Article published online: 2023-07-06

Daridorexant, a Recently Approved Dual Orexin Receptor Antagonists (DORA) in Treatment of Insomnia

Dwaipayan Sarathi Chakraborty[1] Shouvik Choudhury[2] Sandeep Lahiry[3]

[1] Department of Cardiology & Critical Care Medicine, Belle Vue Clinic, Kolkata, West Bengal, India
[2] Burdwan Medical College, Pharmacology, Burdwan, West Bengal, India
[3] Independent Research Scholar, Barasat, Kolkata, West Bengal, India

Address for correspondence Dwaipayan Sarathi Chakraborty, Department of Cardiology & Critical Care Medicine, Belle Vue Clinic, Kolkata, West Bengal, India (e-mail: drdsc2014@gmail.com).

Sleep Sci 2023;16:256–264.

Abstract

Insomnia is one of the major challenges in medical science nowadays as it leads to great socio-economic burden by impairing daytime function as well as the development of exhaustion, depression, and memory disturbance in affected individuals. Several important classes of drugs have been tried, including the BZDs and non-BZD hypnotics. Available drugs to combat this disease have the limitations of abuse potential, tolerance, and cognitive impairment. In some instances, withdrawal symptoms have been observed upon the abrupt cessation of those drugs. The Orexin system has been very recently targeted as a therapeutic option to overcome those limitations. Treatment of insomnia with Daridorexant as a Dual Orexin Receptor Antagonist (DORA) has been evaluated in several preclinical and clinical studies. Available information obtained from those studies has shown a promising future for this drug in the management of insomnia. Beyond its effectiveness in insomnia, it has been successfully used in patients suffering from obstructive sleep apnoea, chronic obstructed airway disease (COAD), Alzheimer's disease (AD), hypertension, and cardiovascular disorders. Larger studies need to address the safety issues as well as obtain robust pharmacovigilance information to safeguard the risk-benefit aspect of this drug in insomniac adults.

Keywords
- Insomnia
- Daytime
- Orexin
- Tolerance
- Withdrawal
- Hypnotics

Introduction

Insomnia is defined as difficulty falling asleep or staying asleep, as well as impairment in daytime performance, and affects approximately 5–20% of the adult population worldwide.[1] Daytime impairment can have a variety of detrimental effects on a person's quality of life. Daytime exhaustion, distress, mood swings, and memory loss can have a substantial impact on social, occupational, educational, academic, and behavioural elements of life.[2] Insomnia is also associated with chronic non-communicable diseases like hypertension, diabetes, and depression.[3] The orexin neuropeptide signalling system plays a role in a variety of physiological functions, including sleep and arousal. Two neuropeptides,

DOI https://doi.org/10.1055/s-0043-1770805.
ISSN 1984-0659.

Thieme Revinter Publicações Ltda., Rua do Matoso 170, Rio de Janeiro, RJ, CEP 20270-135, Brazil

Orexin A (OX-A) and Orexin B (OX-B), both generated from the same pre-pro-orexin precursor, activate two post-synaptically localised G protein-coupled receptors, Orexin Receptor type 1 (OX1R) and Orexin Receptor type 2 (OX2R).[4,5] OXA preferentially interacts with OX1R, but OX2R has a high affinity for both OX-A and OX-B.[6] Activation of OX1R and OX2R reduces the onset of REM sleep, whereas activation of OX2R suppresses non-REM sleep.[7] If orexin binding to either of its receptors promotes arousal (wakefulness), then a drug that acts as an antagonist of OX1R and/or OX2R for a long time can promote sleep by suppressing the wake promotion associated with the orexin signalling pathway.[8,9]

Available Treatment Options

American College of Physicians (ACP) recommends treatment guidelines for insomnia that include drugs approved by the Food and Drug Administration (FDA) like benzodiazepines, non-benzodiazepine hypnotic 'Z-drugs', melatonin receptor agonist Ramelteon, and Doxepin—a first generation histamine antagonist, as well as use of other off-label drugs.[10] However, there isn't enough data to assess the efficacy or benefit-to-risk ratio of many of these medications. The guidelines don't recommend any specific treatment regimens in this regard. Similarly, the American Academy of Sleep Medicine (AASM) recommends that certain pharmacotherapy may be used to treat sleep onset and/or sleep maintenance insomnia, targeting GABA-A, serotonin, melatonin, and histamine receptors on a regular basis.[11] The most extensively used hypnotics, Z-Drugs (Zolpidem, Zopiclone, Zaleplon) are positive allosteric GABA-A subunit alpha-1 receptor modulators that provide a wide range of suppression of Central Nervous System (CNS) activity.[12] The BZD receptor agonist Zaleplon, the BZD triazolam, and the melatonin agonist Ramelteon are all suggested therapy for sleep onset insomnia, and doxepin is advised for sleep maintenance insomnia. Drugs like Trazodone, Tiagabine and a few over the counter (OTC) drugs (e.g., Diphenhydramine, L-tryptophan, valerian) are not recommended by authorities like ACP/AASM due to a lack of efficacy data and potential safety concerns for which they come under the category of "weak" recommendation. But it should not be misunderstood as if those drugs are ineffective in the management of insomnia.

