



## A REVIEW OF DARIDOREXANT-A NEW DUAL OREXIN MEDICINE FOR THE TREATMENT OF INSOMNIA

Preeti Aneja<sup>\*1</sup>, Dr. Rajender Guleria<sup>1</sup>, Santosh Kumari<sup>1</sup>, Yogita Thakur<sup>1</sup>, Bheema Devi<sup>1</sup> and Ankita Sharma<sup>2</sup>

<sup>1</sup>Department of Pharmaceutics, Abhilashi College of Pharmacy, Nerchowk, Mandi, Himachal Pradesh, India.

<sup>2</sup>Department of Pharmaceutical Chemistry, Shiva College of Pharmacy, Bilaspur, Himachal Pradesh, India.



\*Corresponding Author: Preeti Aneja

Department of Pharmaceutics, Abhilashi College of Pharmacy, Nerchowk, Mandi, Himachal Pradesh, India.

Article Received on 23/02/2024

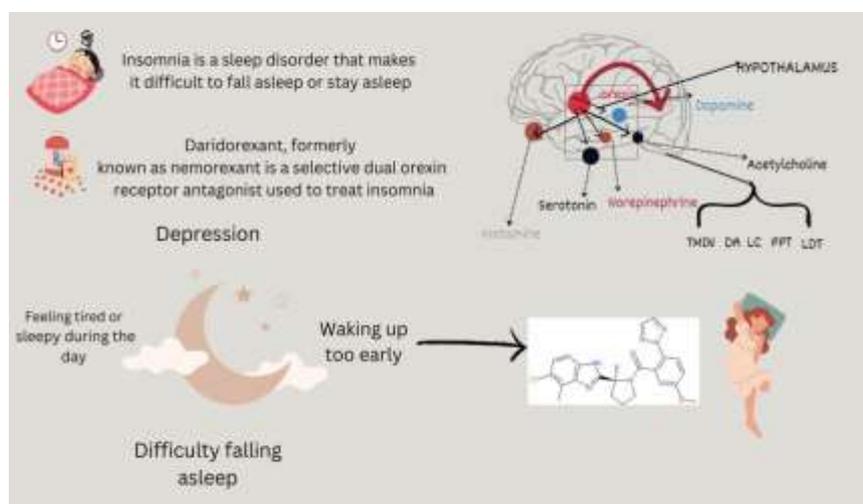
Article Revised on 15/03/2024

Article Accepted on 05/04/2024

### ABSTRACT

Orexin framework was found in late 1990's and it has been recently changed with more powerful way to treat the sleep deprivation. As a sleeping disorder insomnia is responsible for causing other health consequences. It is a typical condition related with checked impedance in capability and personal satisfaction, mental and actual grimness, and mishaps. Objective of newly invented daridorexant for the treatment of a sleeping disorder was to further develop the evening side effects as well as the daytime side effects experienced by patients. Sleep deprivation is to be sure connected with critical trouble or weakness in daytime working including weariness, daytime sluggishness, and temperament aggravations, lessen mental capability, execution, and inspiration, as well as conduct issues. Insomnia is one of the most widely recognized rest problems around the world. It is the second most normal psychological well-being issue, influencing 10%-15% of the total population. Sleep deprivation is a pervasive objection in clinical practice that can introduce freely or co morbidly with another clinical or mental problem. The objective of drug treatments for insomnia is to expand rest great and quantity, as well as daylight working, while at the equal time staying far from unfriendly activities and subsequent-morning last influences. The current review assessed the effect of single and persevered dosing with 50 mg daridorexant on evening time respiration functionality, and relaxation features, in sufferers with gentle and direct obstructive rest apnea.

**KEYWORDS:** DORA, quiviviq (daridorexant), insomnia, orexin, sleep deprivation.



### INTRODUCTION

The wake-promoting orexin (also known as hypocretin) neuropeptides are inhibited by daridorexant, which binds specifically to both orexin receptors. By using this method, the more general inhibition of neural circuits

and the related negative effects that come with positive allosteric GABA-A receptor modulators are avoided.<sup>[1]</sup> Orexin framework was found in 1990's and it has been recently changed with more strong way to treat the sleep deprivation, as sleep cycle shown in fig 1.<sup>[2]</sup>



Fig. 1: Sleep cycle.

