Evaluation of the Effectiveness of Treating Insomnia with New Hypnotic Drugs - Eszopiclone and DORAs

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Abstract

***Objective**:* Insomnia is a disorder that frequently occurs in the adult population and leads to impaired functioning or a reduced quality of life for those affected. It can also have a significant impact on cognitive processes later in life. Consequently, there is an ongoing search for alternatives to the medications currently used to treat this condition. The primary aim of this article is to summarize the latest scientific research on the use of eszopiclone and DORAs (dual orexin receptor antagonists) in the treatment of insomnia. Numerous studies indicate that patients suffering from this condition benefit from their use, both in cases of primary and secondary insomnia.

***Views**:*
Insomnia is one of the most common reasons for patients visiting a doctor's office. Insomnia is a disorder characterized by a persistent feeling of dissatisfaction with the quantity or quality of sleep. Treatment of insomnia involves non-pharmacological methods, with cognitive-behavioral therapy being the most popular, as well as pharmacotherapy. In this article, we will analyze the effectiveness of treating insomnia with new sleep medications - eszopiclone and DORAs, based on the latest scientific works available on PubMed and Google Scholar.

Conclusions: Eszopiclone and DORAs are effective alternatives to current drugs used in the pharmacotherapy of insomnia.

***Keywords**:* eszopiclone, dual orexin antagonist, sleeping disorder, insomnia.

Introduction

Insomnia is a common disorder with significant health and economic implications. In the United States alone, annual losses due to this sleep disorder are estimated at $91.7 billion [1]. Most importantly, insomnia negatively affects not only physical health but also mental health and may increase the risk of cognitive impairment later in life [2]. Despite the undeniable effectiveness of cognitive-behavioral therapy, it may not always yield the desired results, and thus, there is sometimes a need for pharmacotherapy. The currently available pharmacotherapy does not meet all patients' needs, hence the ongoing search for new methods of treating insomnia. Dual orexin receptor antagonists (DORAs) and eszopiclone are new sleep medications.

Characteristics of Orexin Receptor Antagonists

Dual Orexin Receptor Antagonists (DORAs) are new drugs that block specific G-protein coupled receptors—orexin receptor 1 (OX1R) and orexin receptor 2 (OX2R) [3]. Orexin (hypocretin) is a neuropeptide discovered in 1998, with two neurochemical forms: orexin A and orexin B. Their main function is to maintain wakefulness in brain nuclei through continuous depolarizing effects [4]. Understanding the role of orexin in maintaining arousal has opened new therapeutic perspectives in treating various sleep disorders by modulating the orexin system. A substance designed as an orexin receptor antagonist could have sedative effects, making it a potential solution for treating insomnia.
In a 2009 study by Dugovic et al. [5] conducted on an animal model, it was demonstrated that blocking OX2R initiates and prolongs sleep. As a result, substances acting on both types of orexin receptors, their dual antagonists, were synthesized. In 2014, one of these substances, suvorexant, was approved by the Food and Drug Administration (FDA) for the treatment of insomnia [6]. In 2019, lemborexant received a positive opinion from the same organization, and in 2022, daridorexant followed.

Evaluation of the effects of treatment with orexin receptor antagonists

The aim of the study by Rosenberg et al. [7] was to compare the effects of lemborexant with placebo and zolpidem (a drug from the imidazopyridine group used in the treatment of insomnia since the late 1980s [8]). The study group consisted of women aged 55 years or older and men aged 65 years or older who met the criteria for insomnia according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM). Patients were administered 5 mg of lemborexant, 10 mg of lemborexant, 6.25 mg of zolpidem, or placebo. The effectiveness of the treatment was assessed based on sSOL (subjective sleep onset latency), which is the time reported in minutes from the attempt to fall asleep to actually falling asleep. Sleep maintenance was measured using subjective sleep efficiency (resulting from the ratio of total sleep time to time spent in bed) and sWASO (subjective wake-after-sleep onset). The results were as follows: compared to placebo and zolpidem therapy, lemborexant therapy reduced the time to fall asleep and improved sleep maintenance. However, lemborexant was not more effective than zolpidem in terms of subjective sleep efficiency or sWASO. Treatment with a representative of DORAs was well tolerated by patients, and they rated the therapy as effective in treating insomnia. A similar study was conducted by Moline M et al. [9]. In this study, lemborexant at doses of 5 mg and 10 mg extended total sleep time (TST), NREM (non-rapid eye movement) sleep phase, REM (rapid eye movement) sleep phase, and shortened the latency to REM sleep onset compared to placebo.

