Review Article

Lemborexant: A Novel Orexin Antagonist for Insomnia

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ABSTRACT

Adequate sleep is essential for optimal physical and mental health. Insomnia, the most common sleep disorder, is defined as the subjective perception of difficulty in onset and maintenance of sleep despite adequate opportunity. Currently available hypnotic agents target GABA (benzodiazepines and z-drugs), melatonin, or histamine. Traditional sedative-hypnotic drugs for patients with insomnia are complicated by their safety profiles. Orexins are neurotransmitters that regulate the sleep-wake cycle. Dual orexin receptor antagonists (DORAs) function by blocking both the orexin1 and orexin 2 receptors. Targeting the orexin system is an alternative approach to inducing and maintaining sleep. Lemborexant is a DORA that significantly improves mean sleep efficiency, and shortens sleep latency and wake after sleep onset (WASO) in insomnia patients. Adverse effects include somnolence, fatigue, headache, and abnormal dreams. Its discontinuation is not associated with rebound insomnia or withdrawal effects. It is a welcome addition to the options available for treating insomnia.

Keywords: DORA, Insomnia, Lemborexant, Orexin.

INTRODUCTION

Sleep is a basic physiological, yet a complex neurobiological phenomenon. Sleep plays a crucial role in regulating metabolism, memory consolidation, and decreasing mental fatigue.[1] Sleep is an active neurobehavioral state controlled by a complex interaction between wake-promoting neurotransmitters acetylcholine, norepinephrine, serotonin, dopamine, glutamate, and orexin/hypocretin and sleep-promoting transmitters-GABA and galanin.[2]

Sleep deprivation impacts behavior, mood, cognitive performance, as well as motor function of the body.[1] Diagnostic and Statistical Manual of Mental Disorders (DSM) defines insomnia as difficulty with initiating and maintaining sleep for 3 nights/week for 3 months. Underdiagnosed and under treated, insomnia is a risk factor for disorders like depression, anxiety, suicidal tendencies, substance use, hypertension, and diabetes.[3]

Impaired work performance, work-related or vehicle accidents, and poor quality of life are the consequences of insomnia.[4] Worldwide, the prevalence of insomnia ranges from 10 to 30%.[4] Certain subsets of the population show a higher prevalence. Chronic insomnia is more common in older adults, and based on phases of night, initial insomnia is prevalent in 15%-45% while middle insomnia is found in 20%-65%, and late insomnia in 15%-54%.[5] Women and persons with comorbid medical and psychiatric conditions are more likely to suffer from insomnia.[6] This review discusses the pharmacological aspects of Lemborexant, an orexin antagonist approved by the FDA for the treatment of insomnia.

Pharmacotherapy of Insomnia

Clinical guidelines state that non-pharmacological approaches such as cognitive behavioral therapy should be the first-line treatment for chronic insomnia.[7] Choice of medication should be based on the patient's age, sleep-related symptoms, comorbid conditions, reproductive status, and work schedules.[6]

Pharmacotherapy of insomnia includes benzodiazepines (BZDs), non-benzodiazepine receptor agonists-z drugs, and melatonin agonists. Table depicts the FDA-approved hypnotics and their side effects. Besides tolerance and dependence, BZDs are associated with side-effects of daytime sleepiness, rebound insomnia, cognitive impairment, anterograde amnesia, increased risk of falls, and teratogenic effects in pregnant women. BZDs should

be avoided in elderly patients, as they can cause psychomotor retardation, paradoxical inhibition, delirium, and falls resulting in injuries.[8] Abuse potential and the availability of better alternatives have decreased the use of these drugs.[9]

The most commonly prescribed z-drugs have advantage of quicker onset and shorter duration of action, but carry a risk of serious injury due to sleep behaviors such as sleep-walking.[10] Their adverse effects are still being recognized and there is lack of clear-cut guidelines for treatment of insomnia, especially in certain subsets of population, such as young adults.

Melatonin plays an important role in regulating the light-dark cycle and controls the circadian rhythm. Ramelteon is a FDA-approved melatonin agonist recommended for patients with sleep onset difficulty. It has few side effects-dizziness, nausea, and fatigue. It is not associated with cognitive or psychomotor effects.[8] Tricyclic antidepressants such as Doxepin, a strong histamine H1 receptor antagonist, is recommended for insomnia with difficulty in sleep maintenance.[6] Other sedating antihistaminics, antidepressants, anxiolytics, and atypical antipsychotics are off-label treatments for insomnia, used when there is a comorbid condition for which they are indicated.[6,9]

Mechanism of Action

The orexin (OX) system-important for circadian control of the sleep and wake cycle- comprises of two neuropeptides-orexin A and B and two receptors -OX1R and OX2R. Orexin-producing neurons in the lateral hypothalamic region have widespread projections in the CNS like the locus coeruleus, the dorsal raphe the basal forebrain, and the cerebral cortex and work to stabilize the wake state. While orexin A binds to both OX1R and OX2R, orexin B only binds to OX2R.