Excitatory hypothalamic neuropeptides called orexin A and B are involved in a variety of physiological processes, including eating behaviour, spontaneous physical activity, energy metabolism management, sleep/wake cycles, and cardiovascular responses.<sup>[3]</sup> Insomnia is a typical condition related with stamped weakness in capability and personal satisfaction, mental and actual horribleness, and mishap.<sup>[4]</sup> A sleeping disorder is perceived as the most common rest problem and thought about a significant general medical condition. Sleep deprivation has mainly affected to person having financial weight or in some deficiency condition.<sup>[4,5]</sup> It incorporates a trouble starting rest, trouble keeping up with rest or getting up sooner than wanted with daytime weakness not withstanding satisfactory open door and conditions to rest and steady objection of disappointment with rest amount or quality related with at least one a sleeping disorder side effect.<sup>[6]</sup>

The objective of originating daridorexant for the treatment of a sleeping disorder was to further develop the evening time side effects and furthermore the daytime side effects experienced by patients. Sleep deprivation is to be sure connected with critical pain or hindrance in daytime working including weariness, daytime drowsiness, and temperament aggravations, diminish mental capability, execution, and inspiration, as well as conduct issues.<sup>[1,6]</sup> Daridorexant was approved by the European Commission on May 3, 2022, as the first dual orexin receptor antagonist approved in the market, and by Health Canada on April 26, 2023.<sup>[7]</sup> Furthermore, it constantly influences the individual's regular routine and long wellbeing impacts, as it is frequently connected with two or more diseases.<sup>[8]</sup>

Dual orexin receptor antagonists (DORAs), which act as competitive inhibitors of orexin A and orexin B, can promote sleep and mitigate insomnia by selectively binding to orexin receptors 1 and 2. Orexins are two neuropeptides produced exclusively in the lateral hypothalamus that act on two-specific receptors that are

widely distributed throughout the brain and are involved in myriad neurophysiological function.<sup>[9]</sup>

### INSOMNIA

A sleeping disorder is one of the most well-known rest problems around the world. It is the second most normal psychological wellness issue, influencing 10%-15% of the total populace. Sleep deprivation is a predominant grumbling in clinical practice that can introduce freely or co morbidly a disease or medical condition that is simultaneously present with another or others in a patient) with another clinical or mental problem.<sup>[10]</sup> It is ordinarily trailed by daytime tiredness, low energy, peevishness, and discouraged temperament. It might bring about an expanded gamble of engine vehicle impacts, as well as issue centering and learning. A sleeping disorder can be present moment, going on for days or weeks and long haul, enduring over a month as depicted in fig2.<sup>[10,11]</sup>

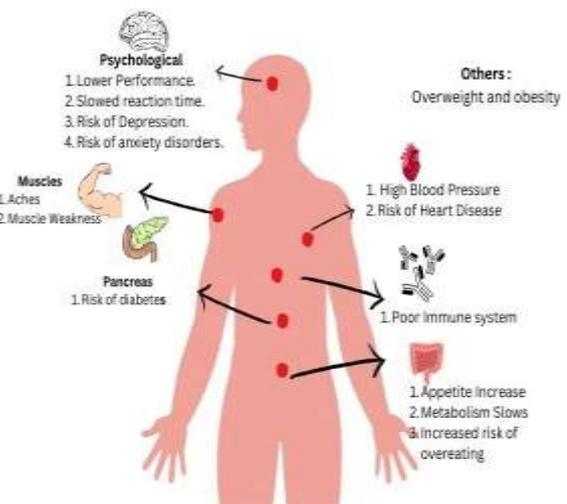


Fig. 2: Complications of Insomnia.

**TYPES OF INSOMNIA**

- **Acute insomnia;** It is because of the different anxieties like individual pressure, clinical pressure, scholastic pressure, or monetary pressure. It is likewise named as transient sleep deprivation, which can endure from not many days to half a month.<sup>[11]</sup>
- **Chronic insomnia;** It is because of clinical problems, substance misuse, mental confusion, rest wake jumble, and so on it keep going for 30 days or longer. Hence, it is likewise named as long-term sleep deprivation. The insomnia cycle is depicted in fig3.