Beuckmann CT et al. [10] studied the effects of lemborexant therapy on sleep disturbances, wakefulness, and circadian rhythm related to Alzheimer's disease (AD). In this experiment, an animal model – SAMP8 mice – was used, with SAMR1 mice with a genotype resistant to aging as the control group (SAMP8 mice exhibit memory and learning deficits similar to those found in AD patients). The basis for this study was the fact that disturbances in circadian rhythm and sleep-wake cycles may be associated with the onset of Alzheimer's disease [11], and 45% of patients with this disease suffer from sleep problems [12]. The test mice were administered 30 mg/kg of lemborexant, and then plasma drug concentrations and orexin (OXA) concentrations in cerebrospinal fluid (CSF) were assessed. Vigilance was measured using EEG and EMG. The study also included the measurement of circadian rhythm through the observation of voluntary activity on a running wheel. Interesting effects beyond the basic action of lemborexant were demonstrated. In addition to the expected reduction in activity and extension of sleep during the rest period, it was also observed that the drug may lead to increased wakefulness and activity during the time when the body should naturally be active. Such an effect would be desirable in the treatment of AD patients. Summarizing this study, it provides evidence for the circadian rhythm-regulating action of orexin receptor antagonists. Moreover, the peak blood concentration of lemborexant for both groups occurred 0.25 h after drug administration, with higher concentrations in the control group (SAMR1 mice). OXA concentrations in CSF were elevated in both groups of mice, but more

pronounced in SAMP8 mice. This is significant because AD patients experience loss of orexin neurons due to tau protein accumulation [13]. The authors emphasize that further research is needed to explore the usefulness of DORAs in treating sleep and circadian rhythm disorders in AD patients.

Ikeda S et al. [14] analyzed the cost-effectiveness of lemborexant therapy compared to no treatment for insomnia, the use of suvorexant, or immediate-release (IR) zolpidem. This Japanese study was based on a model considering falls, traffic accidents, and work accidents. This study considered not only lemborexant (as a representative of "new DORAs") but also suvorexant, which was approved in Japan in 2014 for the treatment of insomnia. Ultimately, it was found that lemborexant is the most cost-effective drug: it is cheaper than the other aforementioned drugs, reduced sleep onset time, and better maintained sleep. Furthermore, it does not affect GABA receptor activity, leading to greater stability and less muscle relaxation, thus potentially reducing the risk of fractures from falls. Lemborexant doses do not need to be adjusted for age, as a population pharmacokinetic (PK) model based on clinical data indicated little correlation between adverse effects during treatment and drug exposure [15]. From the Japanese payer's perspective, lemborexant dominated in terms of cost-effectiveness over zolpidem, suvorexant, and no treatment

Evaluation of the efficacy of insomnia treatment with daridorexant was the subject of a retrospective analysis by Williams SG and Rodriguez-Cué D [16]. The study group consisted of patients with newly diagnosed insomnia and patients previously treated with other sleeping medications that were replaced with a representative of DORAs. Efficacy was measured using the Insomnia Severity Index (ISI) after at least 30 days of using daridorexant. The ISI is a 7-item self-report questionnaire used to assess the nature, severity, and impact of insomnia [17]. Based on patient responses, a score is obtained ranging from 0 to 28. The higher the score, the greater the severity of insomnia. The population consisted of 80 patients with a mean age of 53.5 years. The mean ISI score before using daridorexant was 18 points. After 30 nights of treatment, it dropped to 11. Furthermore, men experienced a greater reduction in this index than women (a decrease of 8.8 and 6.2, respectively). A more pronounced ISI reduction was also observed in the group taking daridorexant at a dose of 50 mg. At a dose of 25 mg, the mean ISI change was smaller (7.5 versus 5.1). The result did not reach statistical significance. Age, race/ethnicity, concomitant CPAP therapy, the number of previous therapies, and the duration of insomnia were also not statistically significant. Subjectively, 78.7% of patients reported improvement in daily functioning. There was also an improvement in subjective sleep assessment measured by four parameters: total sleep time (TST), sleep onset latency (SOL), wakefulness after sleep onset (WASO), and sleep efficiency (SE). An interesting case is of 6 out of 80 patients who switched from other sleeping medications (clonazepam or doxepin) to daridorexant. It turned out that they did not experience improvement. The authors point out that this may be related to the abrupt discontinuation of BZDs or rebound insomnia. Williams SG and Rodriguez-Cué D highlight the need for further research on DORAs.