Table : List of FDA-approved drugs for the treatment of insomnia and their common adverse-effects

S.No.	Name of the hypnotic drug	Half-life (hours)	Dose (mg)	Adverse effects
1.	**Benzodiazepine receptor agonists**			
a).	Estazolam	10-24	0.5-2	Somnolence, dizziness, abnormal coordination
b).	Flurazepam	47-100	15-30	Dizziness, drowsiness, loss of coordination, falls
c).	Quazepam	39-73	7.5-15	Drowsiness, headache
d).	Temazepam	3.5-18.4	7.5-30	Dizziness, drowsiness, light headedness, coordination difficulty
e).	Triazolam	1.5-5.5	0.125-0.25	Dizziness, drowsiness, headache, coordination difficulty, pins and needles
2.	**Non-Benzodiazepine receptor agonists**			
a).	Eszopiclone	6	1-3	Unpleasant taste, headache, somnolence, infections, dry mouth
b).	Zaleplon	1	5-10	Dizziness, drowsiness, light headedness, paresthesia, coordination difficulty
c).	Zolpidem	2.6	5-10	Dizziness, drowsiness, diarrhea
d).	Zolpidem ER	2.8	6.25-12.5	Headache, somnolence, dizziness
e).	Zolpidem SL	2.5	1.75-3.5	Dizziness, drowsiness
3.	**Melatonin receptor agonist**			
a).	Ramelteon	2.5	8	Somnolence, dizziness, fatigue
4.	**Dual orexin receptor antagonists**			
a).	Suvorexant	15	5-20	Somnolence, headache, dizziness
b).	Lemborexant	17-19	5-10	Somnolence, headache, fatigue

ER= extended release; SL= sublingual

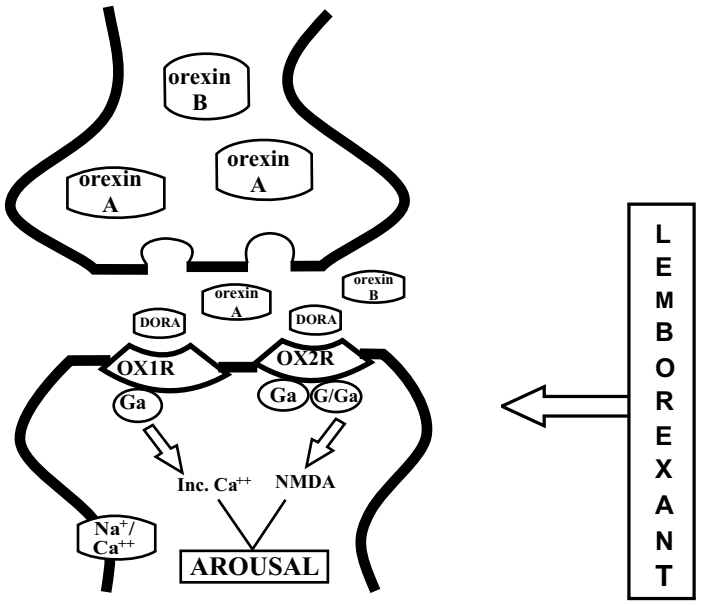

Figure: Mechanism of action of Lemborexant. **Orexinergic neurons of lateral hypothalamus produce the orexin neuropeptides-A and B. Lemborexant, a dual orexin receptor antagonist (DORA) blocks the action of orexin A and orexin B on both the receptors-orexin 1 receptor (OX1R) and orexin 2 receptor (OX2R) and decreases the signaling further down the cascade that leads to arousal state.**

NMDA- n methyl d aspartate.

Orexin antagonists block the typical wake-promoting actions of the orexin system. Suvorexant, the first dual orexin receptor antagonist (DORA), was introduced in 2014 as a schedule IV drug.[6] Suvorexant blocks orexin's stimulation of histaminergic neurons.[11] Lemborexant, a DORA, is a reversible competitive antagonist that binds rapidly to both OX1R and OX2R (Figure). Lemborexant binds and dissociates rapidly from orexin receptors, in contrast to other orexin receptor antagonists. A stronger inhibition of OX2R than OX1R promotes non-rapid eye movement (NREM) sleep.

Pharmacokinetics

Intake of drug with food may delay its action. Lemborexant has a volume of distribution of 1970 L and a half-life of 17 to 19 hours. Its major metabolites - M4, M9, and M10 (major circulating metabolite), are physiologically inactive. It is excreted in both the feces (57.4%) and the urine (29.1%). It should be avoided in severe hepatic impairment. Being primarily metabolized by CYP3A4, it can interact with alcohol, CYP3A4 inducers and inhibitors, CYP2B6 substrates, and CNS depressants.[12]

Dosage: Lemborexant is supplied as 5 and 10 mg tablets. It should be started at 5 mg before going to bed and increased to 10 mg, if needed.