**Fig. 3: Insomnia cycle.**

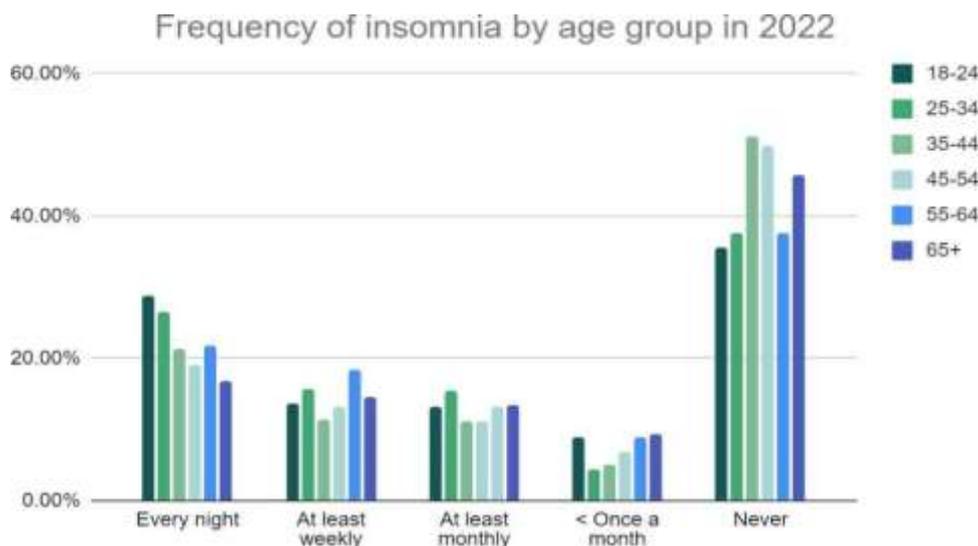
- Idiopathic,
- psycho-physiological,
- perplexing a sleeping disorder

**GLOBAL PREVALENCE**

The predominance of a sleeping disorder in a review relies upon the models' chosen for deciding the commonness<sup>[1]</sup>. It is notable that few variables like sexual orientations, age, mental problems among a few others are risk factors for sleep deprivation.<sup>[12]</sup> The pressure of current metropolitan life adds to the variables liable for an expansion in the pervasiveness. Notwithstanding a few co-sullen elements can essentially affect the pervasiveness of a sleeping disorder.<sup>[13]</sup> Sleep deprivation as a problem is very unique in relation to a concise time of unfortunate rest, and it can negatively affect both physical and psychological well-being. A sleeping disorder is a typical issue with a commonness of roughly 10% of the grown-up populace. On this premise, and expecting a US grown-up populace of around 250 million, there are roughly 25 million grown-ups in the US who experience the ill effects of a sleeping disorder. In Europe, the assessed commonness of sleep deprivation is 6-12% and in Canada, sleep deprivation influences an expected 10%.<sup>[13]</sup> Current suggested treatment of a sleeping disorder incorporates rest cleanliness proposals, mental social treatment, and pharmacotherapy.<sup>[14]</sup> Fig 4. showing the predominance of insomnia among the age numbers.

**Other characterization of sleep deprivation included**

Essential sleep deprivation (based on intense kind)



**Fig. 4: Frequency of insomnia by age group in 2022.**<sup>[13]</sup>

**APPROACHES;** Daridorexant is a newly found medication demonstrated for the treatment of grown-up patients with a sleeping disorder described by hardships with rest beginning and rest support. It was plan by means of a serious medication revelation program to work on the power and amplify the length of activity while limiting next morning lingering movement.<sup>[15]</sup>

Daridorexant previously known as nemorexant, a particular double orexin receptor antagonist as shown in table 1. Traditional viable medicines for a sleeping disorder incorporate medications focusing on gamma-amino-butyric corrosive sort A (GABA-A), serotonin, receptor, or melatonin receptors<sup>[6]</sup>