Miyata S et al. [18] conducted a study aimed at evaluating the effectiveness of lemborexant treatment based on electroencephalography (EEG). Measurements were taken at patients' homes to objectively assess sleep after 4 and 12 weeks of treatment with this orexin receptor antagonist. The study population consisted of 45 people aged 50 or older living in Japan, who were not taking any medications during the study or had potentially stopped taking previous medications a week before data collection began. Lemborexant was administered at doses of 5 mg or 10 mg depending on the subjective severity of insomnia. The sleep parameters evaluated were latency to persistent sleep (LPS; the time elapsed to the start of a 12-minute period in which 10 minutes were recorded as sleep), WASO, TST, and SE. Patients also kept sleep diaries, from which subjective sleep parameters were obtained: sSOL, sWASO, subjective TST (sTST), and subjective SE (sSE). After 12 weeks of treatment, all evaluated parameters, both objective (SE, LPS, WASO, and TST) and subjective (sSOL, sWASO, sTST, sSE), improved. Improvement was also confirmed using the PSQI (Pittsburgh Sleep Quality Index) survey, completed by patients. PSQI is a self-report questionnaire assessing sleep quality over one month [19]. Home EEG monitoring also confirmed positive changes in SE.

Katsuta N et al. [20] evaluated the real-world effectiveness and safety of lemborexant in treating insomnia coexisting with other psychiatric disorders and also checked whether this drug helps reduce benzodiazepine (BZ) doses. The study group consisted of patients treated by a psychiatrist, diagnosed

with a psychiatric disorder according to DSM-5 (Diagnostic and Statistical Manual of Mental Disorders-5), prescribed lemborexant, and who had contact with the psychiatrist within 8 weeks of the first lemborexant prescription. Patients' BZ doses were reduced. Subsequently, the effects of the introduced changes were assessed based on the CGI-I scale (Clinical Global Impression Improvement), which is a seven-point scale where 1 means very much improved and 7 means very much worse. CGI-I was assessed from 1 to 8 weeks after lemborexant prescription. Patients with CGI-I scores of 1 to 3 were classified as responders, while those with CGI-I scores of 4 to 7 were classified as non-responders. Regarding the safety of the drug, 73.2% of patients in the responder group (419 out of 649 patients) did not report any adverse effects. As a result of this study, it was also found that lemborexant is effective in treating secondary insomnia in psychiatric disorders - most patients with such disorders were in the responder group. The described DORAs representative can also be used interchangeably with other hypnotics, showing effective action. Patients previously using BZ had their BZ doses reduced when lemborexant was introduced, which proved effective, allowing further reduction of benzodiazepine doses. In conclusion, lemborexant appears to be an effective and safe medication for treating insomnia coexisting with mental disorders, and it also facilitates the reduction of doses of sleeping medications.
The safety of lemborexant compared to placebo and zolpidem in the elderly was examined in a study conducted by Murphy P et al. [21]. Special attention was given to postural stability, auditory awakening threshold (AAT), and cognitive performance (cognitive performance assessment battery [CPAB]). CPAB is a computerized cognitive performance assessment system that consisted of 9 tasks assessing various aspects of memory and attention. As a result, it was possible to estimate strength of attention, continuity of attention, quality of memory, and speed of memory retrieval. Healthy women aged ≥ 55 years and healthy men aged ≥ 65 years were divided into four groups and given lemborexant at a dose of 5 mg (LEM5), lemborexant at a dose of 10 mg (LEM10), zolpidem (ZOL), or placebo (PBO). Results were collected after about 60 days. It was found that ZOL had a greater negative impact on postural stability than LEM and PBO. No differences were observed in AAT - neither LEM nor ZOL disrupted awakening with noise. LEM10 had a negative impact on memory and attention compared to PBO, while the lower dose of lemborexant did not show such an effect. After waking, patients taking LEM5 or LEM10 fell back asleep faster than those taking PBO. The authors highlight the safety issue of prescribed sleep medications, and lemborexant seems to be a favorable option in this regard.
Takaesu Y et al. [22] analyzed the effects of discontinuing lemborexant after long-term treatment of insomnia. Patients with a history of sSOL (defined as time in minutes from initial attempt to sleep) ≥30 min and/or sWASO (total minutes of wakefulness after initial sleep onset until getting out of bed) ≥60 min at least three times a week for the 4 weeks preceding qualification were included. For the first 2 weeks, patients were given placebo. Then these individuals were randomized 1:1:1 and took either placebo, LEM5, or LEM10 once daily. After 6 months, this population was divided into 2 groups receiving LEM5 or LEM10. The study population consisted of men and women aged ≥18 years (range: 18–88 years) with insomnia. In total, the administration of placebo or medication lasted 12 months, after which therapy was stopped and observation began. Withdrawal effects were measured by sSOL and sWASO. It was found that less than 20% of patients experienced worsening of insomnia after discontinuation of lemborexant, and improvement in sleep parameters persisted during the 2-week observation period. Accordingly, 83.7% and 84.1% of subjects did not report worsening in terms of sSOL and sWASO. This analysis proves that rebound insomnia is unlikely after abrupt discontinuation of lemborexat.

