, allowing for rapid start and a duration of action that was strictly confined to the intended usage. These effects on the central nervous system were clearly dose-related.[40]

Muehlan C et al. conducted a double-blind, placebo-controlled, randomized study to assess the tolerability, safety, pharmacokinetics and pharmacodynamics of daridorexant/ACT-541468. The drug was administered to 31 healthy male and female individuals in three dose groups (10, 25, and 75 mg) in the morning for five days, and 20 healthy subjects were given 25 mg in the evening for seven days (evening part). While the PD parameters were clearly affected by the administration of 25 and 75 mg during the day, there were no effects the following day after the administration of 25 mg in the evening. The medication was well-tolerated and safe. They concluded that multiple-dose of drug were compatible with a drug designated to treat insomnia.[57]

To assess the effectiveness and safety of daridorexant on objective and subjective sleep parameters in participants with insomnia condition, Dauvilliers Y et al. conducted a phase 2 trial at 38 locations in 6 countries at hospitals and sleep centres in Germany, Hungary, Israel, Spain, Sweden, and the USA. The six treatment arms—placebo (0 mg), 5, 10, 25, or 50 mg of daridorexant, or 10 mg of zolpidem—were randomly assigned to the eligible individuals in a ratio of 1:1:1:1:1:1.. Compared to placebo and 10mg zolpidem, the incidence of treatment-emergent adverse events was 35%, 38%, 38%, and 34%, respectively, in patients treated with 5, 10, 25, and 50mg of daridorexant. There were no clinically significant adverse events . [35]In another clinical study conducted by Zammit G, et al. to evaluate the dose-response of daridorexant, on Waking After Sleep Onset (WASO) and latency to persistent sleep (LPS) The drug was well toleratedin elderly patients with insomnia and, dose-dependent improvements in WASO and LPS were statistically significant (dose range: 10–50 mg). The drug and the placebo arm, both experienced treatment-emergent side events at similar rates; the most common were fatigue, nasopharyngitis, gait disruption, and headache (7% in each group). [43]

In a phase 3 randomised, multicenter, double-blind, placebo-controlled study, patients with insomnia disorder were enrolled to assess the effectiveness and safety of daridorexant. The patients were randomly assigned to receive either daridorexant 50 mg, 25 mg, or a placebo every evening for three months, or daridorexant 25 mg, 10 mg, or a placebo. Participants in the daridorexant 25 mg group saw a substantial improvement in their self-reported total sleep time at months one and three compared to the placebo group. It was found thatdaridorexant 25 mg and 50 mg improved sleep outcomes while daridorexant 50 mg also improved daytime functioning, in people with insomnia disorder. [67]

Another phase III study, conducted by Fietze I et al. to compare the safety and effectiveness of daridorexant in patients over 65 years of age with patients who are less than 65 years.Inboth age groups, daridorexant led to comparable decreases in WASO and LPS as well as comparable elevations in self-reported Total Sleep Time (sTST) compared to baseline. Improvements was more with daridorexant 50 mg than 25 mg. It was concluded that, 50 mg daridorexant works best for both daytime and nighttimes factors in older patients with insomnia.This dose is especially necessary for older people to enhance daytime functioning. Older patients are unlikely to experience negative side effects or lingering symptoms the following morning after taking 50 mg daridorexant at night.[9]

In a long-term safety study by Kunz et al, daridorexant (at 50 mg) showed the most pronounced improvements in sleep and daytime functioning. Daridorexant did not cause next-morning sleepiness, withdrawal-related symptoms, or rebound after discontinuation. The overall incidence of adverse events was similar across all groups (10 mg/25 mg/50 mg). Daridorexant 50 mg, when compared to placebo, resulted in increased self-reported total sleep time by a least-squares mean of 20.4 (95% confidence interval [CI] 4.2, 36.5), 15.8 (95% CI − 0.8, 32.5) and 17.8 (95% CI − 0.4, 35.9) minutes. Additionally, the drug improved Insomnia Daytime Symptoms and Impacts Questionnaire total scores by a least-squares mean of − 9.3 (95% CI − 15.1, − 3.6), − 9.5 (95% CI − 15.4, − 3.5) and − 9.1 (95% CI − 15.6, − 2.7), at weeks 12, 24 and 36 of the extension study, respectively. [68]

According to a systematic review and meta-analysis of randomized controlled trials conducted by Albadrani et al., the drug was found to be more effective than placebo in reducing wake time after sleep onset (MD = -13.26; 95% CI, -15.48 to -11.03; P < 0.00001). Daridorexant also reduced latency to persistent sleep (MD = -7.23; 95% CI, -9.60 to -4.85; P < 0.00001), increasing total sleep time (MD = 14.80; 95% CI, 11.18-18.42; P < 0.00001), and subjective total sleep time (MD = 14.80; 95% CI, 11.18-18.42; P < 0.00001). It was discovered that the doses of 25mg and 50mg were the most effective. However, treatment with daridorexant may result in a slightly higher incidence of adverse events, such as somnolence (RR = 1.19; 95% CI, 1.13-3.23; P = 0.005) and fatigue (RR = 2.01; 95% CI, 1.21-3.36; P = 0.007), with an overall increased risk ratio of 1.19 (95% CI, 1.05-1.35; P = 0.005).[69]

In another systematic review and meta-analysis of randomized controlled trials by Jiang et al. included 2271 patients from 4 clinical trials. The study concluded that 50 mg of daridorexant was more effective than placebo for 4 efficacy outcomes: wake

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time after sleep onset, latency to persistent sleep, subjective total sleep time, and Insomnia Daytime Symptoms and Impacts Questionnaire domain score ($P < 0.05$). The study also found no significant difference in adverse events between daridorexant and placebo ($P > 0.05$).[70] The important clinical trialsand metanalysis are summarised in Table 2.