Use of the above-mentioned available drugs is limited by their significant side effects like next-day residual sleepiness, motor incoordination, frequent falls, memory and cognitive impairment, as well as the development of a risk of addiction, dependence, and tolerance in spite of being highly efficacious. Many other medications used in earlier days for this purpose had similar side effects, like next day somnolence, withdrawal symptoms, physiological tolerance and dependency, though they had potential benefits in their use.[14] In addition to that, healthcare workers expressed their concern with regards to initiating the BZDs and non-BZD hypnotic drugs to treat insomnia in elderly individuals due to the safety concern as well as the propensity for drug dependence in that particular age group.[11] Some of the pharmacological agents recommended in the treatment guidelines may have a limited success rate in treating all phenotypes of insomnia, and their use is also limited due to safety and tolerability in special populations like hepato-renal disorders, elderly individuals, and patients suffering from impaired lung function status. Apart from that, the FDA has issued warnings in prescribing medications and patient guidance against the use of drugs like eszopiclone, zolpidem, and zaleplon due to an increased risk of complex sleep behaviours like sleep walking and sleep driving.[15] As a result, the formulation of a pharmacological treatment plan is governed by several factors, the most important of which are sleep patterns (problems with sleep onset vs. sleep maintenance), drug safety, and efficacy.[16]

Orexin as a Therapeutic Target in Sleep Management

There is strong experimental support for the central orexinergic system's role in controlling alertness and sleep. A considerable increase in the amount of time an animal spends awake and a significant decrease in the percentage of REM and non-REM sleep are caused by intracerebroventricular administration of orexin A or orexin B at the start of the typical sleep phase. Additionally, c-fos expression in orexin neurons and orexin levels in cerebrospinal fluid both positively and negatively correlate with the degree of alertness and non-REM and REM sleep, respectively. Furthermore, orexin neurons fire during active waking, decrease discharges during quiet waking, and essentially stop firing during sleep in unanesthetized rats.[17]These results collectively demonstrate that orexin neurons are mostly active during wakefulness and largely quiet during sleep.

Dual Orexin Receptor Antagonists (DORA) inhibit OX1R and OX2R and promote sleep by reducing arousal signalling. It is believed to be a new pharmaco-therapeutic method of insomnia management.[18] Several DORAs have been evaluated in preclinical and clinical trials for the treatment of insomnia. It's worth noting that DORA doesn't alter the sleep architecture.[19,20] These drugs were developed to shorten the Rapid Eye Movement (REM) latency and prolong total sleep time (TST), predominantly by increasing the total time spent in REM sleep. The time spent on non-REM sleep remains either unaltered or reduced.[21] Apart from that, if the therapy is terminated abruptly, the incidence of drug tolerance, withdrawal symptoms, and rebound insomnia has not been found in most cases.[22–24] Another important fact to mention about the mechanism of action of DORA is that it suggests that day-time sleepiness is further aggravated with the use of this drug in patients with narcolepsy as they have a poor orexin-mediated wake signalling system. Hence, DORAs are contraindicated in such individuals.

Pharmacology of Daridorexant

Darodorexant is a selective, highly potent, small-molecule dual OX1R and OX2R antagonist. It is equally efficacious in antagonising both the OX1 and OX2 receptors.[25] By selectively targeting and reducing the activity of wake-promoting neurons, it bypasses the widespread neuronal inhibition and adverse effects associated with the use of positive GABA-A receptor modulators. Daridorexant curtails the time of

wakefulness and promotes sleep without altering the sleep architecture.[26] It preserves the normal sleep architecture (i.e., non-REM/total sleep and REM/total sleep ratios) by increasing REM and non-REM sleep in physiological proportions. It is more efficacious in conditions associated with high orexin neuronal activity, like sleep deprivation, insomnia, activity phase and other situations of high sleep pressure. The salient pharmacokinetic features of Daridorexant are summarised in ►**Table 1**.[27] Daridorexant displays the desired target interaction profile of a dual, equipotent, and insurmountable antagonist of both OX1R and OX2R, which ensures equally efficient inhibition of both arousal-/wake-promoting receptor subtypes.[28]

Adverse Events–2% of patients treated with Daridorexant in one trial (NCT03545191) and those were nasopharyngitis (6% among 310 study participants who received Daridorexant 50 mg, 7% among 310 trial participants treated with Daridorexant 25 mg and 6% with placebo received by 310 trial participants), headache (6%, 5% and 4%), drug overdose (3%, 1% and 2%), fatigue (2%, 2% and 1%), dizziness (2%, 2%, 2% and 1%), nausea (2%, 1% and 1%), and somnolence (2%, 4% and 2% among 930 total study participants. Adverse events leading to treatment discontinuation occurred in 1% of Daridorexant 50 mg recipients, 2% of Daridorexant 25 mg recipients, and 3% of placebo recipients. Serious adverse events (1) occurred in 1% of Daridorexant 50 mg recipients, 1% of Daridorexant 25 mg recipients, and 2% of placebo recipients.

Drug Interaction Features

Concomitant use with a strong or moderate CYP3A4 inhibitor increases exposure to Daridorexant, which may increase the risk of ADRs. Concomitant use of Daridorexant with a strong inhibitor of CYP3A4 is not recommended. Concomitant use with a strong or moderate CYP3A4 inducer decreases exposure to Daridorexant, which may reduce the efficacy of Daridorexant.[29]

Concomitant use of alcohol or other CNS depressants with Daridorexant may lead to additive impairment of psychomotor performance and an increased risk of CNS depression. Co-administration of a single 50 mg dose of Daridorexant with alcohol at a blood level of 0.6 g/L led to additive effects on impairment of psychomotor performance (postural stability and alertness). Daridorexant did not affect alcohol concentrations and alcohol did not affect Daridorexant concentrations.[29]

Age, sex, race (White, Black, Asian), body size, and mild to severe renal impairment (Cockcroft-Gault 30 mL/min, not on dialysis) did not have a clinically significant effect on the pharmacokinetics of Daridorexant. The effect of severe hepatic impairment (Child-Pugh score 10) on the pharmacokinetics of Daridorexant has not been studied.[29]

The drug has not been studied in patients with severe hepatic impairment (Child-Pugh score 10). Use in this population is not recommended. Moderate hepatic impairment may increase daridorexant systemic exposure to a clinically relevant extent, which may increase the frequency or severity of adverse reactions. No dose adjustment is required in patients over the age of 65 years.[29]

In a human abuse potential study conducted in 63 recreational sedative drug users, the effect of single-dose administration of Daridorexant [50 mg, 100 mg (two times the maximum recommended dose), and 150 mg (three times the maximum recommended dose)], zolpidem (30 mg), Suvorexant (150 mg), and placebo on the subjective rating of "drug liking" was evaluated. At the dose of 50 mg, Daridorexant showed significantly lower "drug liking" ratings than zolpidem (30 mg) and Suvorexant (150 mg), but significantly higher than placebo. At doses of 100 mg (two times the maximum recommended dose) and 150 mg (three times the maximum recommended dose), Daridorexant showed similar "drug liking" ratings to zolpidem (30 mg) and suvorexant (150 mg).[30]

Safety and Efficacy Evaluation in Animal Models

Preclinical evaluation in freely moving rats found increased time duration of REM and non-REM sleep of up to 17 and 55 minutes, respectively, and total awake time decreased by up to 66 minutes when Daridorexant was administered at a dose of 10, 30, 100, and 300 mg/kg at night.[31] The latency to the first persistent episode of both REM and non-REM sleep was decreased in DR-treated rats. In Beagle dogs, Daridorexant had a similar activity profile as in rats. Data obtained from pre-clinical models of dogs and mice suggest that the sleep promoting effects of this molecule can be surpassed without any motor function impairment that can be seen in normal physiological conditions. Apart from the clinical benefits, the abuse potential of Daridorexant was also

Table 1 Salient Pharmacokinetic features of Daridorexant.[27]

Pharmacokinetic feature	Daridorexant
Time to reach peak plasma concentration (T max)	1-2 hrs
Bioavailability	62%
Volume of Distribution (Vd)	31 litres
Plasma protein binding	99.7%
Half-life (t1/2)	8 hrs
Metabolism	Extensively by CYP3A4 (89%)
Elimination	57% via faeces, 28% via urine and rest in bile

evaluated in animal models. Based on molecular profiling, it was found that Daridorexant does not bind to any abuse associated CNS targets at clinically relevant doses. Experimental rats treated chronically with Daridorexant didn't show any withdrawal symptoms on discontinuation of the drug, which reveals that this drug lacks the physical dependence property on long term use. Preclinical evidence suggests that anxiety, sympathetic hyperactivity, mood changes, and cognitive impairment may occur as long-term consequences of untreated insomnia, and that these complications can be effectively treated with Daridorexant.Daridorexant exerted a dose-dependent anxiolytic action on three different rat models.[32] In addition to that, pre-clinical experiments have also demonstrated the benefits of alleviating the fear of not being able to sleep properly, poor day-time performance, and memory deficit with the use of drugs in simulated environments. Available pre-clinical data on the safety and efficacy of Daridorexant on animal models has been summarised in ►**Table 2**.[33]

Daridorexant's Role in Clinical Practice

As a part of clinical evaluation, this drug was safe and well tolerated in all Phase 1 studies conducted among healthy participants, where dose-dependent somnolence and fatigue were two predominant adverse events. In current times, two phase 2 trials have been published where the safety and efficacy of Daridorexant were evaluated. In one trial, dose-dependent safety and efficacy were assessed at four different doses (5mg, 10mg, 25 mg, and 50 mg) administered for 30 days in comparison to placebo or 10mg Zolpidem in adults less than 64 years of age suffering from insomnia. Daridorexant produced a dose-dependent reduction in Wake After Sleep Onset (WASO) and subjective latency to sleep onset with no clinically relevant treatment-related serious adverse events and a low rate of discontinuation due to adverse events.[34] In another phase 2 trial, the daridorexant-treated patients developed statistically significant dose-dependent improvements in latency to persistent sleep (LPS), WASO, with almost similar rates of treatment-related adverse events (TEAE) compared with placebo.[35] Results from these trials allowed the drug to progress further in the drug development process, and Phase 3 trials were initiated thereafter. Two consecutive trial results were announced in the months of April 2020 and July 2020, respectively.[36,37] The results of these studies showed objective and subjective improvements in sleep measures (sleep onset, sleep maintenance, and subject-reported Total Sleep Time or sTST) with daridorexant treatment. Additionally, there were no reports of next-day tiredness or indications of rebound or withdrawal symptoms. The Phase 3 programme of Daridorexant consists of three studies investigating its efficacy and safety at dosages of 10, 25, and 50 mg for up to a 12-month treatment term (clinicaltrials.gov: NCT03545191, NCT03575104, and NCT03679884). Apart from analysing objective and subjective impacts on sleep, the Phase 3 programme also looks at potential improvements in next-day functioning as complaints about daytime functioning are a common symptom of insomnia. Available results revealed that treatment with Daridorexant not only improved objective and subjective sleep metrics but also improved patients' daytime functionality following the completion of the first Phase 3 trial.[38] Special emphasis was given to the assessment of the residual next morning effect. Breathing issues, particularly in overweight adults, are frequently linked to insomnia-related symptoms. Therefore, regulatory authorities anticipate corresponding safety studies in these populations. In two safety studies, Daridorexant did not exhibit any clinically relevant effect on nighttime respiratory function in participants with moderate chronic obstructive pulmonary disease (COPD) or obstructive sleep apnea.[40] There are certain limitations to the studies reported as well as the concept of pharmacotherapy. Early PK, PD, and safety studies of the drug were conducted in small groups of people, such as 8–10 healthy subjects per dose group. As a result,

Table 2 Pre-clinical data on safety and efficacy of Daridorexant on animal models.[33]

Type of animal	Effect of Daridorexant	Reference
Free moving rat	Decreases wakefulness and thereby promotes sleep in which sleep architecture is preserved	Treiber et al 2017 Boss et al 2020
Wistar rat	No impact on motor co-ordination or muscle strength	Tang et al 1995 Voss et al 2003
Rat	Did not bind to any known abuse associated CNS targets based on molecular profiling.	Ufer et al 2020
	Decreases orexin neuron firing and OXR activation during sleep	Blouin et al 2013
	Exerted dose dependent anxiolytic effect	Steiner et al 2020
Beagle Dog	Decreases wakefulness up to 77 mins over 6 hrs. post drug administration and increases time spent in both REM & non- REM sleep	Boss et al 2020
Rhesus monkey	Did not produce residual sleep effect as well as no impairment of memory and attention	Gotter et al 2013
Dog	Did not affect their ability to wake up and behave normally upon presentation of food as a salient positive environmental stimulus.	Boss et al 2020

pharmacovigilance experience with Daridorexant is limited, particularly at high exposure following supratherapeutic dosage delivery (75 mg Daridorexant and above were only administered to healthy subjects). As a result, there is currently no information on overdose, rare adverse responses, or intoxication in patients, highlighting the limitations of investigating medication effects in healthy participants.

Daridorexant's safety and effectiveness were evaluated in two multicentre, randomised, double-blind, placebo-controlled phase 3 trials at 156 sites in 17 countries. The findings showed that Daridorexant 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.[41] The lists of clinical trials evaluating the safety and efficacy of Daridorexant have been tabulated in ►**Table 3a** and **3b**.[27]

Current Approval Status

-Daridorexant has been approved recently by the international regulatory authority FDA for the treatment of insomnia in adults. The judgement was based on a clinical trial that involved 1854 adults from 160 clinical trial locations.[42] Treatment with Daridorexant at a dose of 25- and 50-mg resulted in significant improvements in objective measures of sleep onset and maintenance, as well as patient-reported total sleep time, when compared to placebo. The drug improved sleep and daytime functioning among the study participants statistically significantly, as measured by the Insomnia Daytime Symptoms and Impacts Questionnaire, while maintaining a favourable safety profile in adult and paediatric patients.[43]

Daridorexant's place in the current treatment arsenal is as follows:Available treatment options for chronic insomnia do not provide clinical benefits to all patients. Targeting the orexin system could be a promising option in the current scenario. Daridorexant, a recently approved DORA in the treatment armamentarium of adult patients suffering from chronic insomnia, has been developed through an intense drug development program. It has been manufactured with the aim of optimisation of the favourable pharmacokinetic and safety profile of a sleep-promoting agent. Preclinical experiments in animal models have demonstrated its efficacy in sleep promotion and maintaining normal sleep architecture without impairing motor function and the ability to arouse in response to salient stimuli. These features play a significant role in overcoming the usual limitations arising due to the use of traditional hypnotic medications. Reducing the sympathetic drive-in experimental animals has also evolved a new probability in controlling blood pressure and decreasing cardiovascular risk among elderly individuals. Insomnia becomes more common as people get older, and it can be a risk factor for dementia. Several studies have found a bidirectional relationship between sleep disruptions and Alzheimer's disease (AD), with sleep disorders leading to greater AD pathology, which exacerbates sleep issues. Positive GABA-A modulators impair memory and cognition and are linked to

Table 3a. List of clinical trials evaluating safety and efficacy of Daridorexant.[27]

Trial identifier	Phase of trial	Indications	Drug(s)	Location (s)	Status	Trial participants
Trial identifier	Phase of trial	Indications	Drug(s)	Location (s)	Status	Trial participants
NCT04390334	Phase- I	Drug-drug interactions in volunteers	Daridorexant, famotidine, efavirenz	Germany	Completed	24
NCT04250506	Phase- I	Thorough QT study in volunteers	Daridorexant, moxifloxacin, placebo	Czech Republic	Completed	36
NCT04024332	Phase- I	Renal impairment	Daridorexant	Germany	Completed	16
NCT03907215	Phase- I	Drug-drug interactions in volunteers	Daridorexant, citalopram, placebo	Germany	Completed	24
NCT03892902	Phase- I	Driving performance in volunteers	Daridorexant, zopiclone, placebo	Netherlands	Completed	56
NCT03765294	Phase- I	Effects on respiration in patients with obstructive sleep apnoea	Daridorexant, placebo	Germany	Completed	28
NCT03799978	Phase- I	Effects of food on pharmacokinetics in volunteers	Daridorexant	Czech Republic	Completed	20
NCT03646864	Phase- I	Effects on respiration in patients with chronic obstructive pulmonary disease	Daridorexant	Germany	Completed	28
NCT03657355	Phase- I	Abuse potential in healthy recreational drug users	Daridorexant, suvorexant, zolpidem, placebo	USA	Completed	63
NCT03609775	Phase- I	Drug-drug interactions in volunteers	Daridorexant, ethanol, placebo	Netherlands	Completed	22
NCT03713242	Phase- I	Hepatic impairment	Daridorexant	Switzerland	Completed	32

Table 3a. (*Continued*)

Trial identifier	Phase of trial	Indications	Drug(s)	Location (s)	Status	Trial participants
NCT03339752	Phase- I	Drug-drug interactions in volunteers	Daridorexant, rosuvastatin	Czech Republic	Completed	20
NCT03101189	Phase- I	Ethnic sensitivity study in Japanese vs Caucasian volunteers	Daridorexant, placebo	Netherlands	Completed	40
NCT03017495	Phase- I	Drug-drug interactions in volunteers	Daridorexant, midazolam	Germany	Completed	20
NCT02571855	Phase- I	Multiple ascending dose study in volunteers	Daridorexant, placebo	Netherlands	Completed	86
NCT02526888	Phase- I	Drug-drug interactions in volunteers	Daridorexant, diltiazem	Germany	Completed	14
NCT02919319	Phase- I	Single ascending dose study in volunteers	Daridorexant, 14C-labeled Daridorexant micro tracer, placebo micro tracer	Netherlands	Completed	40
NCT02841709	Phase- II	Insomnia disorder	Daridorexant, placebo	USA, Germany	Completed	58
NCT02839200	Phase- II	Insomnia disorder	Daridorexant, zolpidem, placebo	Germany, Hungary, Israel, Spain, Sweden, United States	Completed	360
NCT05423717	Phase- II	Insomnia Disorder	Daridorexant, placebo	USA	Recruiting	
jRCT2031200452	Phase III	Insomnia Disorder	Daridorexant, Placebo	Japan	Recruiting	
JapicCTI-205444	Phase III	Insomnia disorder	Daridorexant, placebo	Japan	Recruitng	
NCT03679884	Phase III	Insomnia disorder	Daridorexant, placebo	Belgium, Bulgaria, Canada, Denmark, Finland, France, Germany, Hungary, Korea, Republic of, Poland, Spain, Sweden, Switzerland, United States Australia, Czechia, Italy, Serbia	Completed	804
NCT03545191	Phase III	Insomnia disorder	Daridorexant, placebo	Australia, Canada, Denmark, Germany, Italy, Poland, Serbia, Spain, Switzerland, United States	Completed	930
NCT03575104	Phase III	Insomnia disorder	Daridorexant, placebo	Belgium, Bulgaria, Canada, Czechia, Finland, France, Germany, Hungary, Korea, Republic of, Sweden, United States	Completed	924

Table 3b Final Outcomes of important clinical trials (conducted at several phases) on Daridorexant.[27]

Phase of Trial	Trial Identifier	Outline of the Study	Final outcome
Phase I	NCT04250506	Impact of Daridorexant, a Dual Orexin Receptor Antagonist, on Cardiac Repolarization Following Bedtime Dosing: Results from a Thorough QT Study Using Concentration- QT Analysis	Daridorexant does not impair cardiac repolarization evidenced by absence of relevant QT prolongation at therapeutic and supratherapeutic doses.
Phase I	NCT04024332	Study of the Way the Body Takes up, Distributes, and Gets Rid of ACT-541468 in Subjects with Abnormal Kidney Function Compared to Healthy Subjects	Similar Pharmacokinetic (PK) profiles and no tolerability issues were observed in patients with severe renal function impairment (SRFI)and control subjects following single- dose administration of 25 mg Daridorexant.
Phase I	NCT03892902	A Clinical Study to Assess Next- day Driving Performance Following Administration of Daridorexant in Middle-aged and Elderly Subjects	Daridorexant impaired simulated driving performance after initial but not after repeated dosing. Results show that a state-of-the-art driving simulation test, conducted under highly standardized conditions, is more sensitive to detect subtle drug effects on driving performance than the on-the- road test.
Phase I	NCT03765294	A study to evaluate the effect of Daridorexant on night-time respiratory function and sleep in patients with mild and moderate obstructive sleep apnoea	Single and repeated doses of 50 mg Daridorexant do not impair night-time respiratory function and improve sleep in patients with mild and moderate obstructive sleep apnoea (OSA)
Phase I	NCT03646864	A Study to Evaluate the Effects of Daridorexant on Respiration in Patients with Moderate Chronic Obstructive Pulmonary	Single and multiple doses of 50 mg Daridorexant do not impair night- time respiratory function and improves sleep in patients with moderate COPD.
Phase I	NCT03657355	A Study to Evaluate the Abuse Potential of Daridorexant in Healthy Recreational Drug Users	Daridorexant showed dose- related drug- liking among recreational sedative drug users with lower effects at the highest phase-3 dose, and similar effects at higher doses compared to supratherapeutic doses of Suvorexant and zolpidem
Phase I	NCT03609775	A Study to Investigate the Drug-drug Interactions Between Daridorexant and Ethanol in Healthy Subjects	Apart from a shift in time to reach maximum plasma concentrations (tmax), no relevant changes in PK parameters were observed following coadministration of Daridorexant and ethanol.
Phase I	NCT03713242	A Study to Evaluate the Pharmacokinetics of Daridorexant in Subjects with Mild, Moderate, and Severe Hepatic Impairment	No safety issue of concern was detected following administration of 25 mg of Daridorexant in the study population. Moderate liver cirrhosis causes impaired hepatic clearance of unbound Daridorexant, which prolongs the half-life. A 25-mg dose of Daridorexant should, therefore, not be exceeded in Child-Pugh B patients. A dose adjustment is not required in Child- Pugh A patients, while avoidance of Daridorexant in patients with Child-Pugh C cirrhosis is recommended.
Phase II	NCT02841709	Efficacy and Safety of ACT- 541468 in Elderly Subjects With Insomnia Disorder	Daridorexant was well tolerated among study participants and Dose-dependent improvements in wake after sleep onset in (WASO) and latency to persistent sleep (LPS) were statistically significant (dose range 10-50 mg) in elderly people with insomnia disorder.
Phase II	NCT02839200	Efficacy and Safety of Daridorexant in Adult Subjects with Insomnia Disorder	Daridorexant induced a dose- dependent reduction in wake time after sleep onset in subjects with insomnia disorder
Phase III	NCT03545191 NCT03575104	Study to Assess the Efficacy and Safety of Daridorexant in Adult and Elderly Subjects with Insomnia Disorder	Daridorexant 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.

an increased risk of dementia and Alzheimer's disease. They are not advised for the treatment of concomitant insomnia in Alzheimer's disease.

Insomnia as a chronic non-communicable disease has a great impact on the socio-economic lives of human beings. It affects the quality of life (QoL) through the development of exhaustion, depression, daytime somnolence, and many other related problems, ultimately increasing the risk of serious health issues like diabetes, hypertension, and cardiovascular diseases. Available treatment options have limitations in drug abuse, drug tolerance, and drug withdrawal, which are significant drawbacks. Targeting the orexin system may overcome these limitations and has proven to be a promising option in the current drug regimen for the treatment of insomnia. Daridorexant has been developed by a vast drug development programme as a novel Dual Orexin Receptor Antagonist (DORA) for insomnia treatment. Both the available pre-clinical and clinical data have demonstrated the safety, tolerability, and efficacy of this molecule over the other classes of drugs used for this purpose. Use of this drug in animal models also showed promising benefits in managing hypertension and other cardiovascular disorders. In spite of all the positive results recently published on the safety and efficacy of Daridorexant, the available information on pharmacovigilance data of this DORA is limited, which needs to be addressed on the basis of results of larger clinical trials to be conducted in the coming days.

Consent for Publication
Not applicable

Authors' Contributions
We all have equally contributed in planning, formatting and preparing the manuscript

Funding
Not applicable

Conflict of interests
No conflict of interest is present

Acknowledgements
Nil

References

1 Roth T, Coulouvrat C, Hajak G, et al. Prevalence and perceived health associated with insomnia based on DSM-IV-TR; International Statistical Classification of Diseases and Related Health Problems, Tenth Revision; and Research Diagnostic Criteria/International Classification of Sleep Disorders, Second Edition criteria: results from the America Insomnia Survey. Biol Psychiatry 2011;69(06): 592–600

2 Hudgens S, Phillips-Beyer A, Newton L, Seboek Kinter D, Benes H. Development and Validation of the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ). Patient 2021;14(02):249–268

3 Wilson S, Anderson K, Baldwin D, 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(08):923–947

4 Chieffi S, Carotenuto M, Monda V, et al. Orexin system: the key for a healthy life. Front Physiol 2017;8:357. Doi: 10.3389/ fphys. 2017.00357

5 Scammell TE, Arrigoni E, Lipton JO. Neural circuitry of wakefulness and sleep. Neuron 2017;93(04):747–765. Doi: 10.1016/j. neuron.2017.01.014

6 Barson JR, Leibowitz SF. Orexin/hypocretin system: role in food and drug overconsumption. Int Rev Neurobiol 2017; 136:199–237. Doi: 10.1016/bs.irn.2017.06.006

7 Willie JT, Chemelli RM, Sinton CM, et al. Distinct narcolepsy syndromes in Orexin receptor-2 and Orexin null mice: molecular genetic dissection of Non-REM and REM sleep regulatory processes. Neuron 2003;38(05):715–730. Doi: 10.1016/s0896- 6273 (03)00330-1

8 Beuckmann CT, Suzuki M, Ueno T, Nagaoka K, Arai T, Higashiyama H. In vitro and in silico characterization of lemborexant (E2006), a novel dual orexin receptor antagonist. J Pharmacol Exp Ther 2017; 362(02):287–295. Doi: 10.1124/ jpet.117.241422

9 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(08):1399–1408. Doi: 10.5664/ jcsm.7282

10 Qaseem A, Kansagara D, Forciea MA, Cooke M, Denberg TDClinical Guidelines Committee of the American College of Physicians. Clinical Guidelines Committee of the American College of Physicians. Management of chronic insomnia disorder in adults: a clinical practice guideline from the American College of Physicians. Ann Intern Med 2016;165(02):125–133. Doi: 10.7326/ M15-2175

11 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(02): 307–349. Doi: 10.5664/ jcsm.6470

12 ClinCalc.com(2019) The Top 200 Drugs of 2019. Accessed 28/11/ 2019 https://clinc alc.com/DrugS tats/

13 Frey DJ, Ortega JD, Wiseman C, Farley CT, Wright KP Jr. Influence of zolpidem and sleep inertia on balance and cognition during nighttime awakening: a randomized placebo-controlled trial. J Am Geriatr Soc 2011;59(01):73–81

14 Rosenberg RP. Sleep maintenance insomnia: strengths and weaknesses of current pharmacologic therapies. Ann Clin Psychiatry 2006;18(01):49–56. Doi: 10.1080/10401230500464711

15 US Food and Drug AdministrationFDA adds boxed warning for risk of serious injuries caused by sleepwalking with certain prescription insomnia medicines. Available from: Accessed January 31, 2020. https://www.fda.gov/drugs/drug-safety-and-availability/fda-adds-boxed-warning-risk-serious-injuries-caused-sleepwalking-certain-prescription-insomnia

16 Schutte-Rodin S, Broch L, Buysse D, Dorsey C, Sateia M. Clinical guideline for the evaluation and management of chronic insomnia in adults. J Clin Sleep Med 2008;4(05):487–504. Doi: 10.5664/ jcsm.27286

17 Lee MG, Hassani OK, Jones BE. Discharge of identified orexin/hypocretin neurons across the sleep-waking cycle. J Neurosci 2005;25(28):6716–6720

18 Gotter AL, Winrow CJ, Brunner J, et al. The duration of sleep promoting efficacy by dual orexin receptor antagonists is dependent upon receptor occupancy threshold. BMC Neurosci 2013; 14:90. Doi: 10.1186/1471-2202-14-90

19 Clark JW, Brian ML, Drummond SPA, Hoyer D, Jacobson LH. Effects of orexin receptor antagonism on human sleep architecture: A systematic review. Sleep Med Rev 2020;53:101332. Doi: 10.1016/ j.smrv.2020.101332

20 Snyder E, Ma J, Svetnik V, et al. Effects of suvorexant on sleep architecture and power spectral profile in patients with insomnia: analysis of pooled phase 3 data. Sleep Med 2016;19:93–100. Doi: 10.1016/j.sleep.2015.10.007

21 Moline M, Zammit G, Cheng JY, Perdomo C, Kumar D, Mayleben D. Comparison of the effect of lemborexant with placebo and zolpidem tartrate extended release on sleep architecture in older adults with insomnia disorder. J Clin Sleep Med 2021;17(06): 1167–1174. Doi: 10.5664/jcsm.9150
22 Herring WJ, Connor KM, Ivgy-May N, et al. Suvorexant in patients with insomnia: results from two 3-month randomized controlled clinical trials. Biol Psychiatry 2016;79(02):136–148. Doi: 10.1016/j.biopsych.2014.10.003
23 Michelson D, Snyder E, Paradis E, et al. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. Lancet Neurol 2014;13(05): 461–471. Doi: 10.1016/S1474-4422(14)70053-5
24 Rosenberg R, Murphy P, Zammit G, et al. Comparison of lemborexant with placebo and zolpidem tartrate extended release for the treatment of older adults with insomnia disorder: a phase 3 randomized clinical trial. JAMA Netw Open 2019;2(12): e1918254. Doi: 10.1001/jamanetworkopen.2019.18254
25 Treiber A, de Kanter R, Roch C, 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(03):489–503
26 Boss C, Gatfield J, Brotschi C, et al. The quest for the best dual orexin receptor antagonist (daridorexant) for the treatment of insomnia disorders. ChemMedChem 2020;15(23):2286–2305
27 Markham A. Daridorexant: First Approval. Drugs 2022;82(05): 601–607
28 Grandjean CM, Kiry M, Vaillant C, Nayler O, Gatfield J. 059 Daridorexant: A dual, equipotent, and insurmountable antagonist of both orexin-1 and orexin-2 receptors. Sleep (Basel) 2021;44 (Supplement_2):A25
29 https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2022/214985Orig1s000ltr.pdf
30 Ufer M, Kelsh D, Schoedel KA, Dingemanse J. Abuse potential assessment of the new dual orexin receptor antagonist daridorexant in recreational sedative drug users as compared to suvorexant and zolpidem. Sleep 2022;45(03):zsab224
31 Steiner MA, Locher R, Lecourt H, Jenck F. W15. The novel insomnia drug daridorexant also reduces behavioral and physiological stress responses in rats. Neuropsychopharmacology 2020;45:286
32 Dauvilliers Y, Zammit G, Fietze I, et al. Daridorexant, a new dual orexin receptor antagonist to treat insomnia disorder. Ann Neurol 2020;87(03):347–356. Doi: 10.1002/ana.25680
33 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 (10):2693–2708
34 Zammit G, Dauvilliers Y, Pain S, Sebök Kinter D, Mansour Y, Kunz D. Daridorexant, a new dual orexin receptor antagonist, in elderly subjects with insomnia disorder. Neurology 2020;94(21): e2222–e2232. Doi: 10.1212/WNL.0000000 000009475
35 Idorsia Pharmaceuticals Ltd. Idorsia announces positive results in the first Phase 3 study of daridorexant with improved overall sleep and daytime performance of patients with insomnia [press release]. Available from: details?newsId = 2284972. Accessed February 22, 2021. https://www.idorsia.com/media/news-
36 Idorsia Pharmaceuticals Ltd. Idorsia announces positive results in the second Phase 3 study of daridorexant [press release]. Available from: Accessed February 22, 2021. https://www.idorsia.com/investors/news-and- events/media-release-details?newsId=2329316
37 Idorsia Ltd. Idorsia announces positive results in the first Phase 3 study of daridorexant with improved overall sleep and daytime performance of patients with insomnia [Press release]. 20 Apr 2020.
38 Boof ML, Dingemanse J, Brunke M, et al. Effect of the novel dual orexin receptor antagonist daridorexant on night-time respiratory function and sleep in patients with moderate chronic obstructive pulmonary disease. J Sleep Res 2021;30(04):e13248
39 Boof ML, Dingemanse J, Lederer K, Fietze I, Ufer M. Effect of the new dual orexin receptor antagonist daridorexant on nighttime respiratory function and sleep in patients with mild and moderate obstructive sleep apnea. Sleep 2021;44(06):zsaa275. Doi: 10.1093/sleep/zsaa275
40 Idorsia recieves US FDA approval of Quiviviq (daridorexant) 25 and 50 mg for the treatment of adults with insomnia. News release. Idorsia. January 10, 2022. Accessed January 10, 2022. https://www.biospace.com/article/releases/idorsia-receives-us-fda-approval-of-quviviqdaridorexant-25-and-50-mg-for-the-treatment-of-adults-with-insomnia/?s=85
41 Mignot E, Mayleben D, Fietze I, et al; investigators. Safety and efficacy of daridorexant in patients with insomnia disorder: results from two multicentre, randomised, double-blind, placebo-controlled, phase 3 trials. Lancet Neurol 2022;21(02): 125–139
42 Zammit G, Mayleben D, Fietze I, et al. Daridorexant improves total sleep time (TST) In insomnia patients without altering the proportion of sleep stages Presented at SLEEP 2021 Annual Meeting; June 10-13. Abstract 344 .
43 Li A, Hindmarch CC, Nattie EE, Paton JF. Antagonism of orexin receptors significantly lowers blood pressure in spontaneously hypertensive rats. J Physiol 2013;591(17):4237–4248