Characteristics of Eszopiclone Action

Eszopiclone (ESZ) is a hypnotic from the Z-drug class, specifically the (S)-isomer of zopiclone. Scientific studies indicate that it has a favorable safety profile and is well-tolerated by both younger and older individuals. Its use brings numerous benefits, including shortening sleep onset time, reducing the number of awakenings, shortening wake time after sleep onset, lengthening total sleep time, and improving sleep quality.
The mechanism of action of eszopiclone involves antagonism of GABA receptors. The drug is rapidly absorbed and distributed to body tissues, including the brain. It reaches maximum plasma concentration 1.0 to 1.6 hours after administration of a therapeutic dose of 3mg. Its half-life is approximately 6 hours.

Eszopiclone is metabolized in the liver to two metabolites: (S)-N-desmethylzopiclone and (S)-zopiclone-N-oxide, with 10% of the dose excreted unchanged in the urine. [23]
Studies conducted on rats have shown that eszopiclone, depending on the dose, lengthens the phase of light sleep and delta sleep during the active phase, while simultaneously shortening the REM phase. Moreover, sleep induced by eszopiclone differs from physiological sleep, which can be observed in EEG.[24]

Evaluation of Eszopiclone Treatment Effects

One of the first meta-analyses, covering 6 randomized studies involving 2809 patients, confirmed that the use of eszopiclone reduced the time of subjective sleep latency in participants. The speed of falling asleep was shortened in the first week of use and remained shorter than in the placebo group throughout the study period (6 months). In those using the medication, there was a reduction in the number of nighttime awakenings, as well as an improvement in subjective sleep time and its quality. These parameters contributed to a subjective improvement in daytime functioning, increased alertness, and better well-being. [25]
A review by Rösner S, Englbrecht C, and colleagues (2018) [26] based on 14 randomized, parallel-group trials (RCTs) of varying durations (short-term <4 weeks, medium-term > 4 weeks ≤ 6 months, and long-term treatment > 6 months) showed that patients using eszopiclone benefit regardless of age. In the group taking the medication, the time to fall asleep was reduced by an average of 12 minutes, and the time awake after falling asleep was reduced by 17 minutes, resulting in an increase in total sleep time of about 30 minutes. Two of the included RCTs lasted more than 6 months, and their results confirmed that the therapeutic benefits of eszopiclone use can persist in both the medium and long term. Importantly, discontinuation of therapy was not associated with withdrawal symptoms, although there were cases of relapse of sleep problems. [26]
A network meta-analysis and systematic review published in The Lancet in 2022 showed that patients with sleep disorders treated with sleep medications, including eszopiclone, benefited both in the short and long term compared to the control group. However, in direct comparison, after four weeks of use, eszopiclone was less effective than short-acting benzodiazepines. An important added value of this study was the evaluation of eszopiclone and lemborexant as substances with the best profile in terms of efficacy (sleep quality), acceptability (discontinuation for any reason), tolerance (discontinuation due to any adverse event), and safety (presence of at least one adverse event). [27]
The above studies address the problem of primary insomnia, but a significant number of patients struggle with secondary insomnia. In recent years, this problem has been recognized by the authors of the studies cited below. They focused on analyzing the effects of sleep medications in narrower groups, including individuals with nervous, cardiovascular, and digestive diseases.
Another meta-analysis, focusing on the pharmacotherapy of insomnia in post-stroke patients, analyzing 18 RCTs involving nearly 1650 patients, provides evidence suggesting that combination therapies based on eszopiclone improve patients' sleep quality. Clinically, the most effective was the combination of ESZ + XFZYC (xuefu zhuyu capsule). [28]
A prospective study conducted by Shuyu Huo et al., involving a group of 96 elderly patients suffering from Alzheimer's disease, showed that the problem of insomnia in this group could be alleviated. Compared to the control group, it was observed that individuals receiving eszopiclone (ESZ) had shorter sleep latency, and their sleep efficiency and quality improved. Additionally, cognitive functions in the studied group also increased – patients showed better orientation, improved language and counting abilities, as well as greater alertness and better memory. Eszopiclone therapy contributed to the improvement of self-care abilities.[29]
A randomized controlled trial conducted on 79 individuals suffering from migraines showed that a dose of 3 mg ESZ taken before bedtime increased the total sleep time by 48 minutes, reduced sleep latency by 13.9 minutes, and decreased the number of nocturnal awakenings by 0.2 compared to the control group. It was also observed that the use of the drug led to a reduction in daytime fatigue due to longer and more effective sleep. However, the intensity, frequency, and duration of headaches remained unchanged.[30]
The effectiveness of ESZ was also evaluated in a population of individuals with diagnosed heart failure (HF) and accompanying insomnia. Results of a cohort observational study showed that the choice of

