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DARIDOREXANT: A NEW HORIZON IN THE TREATMENT OF INSOMNIA - CHARACTERISTICS, SAFETY AND USE IN GERIATRIC THERAPY

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ABSTRACT

Background: Chronic insomnia affects up to 20% of the general population and is associated with significant impairment in quality of life and increased health risks. The limitations of traditional pharmacotherapy, including benzodiazepines and Z-drugs, have prompted interest in novel therapeutic agents with improved safety profiles.

Aim: The aim of the authors of this study was to review the available treatments for chronic insomnia with a special focus on the most modern solutions, i.e. drugs from the dual orexin receptor antagonist (DORA) group, and to present their representative, daridorexant, as an effective and safe agent in the treatment of insomnia even in groups prone to side effects, i.e. seniors.

Methods: A narrative literature review was conducted with a focus on pharmacological treatments for chronic insomnia. Special attention was given to dual orexin receptor antagonists (DORAs), particularly daridorexant, as a recent development in this drug class.

Results: Daridorexant has demonstrated efficacy in the treatment of chronic insomnia with a favorable safety profile, including in older adults. Compared to traditional hypnotics, it exhibits a lower risk of residual next-day sedation, psychomotor impairment, and dependence.

Conclusions: Daridorexant represents a promising alternative for managing chronic insomnia, especially in populations vulnerable to adverse effects from older hypnotics. Its mechanism of action and tolerability profile position it as a modern, evidence-based option for individualized treatment of sleep disorders.

Keywords: chronic insomnia, DORA, daridorexant, sleep disorders, pharmacotherapy, older adults

INTRODUCTION

Insomnia is a prevalent and clinically significant condition, recognized as the most common sleep disorder and the

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second most frequent psychiatric complaint in the general population [1]. It is characterized by difficulty initiating or maintaining sleep, early morning awakenings, and non-restorative sleep, despite adequate opportunity and circumstances for rest [2,3]. These disturbances are frequently accompanied by impaired daytime functioning, including reduced cognitive performance, decreased productivity, depressed mood, and increased irritability [2]. Chronic insomnia disorder (CID) is defined by persistent sleep difficulties occurring at least three times per week for a duration of three months or longer [4]. Epidemiological data indicate that up to 20% of the population is affected, with higher prevalence among women, older adults, and individuals with lower levels of education [1]. Additional high-risk populations include military personnel and veterans, individuals with mood or anxiety disorders, those with substance use disorders, patients with traumatic brain injury, and postmenopausal women [5]. Insomnia is increasingly recognized as a risk factor for a wide range of medical conditions, including epilepsy, headaches, dementia, cardiovascular disease, asthma, diabetes, and depression [1,4]. It has also been linked directly or indirectly—to increased risk of stroke through its association with other vascular comorbidities [6]. Furthermore, insomnia frequently coexists with obstructive sleep apnea syndrome, compounding the risk of cardiovascular and metabolic dysfunction [7]. The consequences of chronic insomnia extend beyond health-related outcomes, negatively affecting occupational and academic performance, increasing the likelihood of motor vehicle accidents, impairing social functioning, and reducing overall quality of life [4]. Given its broad clinical implications and impact on public health, effective and safe therapeutic strategies are of critical importance, particularly for vulnerable populations.

OBJECTIVE

The authors would like to emphasize the importance of the problem of insomnia in society and present an innovative line of treatment for chronic insomnia - a group of dual orexin receptor antagonists (DORA). The subject of the review paper is daridorexant - a representative of DORA, which is an alternative to existing pharmacological options for the treatment of this disease entity, burdened with a high risk of addiction or psychomotor disorders. The aim of the paper is to present daridorexant and its properties, and to raise awareness of the effectiveness and high degree of safety of DORA especially among seniors.

MATERIALS AND METHODS

This article is based on a narrative review of the literature concerning pharmacological treatment options for chronic insomnia, with a particular emphasis on dual orexin receptor antagonists (DORAs) and daridorexant. A literature search was conducted in PubMed, Scopus, and Web of Science databases up to April 2024. Search terms included combinations of keywords such as "chronic insomnia," "orexin receptor antagonists," "DORA," "daridorexant," "benzodiazepines," "Z-drugs," and "elderly."

Parameter Description Narrative literature review Type of Review **Databases Searched** PubMed, Scopus, Web of Science Search Time Frame 2018-2024 "daridorexant", "DORA", "dual orexin receptor antagonist", Keywords Used "chronic insomnia" Peer-reviewed articles, reviews, clinical trials on DORA and Inclusion Criteria daridorexant Non-English articles, non-peer-reviewed sources, studies on **Exclusion Criteria** children Number of Included 24 Studies Randomized controlled trials, real-world evidence, systematic Type of Studies reviews

Table 1. Literature Search Parameters and Inclusion Criteria

The selected studies were reviewed for relevance to the efficacy, safety, pharmacokinetics, and clinical applicability of daridorexant compared to traditional insomnia treatments. Due to the narrative nature of this review, no formal risk-of-bias assessment or statistical meta-analysis was performed. However, emphasis was placed on including up-to-date, high-quality sources and guidelines.

RESULTS

Until recently, available treatments for insomnia were primarily benzodiazepines, benzodiazepine receptor agonists (so-called Z-drugs), histamine receptor antagonists, melatonin agonists and selected antidepressants (e.g., trazodone). [8][9] The most commonly prescribed drugs are Z-drugs, namely zopiclone, zolpidem and zaleplon. [10] Both this group of drugs and BDZs have the same pharmacodynamic effect - they are GABA-A receptor modulators that cause global sedation of the central nervous system. [11][12] This translates into numerous side effects like high addictive potential with long-term use, rapid development of tolerance to the drug, post-dose insomnia, and decreased cognitive and motor function the next day. [8][10][11] In addition, they are a significant risk factor for traffic accidents and injuries. [10] These side effects have led the US Food and Drug Administration (FDA) to issue a warning on the use of Z-drugs. [10] Benzodiazepines exhibiting the same pharmacodynamic mechanism have similar side effects, but of greater severity, resulting in the need for even greater scrutiny of their use and requiring higher vigilance about the appropriateness of their prescription. [10]

Table 2. Classification of Current Pharmacological Options for Chronic Insomnia

Drug Class	Representative Agents	Mechanism of Action	Key Adverse Effects	
Benzodiazepines (BDZs)	Diazepam, Lorazepam	GABA-A receptor agonism	Tolerance, dependence, daytime drowsiness	
Z-drugs	Zolpidem, Zopiclone	GABA-A receptor agonism	Similar to BDZs, but shorter duration	
Melatonin Receptor Agonists	Ramelteon	Melatonin receptor agonism	Headache, dizziness	
Antidepressants (off-label)	Trazodone	Serotonin receptor antagonism	Daytime sedation, hypotension	
Antihistamines (off-label)	Diphenhydramine	Histamine receptor blockade	Cognitive impairment, dry mouth	
DORAs	Suvorexant, Lemborexant, Daridorexant	Dual orexin receptor antagonism	Mild: nasopharyngitis, headache, rare REM effects	

Other treatments for insomnia include cognitive-behavioral therapy for insomnia (CBTI). It combines elements of cognitive therapy, behavioral interventions and sleep hygiene education. There is also a fully automated digital CBTI or dCBTI, which does not require the participation of a physician.[5] Underlying the above therapy is the theory that when a patient with certain predispositions experiences a triggering stimulus, he or she develops an abnormal coping pattern, which leads to the perpetuation of insomnia. This theory forms the basis of CBTI.[13] [14] The goal of behavioral treatment is to change the pattern in which there is a relationship between falling asleep and overstimulation. This is done through two strategies - sleep restriction and stimulus control. Sleep restriction is designed to lead to an increased need for sleep by reducing the time spent in bed. It is restricted to adapt to the patient's actual sleep time and requires monitoring of daily falling asleep and waking hours. Stimulus control serves to break the link between lying in bed and the negative aspects of insomnia, such as wakefulness and frustration. This is based on the premise that eliminating them allows the bed to be re-associated with sleep rather than arousal.[14] However, many insomniacs do not experience sufficient relief, and despite promising research results, post-treatment sleep efficiency, as assessed by an integrated measure of sleep quality, statistically does not exceed 80%, the cutoff for normal sleep. [3] Other non-pharmacological methods that may benefit some patients include a variety of relaxation techniques and practicing mindfulness.[5]

A breakthrough in the treatment of insomnia in adult patients came in 2022 with the approval of daridorexant by the European Medicines Agency. [15]. It is the only DORA representative available in the European Union. [15] It is also approved in the US, Canada, Switzerland and the UK. [11] DORA's mechanism of action involves blocking the binding of the neuropeptides orexin A and B to orexin type 1 and type 2 receptors. [11] The function of orexin is to regulate basic vital functions: arousal, response to stressful situations, appetite levels or cognitive functions. [8] In the context of insomnia treatment, its effect is to inhibit hypervigilance by lowering the intensity of wakeful stimuli that impede nighttime sleep. [8][11]. There are currently three types of DORA: suvormexant (20 mg), lemborexant (5 mg, 10 mg) and daridorexant (50 mg). [8][16] Daridorexant is characterized by faster absorption, lack of accumulation and the shortest half-life of 8 hours compared to the other members of this group. [8][10] It is metabolized by CYP3A4 and excreted mainly in feces. [10] Daridorexant is indicated for the treatment of moderate to severe chronic insomnia in adults. [17] Phase II studies confirm the efficacy of the drug through the improvement of the following parameters in the results - latency to persistent sleep (LPS) and so-called wake after sleep onset (WASO) compared to baseline. [10][11]

Table 3 summarizes key clinical and pharmacological characteristics of daridorexant, a representative agent of the dual orexin receptor antagonist (DORA) class. The table includes data on its mechanism, pharmacokinetics, dosage, safety profile, and specific advantages in populations vulnerable to adverse effects—such as the elderly. It emphasizes daridorexant's low risk of dependence, reduced fall risk, and minimal next-day impairment, supporting its relevance as a modern therapeutic option for insomnia management.

Parameter	Daridorexant Characteristics		
Drug Class	Dual orexin receptor antagonist (DORA)		
Target Mechanism	Inhibition of orexin A and B signaling pathways		
Half-life	Approximately 8 hours		
Approved Dose Range	25-50 mg before bedtime		
Addictive Potential	Low (minimal withdrawal or rebound insomnia observed)		
Suitability in Elderly Patients	High (favorable safety and tolerability profile)		
Cognitive Impairment Risk	Lower compared to benzodiazepines and Z-drugs		
Fall Risk	Reduced in clinical trials with older adults		
Next-day Residual Effects	Minimal, especially at 25 mg dose		
Adverse Events (most common)	Headache, somnolence, fatigue		

Table 3. Clinical Profile of Daridorexant Based on Recent Studies

The recommended starting dose of daridorexant is 50 mg/day.[15][18][19] Studies comparing the degree of safety showed no differences between 25 mg and 50 mg doses. [11] In both cases, the following were not observed: symptoms of dependence, increased daytime sleepiness, injury or withdrawal symptoms. [11] The drug shows no evidence of dose dependence. [10] The key difference was a significant improvement in daytime functioning at the higher (50 mg) dose of daridorexant, taking into account parameters such as next-day sleepiness, mood and alertness. [11] According to U.S. recommendations, daridorexant should be taken 30 minutes before going to bed and at least 7 hours before a scheduled awakening. [20]

The most commonly reported side effects included nasopharyngitis, headache fatigue and drowsiness.[10][17] It is distinguished from benzodiazepines and so-called Z-drugs by its lack of addictive potential and insomnia after withdrawal. [12] