Lemborexant: mechanism, efficacy, and clinical implications

RM Moosa-Battey

Department of Pharmaceutical Sciences, Tshwane University of Technology, South Africa

Corresponding author, email: batteyrm@tut.ac.za

Abstract

Lemborexant, a dual orexin receptor antagonist (DORA), has emerged as an effective treatment for insomnia by modulating the orexin signalling pathway, which is critical in maintaining wakefulness. This review explores lemborexant's mechanism of action, clinical efficacy, pharmacokinetic profile, safety, and tolerability in treating sleep disorders, with a focus on insomnia. Through a synthesis of recent clinical trials and comparative studies, this article provides a comprehensive view of lemborexant's therapeutic role and potential in addressing the unmet needs of patients with sleep disturbances.

Keywords: lemborexant, insomnia, orexin receptor antagonist

https://doi.org/10.36303/SAPJ.1127

Introduction

Insomnia, a prevalent sleep disorder, affects millions globally and is associated with significant impairment in quality of life, mental health, and productivity.[1] Insomnia is frequently treated with benzodiazepine receptor agonists, which include benzodiazepines and non-benzodiazepine "Z-drugs".[1] Short-term (no more than three months) randomised controlled trials have shown that the "Z-drugs", such as zolpidem, zaleplon, and eszopiclone, are effective in improving sleep outcomes for individuals with insomnia.[1] These treatments might not be the best option for long-term care; there are some long-term data (six months or longer) available.[1] Lemborexant, a novel dual orexin receptor antagonist (DORA), represents a new approach to managing insomnia by targeting the orexin system, a key regulator of the sleep-wake cycle.[1]

By encouraging wake drive and arousal, the orexin/hypocretin system contributes significantly to the regulation of the sleep/wake cycle. It has been suggested that insomnia is a hyperarousal disorder.[2] By inhibiting orexin-mediated wake drive, DORAs – a class of agents that target the orexin system – are believed to reduce wakefulness and promote sleep. Furthermore, compared to benzodiazepine receptor agonists, DORAs might have a better safety record.[2]

Mechanism of action

Lemborexant works by selectively antagonising orexin receptors OX_1R and OX_2R, which play essential roles in promoting wakefulness.[3] The orexin signalling pathway is involved in the central nervous system's ability to maintain wakefulness.[3] By blocking the activity of orexin, lemborexant reduces arousal and helps facilitate the onset and maintenance of sleep.[3] This mechanism differs from traditional hypnotics, offering an alternative for patients who may not tolerate or respond well to other sedative-hypnotics.[3]

Pharmacokinetics and pharmacodynamics

Lemborexant has a favourable pharmacokinetic profile, with a half-life of approximately 17–19 hours, supporting its use as a once-daily bedtime medication.[4] It is rapidly absorbed, reaching peak plasma concentrations within 1–3 hours post-administration.[4] Studies indicate that lemborexant is metabolised primarily in the liver by cytochrome P450 enzymes, CYP3A4 being the primary pathway.[4] This drug's pharmacodynamics reflect a significant and sustained antagonism of orexin receptors, contributing to improved sleep duration and quality without substantial residual daytime sedation.[4]

Clinical efficacy

Efficacy in treating insomnia

Lemborexant has demonstrated efficacy in treating both sleep onset and sleep maintenance insomnia. Key clinical trials, such as SUNRISE-1 and SUNRISE-2, showed significant improvements in sleep parameters:

- **SUNRISE-1**: A randomised, double-blind, placebo-controlled trial comparing lemborexant to zolpidem.[5] Results indicated that lemborexant significantly improved sleep onset and maintenance, with fewer adverse cognitive effects than zolpidem.[5]
- **SUNRISE-2**: A six-month study assessing long-term efficacy and safety of lemborexant.[6] This trial confirmed the sustained effectiveness of lemborexant in improving sleep quality over a prolonged period.[6]

Safety and tolerability

Lemborexant has shown a favourable safety profile with minimal risk of residual effects or dependency. Common adverse effects include headache, somnolence, and, less frequently, sleep paralysis.[7] Compared to other sedative-hypnotics, lemborexant poses a lower risk for adverse events related to falls, balance issues, and next-day drowsiness, especially in elderly populations.[7] While lemborexant's profile is generally positive, caution is advised in patients with hepatic impairment due to its hepatic metabolism.[7]

Potential clinical implications

1. Insomnia management in the elderly

The elderly population often experiences sleep disturbances that are difficult to treat due to sensitivity to drug-related adverse events.[7] Lemborexant's reduced cognitive and psychomotor impairment profile makes it an appealing option for insomnia management in this demographic, as it offers symptom relief without significantly increasing fall risk or next-morning grogginess.[7]

2. Addressing comorbid insomnia and mental health disorders

Insomnia frequently coexists with psychiatric disorders such as depression and anxiety, conditions often exacerbated by poor sleep quality.[8] Lemborexant may offer benefits for these patients by providing effective sleep management with lower risk of mood alteration or dependence.[8]

3. Expanding treatment options in patients unresponsive to traditional hypnotics

Patients who experience tolerance, dependence, or adverse effects from traditional sleep medications may benefit from lemborexant due to its novel mechanism.[5] Lemborexant can thus be considered a second-line option in patients for whom other hypnotics are unsuitable or ineffective.[5]

Challenges and future directions

While lemborexant presents numerous benefits, ongoing research is necessary to address some limitations and areas for improvement. Long-term studies exploring the chronic use of lemborexant are needed to fully understand its long-term effects on sleep architecture and dependency potential. Additionally, studies focusing on populations with comorbid conditions and different ethnic groups could provide more comprehensive insights into the drug's efficacy and safety.

Further exploration into combination therapies with lemborexant could also be valuable, particularly for patients with complex sleep and mental health needs. As research progresses, more data on optimal dosing, safety in diverse populations, and comparative effectiveness with emerging sleep aids will help refine lemborexant's place in clinical practice.

Conclusion

Lemborexant represents a significant advancement in the pharmacological management of insomnia, offering effective relief for sleep onset and maintenance issues through its dual orexin receptor antagonism. Its favourable safety and tolerability profile, especially in elderly patients, positions it as a promising alternative to traditional hypnotics. As insomnia remains a challenging condition with broad impacts on health and quality of life, lemborexant offers a new avenue for addressing sleep disturbances in a way that minimises many of the common risks associated with other sleep medications. Future studies will further clarify its role and broaden its application in the treatment of complex and chronic insomnia cases.

Conflict of interest

The author has no conflict of interest.

ORCID

RM Moosa-Battey https://orcid.org/0000-0002-1953-143X

References

1. Yardley J, Kärppä M, Inoue Y, et al. Long-term effectiveness and safety of lemborexant in adults with insomnia disorder: results from a phase 3 randomized clinical trial. Sleep Medicine. 2021;80:333-42. https://doi.org/10.1016/j.sleep.2021.01.048.
2. Arnold V, Ancoli-Israel S, Dang-Vu TT, et al. Efficacy of lemborexant in adults ≥ 65 years of age with insomnia disorder. Neurology and Therapy. 2024;13(4):1081-98. https://doi.org/10.1007/s40120-024-00622-9
3. Zammit G, Krystal A. Evaluating lemborexant for the treatment of insomnia. Expert Opinion on Pharmacotherapy. 2021;22(10):1235-43. https://doi.org/10.1080/14656566.2021.1902987.
4. Suzuki H, Hibino H. The effect of lemborexant for insomnia disorder. SAGE Open Medicine. 2021;9:205031212110390. https://doi.org/10.1177/20503121211039098.
5. 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. JAMA Network Open. 2019;2(12):e1918254. https://doi.org/10.1001/jamanetworkopen.2019.18254.
6. Inoue Y, Watanabe T, Takashima S, et al. Efficacy and safety of lemborexant in adults with insomnia: comparing Japanese and non-Japanese subgroups from the global, phase 3, randomized, double-blind, placebo-controlled SUNRISE 2 study. Journal of Clinical Sleep Medicine. 2021;17(5):1067-74. https://doi.org/10.5664/jcsm.9148.
7. Rosenberg R, Filippov G, LoPresti A, et al. safety of lemborexant in elderly subjects with insomnia: results from a phase 3 study (Sunrise 1). American Journal of Geriatric Psychiatry. 2019;27(3):S196-7. https://doi.org/10.1016/j.jagp.2019.01.109.
8. Katsuta N, Takahashi K, Kurosawa Y, et al. Safety and real-world efficacy of lemborexant in the treatment of comorbid insomnia. Sleep Medicine X. 2023;5:100070. https://doi.org/10.1016/j.sleepx.2023.100070.