Clinical trials

A one-month comparative study of Lemborexant, placebo, and Zolpidem tartrate (6.25 mg, extended-release) in patients aged 55 and above, SUNRISE 1, evaluated latency to persistent sleep (minutes from lights off to the first 10 minutes of non-wakefulness, measured by polysomnography). The least-squares geometric means (LSM) treatment ratio was statistically significant for Lemborexant compared to the placebo. Subjective Sleep Efficiency (sSE)- the proportion of time spent asleep, Wake-After-Sleep Onset (WASO)- the minutes of wake from the onset of persistent sleep, and subjective Sleep Onset Latency (sSOL), reported as minutes from the time the subject attempted to sleep until sleep onset were evaluated. Lemborexant improved sSE by providing >60 minutes of sleep per night and reduced WASO by >45 minutes. Lemborexant therapy provided a statistically significant benefit in sSOL and WASO in the second half of the night compared with Zolpidem therapy.[13]

Results from SUNRISE 2 trial conducted on adults, after 6 months, showed median reductions in sSOL with Lemborexant 5 mg (-21.81 minutes) and 10 mg (-28.21 minutes) to be statistically significant compared to placebo (-11.43 minutes) ($p<.0001$). 80% improvement in sSE was also seen with Lemborexant 5 mg (14.19%, $p = .0001$) and 10 mg (14.31%, $p<.0001$) - an important goal of insomnia treatment; sWASO was found to be significantly reduced with Lemborexant 5 mg (-46.75 minutes, $p= .0005$) and 10 mg (-41.95 minutes, $p = .0105$).[14]

Adverse Effects

The commonly observed side effects are somnolence, fatigue, headache, abnormal dreams or nightmares, nasopharyngitis, and influenza. Sleep paralysis, hypnagogic hallucinations, and complex sleep behavior have been observed in less than 2% of patients. Caution is advised while driving especially with higher doses. The risk of somnolence may be increased in mild hepatic or severe renal impairment.

In a systematic review and network meta-analysis, based on sTSO at the end of one month, Lemborexant was more effective than Suvorexant and Zolpidem for patients with difficulty falling asleep. However, there was no difference in efficacy between Suvorexant and Lemborexant based on other parameters. Zolpidem showed a higher discontinuation rate compared to both DORAs. As lemborexant (10 mg) showed a slightly higher incidence of somnolence and discontinuation rate than Suvorexant, a 5 mg dose should be initiated.[15] Cost comparison show that DORAs-Lemborexant ($11/tablet) and Suvorexant ($13/tablet) are priced higher than z-drugs (Rs.6/tablet). Although data regarding cost in Indian rupees for the orexin antagonists was unavailable, they are expensive drugs.

Current status

The FDA has approved Lemborexant in 2019 for the treatment of insomnia characterized by difficulties with sleep onset and/or maintenance. The permission for import and marketing of Lemborexant in India was given in 63rd subject expert committee (SEC) meeting of Central Drugs Standard Control Organization (CDSCO) on the condition that phase IV trials be conducted.[16] DORAs score over conventional hypnotics in better preservation of sleep architecture as they promote sleep without disrupting the normal circadian rhythm, greater objective efficacy, reduced impact on motor coordination, memory, and cognition.[10] They are considered better for sleep maintenance and have lesser residual sleepiness, anterograde amnesia, rebound insomnia, complex sleep-related behaviors, and abuse potential.[10] It has been proposed that an increase in endogenous orexin levels in the morning may off-set some residual effects of receptor blockade.[12,17,18] Additionally, GABAergic drugs impair the ability to wake to important stimuli whereas DORA retains the desired ability to awaken to emotionally salient acoustic stimuli (e.g.-home alarm) while ignoring irrelevant stimuli (e.g.-fan humming).[2,19]

A good efficacy and absence of side-effects of GABAergic drugs such as tolerance, dependence, withdrawal effects, rebound insomnia, or next-day postural stability and memory, validates the success of the novel approach to treat insomnia.[10] Orexin antagonists do not impair motor function.[20] Multiple clinical studies were evaluated to demonstrate that Lemborexant has minimal effects on next day performance.[21] Also, Lemborexant was demonstrated to be safe for use in obstructive sleep apnea.[22] However, next day somnolence (related to a long half-life), potential for drug interactions, non-superiority to Suvorexant, and increased cost are associated drawbacks. At present, it may not replace the more popular z-drugs but it holds promise for patients who do not tolerate or respond to conventional hypnotics.[21] Orexin antagonists with short half-lives (Daridorexant, Seltorexant) are in phase 3 trials. A multicenter pilot study is underway to assess the optimum dose for transition from Zolpidem to Lemborexant.[23] Lemborexant is currently being evaluated in irregular sleep-wake rhythm disorder in Alzheimer's dementia.[10]

CONCLUSION

Insomnia is an important and common public health problem. Patients report difficulty with onset or maintenance of sleep. Most of the available hypnotics are associated with adverse effects, paving the research for new targets and new molecules. The orexin antagonist, Lemborexant, is the latest addition to the armamentarium of hypnotic drugs. It is devoid of the diverse adverse effects associated with GABA-modulating drugs such as on cognition, memory, and motor functions. Future research

and more real-world data will establish its place in the therapy of insomnia.

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