**Table 1: Detailed information of Daridorexant (DORA).**

<b>DRUG NAME</b>	<b>Daridorexant</b>
TRADE NAME	Quvig
OTHER NAME	Nemorexant
IUPAC NAME	[(2S)-2-(5-Chloro-4-methyl-1H-benzimidazol-2-yl)-2-methylpyrrolidin-1-yl]-[5-methoxy-2-(triazol-2-yl)phenyl]methanone
FORMULA	C <sub>23</sub> H <sub>23</sub> C <sub>1</sub> N <sub>6</sub> O <sub>2</sub>
PROTEIN BINDING	99.7%
ROUTE OF ADMINISTRATION	By mouth
DRUG CLASS	Orexin receptor
BIOAVAILABILITY	62%
METABOLISM	Extensive(89%)
ONSET OF ACTION	T <sub>max</sub> 1-2 hours(delayed ny 1-3 hours with food)
ELIMINATION HALF LIFE	8hours(6-10)
DURATION OF ACTION	8 hours(50mg)
EXCRETION	Feces-57%, urine-28%
MOLAR MASS	450.95%
LEGAL STATUS	US:schedule IV EU: Rx only
APPROVED BY FDA	7 January 2022 (USA)

### DISCOVERY AND DEVELOPMENT OF DARIDOREXANT (DORA)

Lately, the orexin has been seen as an objective for the improvement of a shiny new polish of rest cure<sup>[17]</sup>. Prober, the disclosure of orexin started with two separate organizations of specialists who wound up running over the equivalent peptide on the surrender, one association drove via Lecea and partners worked on substances emitted from the nerve center, simultaneously as the contrary gathering drove through Sakura and partners

worked on vagrant G-protein coupled receptors<sup>[17,18]</sup>. Since emitted from the nerve center, one association alluded to hypocretins, even as the contrary association presumed that because of their desire for food- animating movement, these peptides should be named orexins. To avoid disarray inside the terminology the time span hypocretins could consult with quality and orexin will examine quality items.<sup>[18]</sup>The clinical phases of studies done on the drug are enumerated as in table2.

**Table 2: Clinical studies done on daridorexant (n= number of patients).**

Clinical Study	Doses given in adults(>18) and elderly patients(>65)total n=1854		No. of patients received placebo treatment	Time period of treatment	Conclusion	Reference
	Daridorexant	No. of patients involved (total n=1854)				
STUDY-1	50 mg	N=310	N=310	3 Month	Daridorexant is well tolerated in the elderly population for the use of insomnia. 50 mg daridorexant improved sleep outcomes and daytime functioning.	[19]
	25 mg	N=310				
STUDY-2	25 mg	N=309	N=308	3 Month	25 mg daridorexant improved sleep outcomes in patients with insomnia disorder when compared to placebo. 10 mg	[19]
	10 mg	N=307				
STUDY- 3	Both studies are evaluated	Double blind, placebo controlled extension study	No. of patients involved in both study 1 and study 2	Month	576 patients treated for 6 months of cumulative treatment. 331 treated for 12 months.	[20]

## OREXIN RECEPTORS TARGET IN DISEASE STATES

1. Sleep-related disorders
2. Mood swings
3. Neurodegenerative disorders
4. Inflammation, obesity, and colon cancer

### About the orexin system

Orexin A is a neuropeptide composed of 33 amino acids with an amino(N)-terminal pyroglutamyl residue, two

intra-chain disulphide bonds and carboxy (C)-terminal amidation, while Orexin B is a linear neuropeptide sized 28 aminoacids, C-terminallyamidated.<sup>[21]</sup>

These are G protein-coupled receptors that have 7-transmembrane domains and some similarity to other neuropeptide receptors. OX1R and OX2R are strongly conserved across mammals, with 94% identity in the amino acid sequences between humans and rats.<sup>[22]</sup> The functions of orexin system is depicted in fig5.

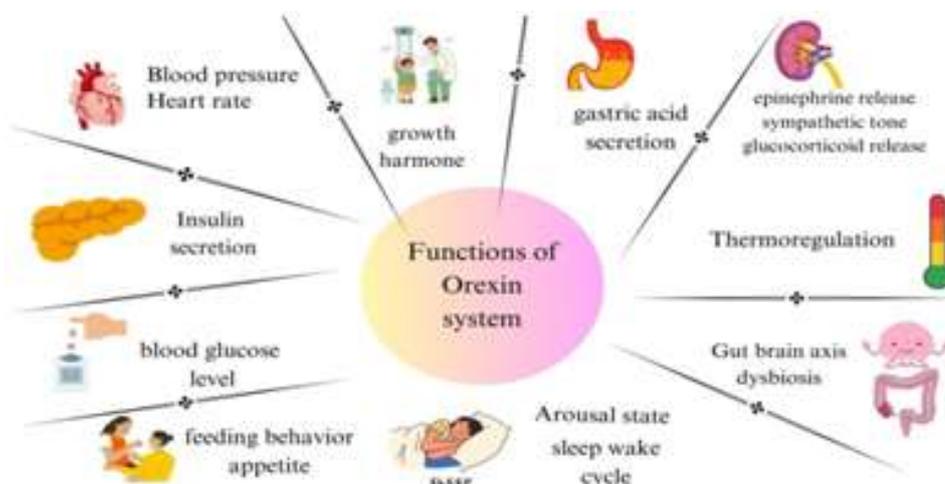


Fig. 5: Functions of orexin system.

### Categories of orexin antagonists are of two types

- Single orexin receptor antagonists (SORAs) and
- Dual orexin receptor antagonists (DORAs).

### OX1R

Of the accessible SORAs, SB-334867 was the main medication intended to specifically antagonize OX1R (This SORA can balance the suppression of REM rest after ICV implantation of OXA in rats.<sup>[23]</sup> In any case, it doesn't diminish alertness, or increment how much time spent in rest, nor does it ' reduce sleep latency without anyone else at any given dose.<sup>[24]</sup>

### OX2R

Type 2 orexin receptors are specifically communicated both in the PVN and the TMN. PVN is essential for the HPA, and the overactivation of the HPA has been proposed to be engaged with the etiology of PI. Keeping

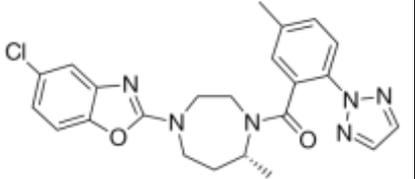
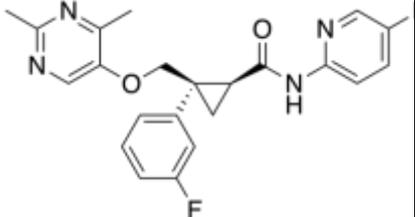
the orexinergic boosts to the HPA could assist with the advancement of the endless cycle proposed before. Moreover, the TMN, a histaminergic core, plays a significant part in the excitement impact saw after orexinergic feeling.<sup>[25]</sup>

### DORAs

It had been for quite some time thought that antagonizing both orexin receptors would inspire the most impressive rest advancing impacts; in this way, a significant number of theexaminations around orexin antagonist have focused in on DORAs. Up to this point, proof has shown this to be the situation to the point that DORAs are the orexin antagonists as of now going through clinical preliminaries with the expectation that they will be endorsed by the FDA for the treatment of sleep deprivation.<sup>[26]</sup> The market formulations of Daridorexant are enlisted in table 3.

Table 3: Marketed formulations of Antagonists of dual orexin receptors.

DRUG	OTHER NAME	BRAND NAME	DRUG CLASS	Structure
Daridorexant	Nemorexant	Quviviq	Hypnotic, Sedative, Orexin receptor antagonist	

<b>Survorexant</b>	MK-4305	Belsomra	Hypnotic, Sedative, Orexin receptor antagonist	
<b>Lemborexant</b>	E-2006	Dayvigo	Hypnotic, Sedative, Orexin receptor antagonist	

### PHARMACOLOGY

In clinical preliminaries stages it was accounted for that daridorexant further developed rest beginning and rest support, and patient-announced absolute rest time. Patient detailed day time lethargy was likewise supposedly diminished. Be that as it may, at clinically applicable fixations doesn't tie to the maltreatment related CNS targets.<sup>[27]</sup>

As indicated by the review reports, the affinities of daridorexant for the orexin receptors are 0.47nM for OX1 receptor and 0.93nM for the OX2 receptor.<sup>[1]</sup> Its Kb for human orexin receptors have been accounted for to be 0.5 Nm for the OX1 AND 0.8Nm for the OX2 receptor. Consequently, daridorexant is equipotent in its opposition of orexin receptors. It is exceptionally particular for the orexin receptors over many targets.<sup>[1,10,12]</sup>

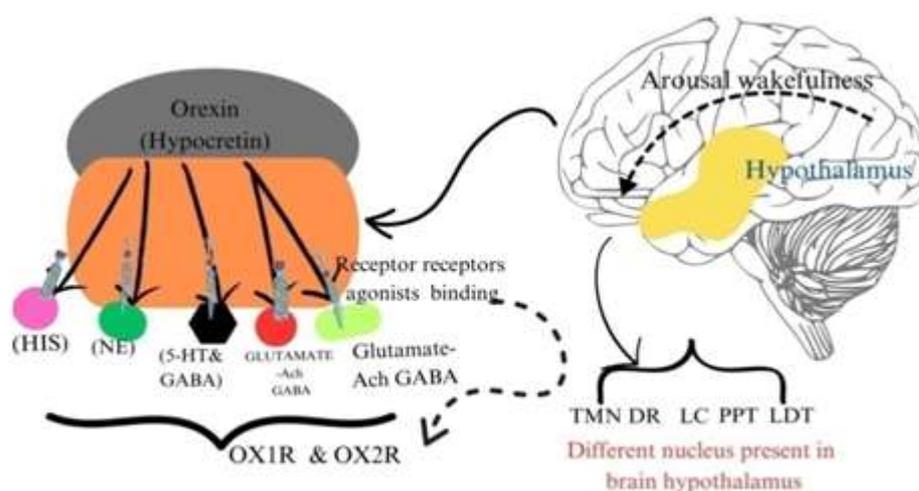
### MECHANISM OF ACTION

Research suggests that orexin signaling may change with age, and this has been implicated in age-related sleep disturbances.<sup>[28]</sup> The endogenous orexin neuropeptides

are involved in the regulation of sleep-wake cycle and act to promote wakefulness.<sup>[1,29]</sup> As deficiency of orexin signaling is thought to be the primary cause of the sleep disorder narcolepsy and disturbances in orexin signaling may involve in insomnia.<sup>[1]</sup> By blocking the actions of orexins and modulating sleep-wake cycles, orexin receptor antagonists like daridorexant which reduce wakefulness and improve sleep.<sup>[1,12,28]</sup> The sleep promoting effects of dual orexin receptor antagonists are thought to be mediated specifically by blocking the OX2 receptor in the lateral hypothalamus.<sup>[1]</sup> The mechanistic approach showing the binding of receptors with antagonists are illustrated in fig 6.

### ADVERSE EFFECTS<sup>[32]</sup>

- Dizziness
- Feeling of constant movement of self or surroundings
- Headache
- Nausea
- Sensation of spinning



**Fig. 6: Mechanism of action showing binding of orexin receptors with OX1R & OX2R antagonists.**

### COMPLICATIONS

In choosing to utilize a medication, the dangers of taking the medication should be weighed against the great it will

do. There may be sure entanglements and state which might happen due to daridorexant, some of them is expressed underneath:

**Allergies**

On the off chance that you at any point had any uncommon or unfavorably susceptible response to this medication, telling your doctor is extremely important. Additionally illuminate to medical care proficient, in the event that you have some other sorts of sensitivities, for example, food sources, colors, additives and so on.<sup>[33]</sup>

**Pregnancy**

There are no data on the use of daridorexant in pregnant women. Animal studies did not indicate harmful effects with respect to reproductive toxicity. Consequently, Quviviq should be used during pregnancy only if the clinical condition of the pregnant woman requires treatment with daridorexant.

**Breastfeeding**

There are no satisfactory examinations in people for

deciding babies risk utilizing this prescription during breastfeeding.

**Fertility**

There are no data concerning the effect of exposure to daridorexant on human fertility. Animal studies indicate no impact on male or female fertility.

**Contraindications**

- Hypersensitivity to the active substance or to any of the excipients .
- Narcolepsy
- Concomitant use with strong CYP3A4 inhibitors. The data showing the drug-interactions with daridorexant is given in table 4.

**Table 4: Drugs that interact with daridorexant.**

S.No.	Drugs	Interactions	Effects	Reference
1.	CYP3A4 inhibitors	Intake with daridorexant 25 mg	Increased daridorexant parameters AUC and Cmax by 2.4 times and 1.4 times.	[30]
2.	CYP3A4 inducers	Intake with efavirenz (600 mg once daily)	Decreased daridorexant exposure parameters AUC and Cmax by 61% and 35%, respectively.	[30]
3.	Gastric pH-modifiers	Intake with famotidine (40 mg)	Decreased daridorexant Cmax by 39% while AUC remained unchanged.	[30]
4.	Opioid pain or cough relievers	Codeine, marijuana, alcohol	Can cause slow breathing and drowsiness.	[31]
5.	Sedatives	Benzodiazepines, tricyclic-depressants	Increase the risk of CNS depression and daytime impairment	[31]

**Precautions for use<sup>[34]</sup>**

1. Patients should be cautioned about drinking alcohol during treatment.
2. Sleep paralysis and hypnologic/hypnopompic hallucinations can occur, mainly during the first weeks of treatment. Symptoms similar to mild cataplexy have been reported with dual orexin receptor antagonists. Prescribers should explain this to patients and should consider discontinuing in case events occur.
3. Use carefully in patients exhibiting symptoms of depression.
4. Use carefully in patients with psychiatric comorbidities due to limited efficacy and safety data.
5. Daridorexant did not have significant respiratory effects in patients with mild or moderate COPD.

**CONCLUSION**

Daridorexant allowed human beings to doze off quicker and to live asleep longer. We need to better apprehend if there are any long-time period consequences. Orexin receptors have extra or less become a fascinating goal for the improvement of therapeutics following the current approvals. As of now, the orexin receptor is known to the

level of drug discovery and further objectives exploration handiest in veryselective ailment states like insomnia and addiction. More studies are required to identify the precise neuronal website online worried as opposed to a generalized speculation. Similarly, assessment of OXR antagonists is needed in a specific organization of insomnia instances like co-morbidities, liver, renal impairment, and other coexisting psychiatric problems. Daridorexant, a DORA, turned into observed, way to an excessive drug discovery program geared toward optimizing each the efficacy and pharmacokinetic profile of a snooze-selling agent. Consistent with different DORAs, daridorexant is likewise anticipated to maintain cognitive characteristic, to have very low abuse capability, and to no longer set off tolerance or rebound following chronic use, as a result overcoming the various boundaries associated with greater traditional hypnotic medications.

Current pharmacological options for the remedy of continual insomnia do no longer meet the desires for all patients. But targeting the orexin represents a promising healing alternative. Future research will want to set up the protection of this compound in patients after longer

period of treatment and discover the feasible development of dependence or abusability.

## REFERENCES

- Roch C, Bergamini G, Steiner MA, Clozel M. Nonclinical pharmacology of daridorexant: a new dual orexin receptor antagonist for the treatment of insomnia *Psychopharmacology*, 2021; 238(10): 2693-2708.
- Winrow CJ, Renger JJ. Discovery and development of orexin receptor antagonists as therapeutics for insomnia *Br J Pharmacol*, 2014; 171(2): 283-93.
- Chieffi S, Carotenuto M, Monda V, Valenzano A, Villano I, Precenzano F, Tafuri D, Salerno M, Filippi N, Nuccio F, Ruberto M. Orexin system: the key for a healthy life. *Frontiers in physiology*, 2017; 8: 357.
- Krystal AD, Prather AA, Ashbrook LH. The assessment and management of insomnia: an update *World Psychiatry*, 2019; 18(3): 337-352.
- Roth T. Insomnia: definition, prevalence, etiology, and consequences *J Clin Sleep Med.*, 2007; 15: 3.
- Benca RM. Diagnosis and treatment of chronic insomnia: a review *Psychiatr Serv*, 2005; 56(3): 332-43.
- 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(2): e12782.
- Nie T, Blair HA. Daridorexant in insomnia disorder: A profile of its use. *CNS Drugs*, 2023; 37(3): 267-274.
- Jacobson LH, Hoyer D, de Lecea L. Hypocretins (orexins): the ultimate translational neuropeptides *J Intern Med.*, 2022; 291: 533-56.
- Bhaskar S, Hemavathy D, Prasad S. Prevalence of chronic insomnia in adult patients and its correlation with medical comorbidities *J Family Med Prim Care*, 2016; 5(4): 780-784.
- Ziemichoid W, Grabowska K, Kurowska A. A comprehensive review of Daridorexant, A dual orexin receptor antagonist a new approach for the treatment of insomnia. *Molecules*, 2022; 27(18): 6041.
- Markham A. Daridorexant: First approval. *Drugs*, 2022; 82: 601-607.
- Global Insomnia Statistics in 2022 & 2024. <https://www.helsestart.no/news/global-insomnia-statistics>.
- Lie JD, Tu KN, Shen DD, Wong BM. Pharmacological Treatment of Insomnia. *PT*, 2015; 40(11): 759-71.
- Madaan V, Sharma A, Sharma V. Daridorexant A New Drug Approach In Insomnia Disorder- A Review *Dickensian J.*, 2021; 21(12): 274-279.
- Dos S JBR, da silva MRR. Daridorexant for the treatment of insomnia disorder: findings and implications. *Eur J. Clin Pharmacol*, 2022; 78(11): 1749-1761.
- Prober DA. Discovery of Hypocretin/Orexin Ushers in a New Era of Sleep Research *Trends Neurosci*, 2018; 41(2): 70-72.
- Subramanian S, Ravichandran M. Orexin receptors: Targets and applications. *Fundam Clin Pharmacol*, 2022; 36(1): 72-80.
- Zammit G, Dauvilliers Y, Pain S, Sebok 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.
- Mignot E, Mayleben D, Fietze I, et al. 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(2): 125-139.
- Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities, *Annu Rev Pharmacol Toxicol*, 2011; 51: 243-266.
- Lee JH, Bang E, Chae KJ, Kim JY, Lee DW, Lee W. Solution structure of a new hypothalamic neuropeptide, human hypocretin-2/orexin-B, *Eur J Biochem*, 1999; 266: 831-39.
- Sakurai T, Amemiya A, Ishii M, Matsuzaki I, Chemelli RM, et al. Orexins and orexin receptors: a family of hypothalamic neuropeptides and G protein-coupled receptors that regulate feeding behavior *Cell*, 1998; 92: 573-85.
- Morairty SR, Revel FG, Malherbe, P, Moreau JL, Valladao D, Wettstein JG, et al. Dual hypocretin receptor antagonism is more effective for sleep promotion than antagonism of either receptor alone. *PLoS ONE*, 2012; 7: e39131.
- Smart D, Sabido-David C, Brough SJ, Jewitt F, Johns A., Porter RA, et al. The first selective orexin-1 receptor antagonist *Br J Pharmacol*, 2001; 132: 1179-1182.
- Lebold T, Bonaventure P, and Shireman BT. Selective orexin receptor antagonists *Bioorg Med. Chem. Lett.* 2013; 23: 4761-4769.
- Muehlan C, Vaillant C, Dingemans J. The orexin story and orexin receptor antagonists for the treatment of insomnia. *J Sleep Res.*, 2023; 32(6): e13902.
- Nixon JP, Mavanji V, Butterick TA, Billington CJ, Kotz CM, Teske JA. Sleep disorders, obesity, and aging: the role of orexin *Ageing Res Rev.*, 2015; 20: 63-73.
- FDA Approves Daridorexant for treatment of insomnia. <https://www.pharmacytimes.com/view/fda-approves-daridorexant-for-treatment-of-insomnia>.
- Quviviq Epar Product Information pdf. Idorsia Pharmaceuticals US., 2022, <http://www.ema.europa.eu/en/medicines/human/epar/quviviq>.
- Park J, Render KP, Cates DW. Daridorexant: Comprehensive Review of A New Oral Agent for the Treatment of Insomnia *The Annals of Pharmacotherapy*, 2023; 57(9): 1076-1087.
- QUVIVIQ EPAR Product Information pdf. Idorsia

Pharmaceuticals US 2022.  
<http://www.ema.europa.eu/en/medicines/human/epar/quiviq>.

33. Quviviq- daridorexant tablet, film coated. DailyMed. 23 March 2022.
34. Daridorexant(OralRoute)sideeffects-mayoclinic.<https://www.mayoclinic.org/drugs-supplements/daridorexant-oral-route/side-effects/drg-20528341?p=1>