Table 2: Summary of the important clinical trials

Sr. No	Author/year	Clinical trial Phase	Groups, Outcomes assessed	Key findings
1	Muehlan C et al./ 2018[40]	I	• Median time to reach maximum concentration (tmax) of 0.8-2.8 h Geometric mean terminal half-life ($t_{1/2}$) of 5.9-8.8 h. • If the PK-PD profile suitable	• PK-PD profile is favorable Rapid onset and duration of action; limited to the intended use.
2	Muehlan C et al./ 2019[57]	I	• 3 dose-groups (10, 25, and 75 mg) PK, PD, SPV, adaptive tracking, body sway, Bond and Lader VAS, KSS, VAS Bowdle for assessment of psychedelic effects, DSST, andSRTT tested. • Weather safe and tolerable	• Favorable safety and tolerability • Multiple-dose PK/PD of ACT-541468 were compatible to treat insomnia.
3	Dauvilliers Y et al. / 2020[35]	II	6 groups- oral placebo, daridorexant (5, 10, 25, or 50mg), or 10mg zolpidem change in wake time after sleep onset and change in latency to persistent sleep was assessed	• Drug induced a dose-dependent reduction in wake time after sleep onset in subjects with insomnia disorder
4	Zammit G et al. /2020[43]	II	5 treatment groups- (5, 10, 25, and 50 mg daridorexant and placebo) Change inWASO& LPSwere assessed	• The drug is well tolerated. Dose-dependent improvements in WASO and LPS were statistically significant (dose range 10-50 mg) in elderly population with insomnia
5	Mignot E et al. / 2022[67]	III	Three groups receive daridorexant 50 mg, 25 mg, or placebo (study 1) or daridorexant 25 mg, 10 mg, or placebo (study 2) every evening for 3 months • Change in WASO and LPS through polysomnography was assessed	Drug at a dose of 25 mg and 50 mg improved sleep outcomes, and daridorexant 50 mg also improved daytime functioning, in people with insomnia disorder, with a favourable safety profile
6	Fietze I et al. / 2022[09]	III	Three groups receiveddaridorexant 50 mg, 25 mg, or placebo Change in polysomnography-measured WASO and LPS, sTST, and daytime functioning assessed using the validated IDSIQ was assessed	• The efficacy of daridorexant is maximal at a dose of 50 mg on night-time and daytime variables Dose does not need to be decreased for older patients There is no increased risk of adverse events or residual effects the next morning after night-time administration
7	Kunz et al /2023 [68]	III	• To assess safety/tolerability • Four groups daridorexant (10 mg/25 mg/50 mg) and placebo	Sustained improvements in sleep and daytime functioning with daridorexant 50mg support its use for long-term treatment of insomnia disorder, without concerns of new safety signals.
8	Albadrani et al. /2023 [69]	systematic review and meta-analysis	• 07 randomized controlled trials were included with 2425 participants enrolled	Daridorexant treatment is associated with a slightly higher incidence of adverse events, including somnolence and fatigue. The risk ratio for daridorexant is 1.19 with a 95% CI of 1.05-1.35 and a P-value of 0.005.

				Somnolence has a risk ratio of 1.19 with a 95% CI of 1.13-3.23 and a P-value of 0.005, while fatigue has a risk ratio of 2.01 with a 95% CI of 1.21-3.36 and a P-value of 0.007.
9	Jiang et al/2023 [70]	systematic review and meta-analysis	• 04 randomized controlled trials were included with 2271 participants enrolled	• Daridorexant demonstrated better efficacy and safety in treating insomnia at 25 and 50 mg doses. Additionally, adverse events were not significantly different (P >0.05) between daridorexant and placebo.

CURRENT STATUS

On January 7, 2022, Daridorexant received its first approval by the US-FDA for the treatment of adult patients with insomnia who have trouble falling asleep or staying asleep. [71].Thus it is accepted that Daridorexant at 50 mg once a day preferably at bedtime for 3 months isequally safe and efficacious in the younger as well as the elderly adult population. It improves sleep onset, sleep maintenance, objective and subjective total sleep time, and daytime functioning in the domains of sleepiness, alert/cognition and mood.[9]

CONCLUSION

All patients' needs are not met by the pharmaceutical treatments available today for the treatment of chronic insomnia. A possible therapeutic option is to target the orexin system. A rigorous drug development approach targeted at improving the efficacy and pharmacokinetic characteristics of a sleep-promoting medication led to the discovery of the DORA daridorexant. Animal studies have demonstrated the effectiveness of daridorexant in promoting sleep and maintaining healthy sleep architecture without compromising one's capacity to arouse in response to salient stimuli or compromising one's ability to move. Similar to other DORAs, dariorexant is anticipated to preserve cognitive function, have a very low potential for addiction, and not cause tolerance or rebound after prolonged usage, thus eliminating many of the drawbacks of more conventional hypnotic drugs. After phase III trials proved daridorexant's safety and effectiveness, the FDA approved it. However, nasopharyngitis, headaches, weariness, dizziness, nausea, and somnolence were some of the frequent side effects seen in these trials. Nevertheless, daridorexant was successful in relieving the symptoms of insomnia, enhancing daytime performance, and raising sleep quality.

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