sleeping medication plays a crucial role in patients' prognosis. Participants taking benzodiazepines (BDZ) showed a higher risk of HF exacerbation and rehospitalization, as well as a higher risk of cardiac death, compared to those taking so-called Z-drugs (zolpidem, zopiclone, and eszopiclone). The authors emphasized that pharmacotherapy is a modifiable factor that has a significant impact on patients' prognosis. Therefore, the conclusions of their study should serve as an impetus for further research and be implemented in clinical practice.[31]

In a four-week prospective study, the effect of eszopiclone on sleep disorders accompanying patients with functional dyspepsia (FD) was assessed. The aim was to evaluate the impact of sleeping medications on gastrointestinal symptoms in individuals with FD. Of the 16 participants who completed the study, nine received eszopiclone, while the others received zolpidem and suvorexant. Scales were used for assessment, and results were compared before and after the study. The results confirmed that sleep disorders improved after four weeks of administering sleeping medications. Additionally, dyspeptic and reflux symptoms assessed using the mFSSG (Frequency Scale for the Symptoms of Gastroesophageal Reflux Disease) and GSRS (Gastrointestinal Symptom Rating Scale) scales significantly improved, with the median decreasing from 21.0 to 16.0 points in mFSSG and from 44.0 to 31.0 points in GSRS. Statistically significant improvements were also observed in the HADS (Hospital Anxiety and Depression Scale) scores, decreasing from 13.0 before the study to 12.5 points after taking sleeping medications. Participants showed a reduction in anxiety levels, but depression scores remained unchanged. The SF-36 (Short-Form 36-Item Health Survey) showed a statistically significant improvement in the median total score from 63.9 to 71.9 points.[32]

Liver cirrhosis significantly reduces quality of life, and accompanying portal hypertension is treated surgically by creating a transjugular intrahepatic portosystemic shunt (TIPS). The aim of the study by Zhao M, Yan Yi et al. was to examine the frequency of sleep disturbances (SD) in patients after TIPS. A total of 119 patients were screened for the study. 26% (19 individuals) were observed to have newly developed SD after surgery. The first episodes of SD occurred on average 67 days after TIPS. Patients reported difficulties in falling asleep, nocturnal awakenings, and poor sleep quality. Among the previously mentioned 19 patients, six were treated with eszopiclone at an average dose of 1.3 mg for 12 weeks. After this period, an improvement in the Pittsburgh Sleep Quality Index (PSQI) was noted, from approximately 8 to 4 points. Total sleep time increased from an average of 375 minutes to 435 minutes, and sleep latency decreased from an average of 120 minutes to 30 minutes. The number of nocturnal awakenings decreased from a median of 0-3 to 0-1.[33]

Summary

Insomnia has many negative consequences for both mental and physical health. To prevent these effects, behavioral treatment and pharmacotherapy are used. Currently used medications do not eliminate insomnia-related problems in all patients, hence the need to search for new substances. New sleeping pills include, among others, dual orexin receptor agonists and eszopiclone. Studies on the effects of these drugs indicate that patients benefit from them and suggest they may offer a better option compared to existing pharmacological therapies. In conclusion, eszopiclone and DORAs may represent the future of insomnia treatment, although the authors of the cited studies emphasize the need for further research to determine their efficacy.

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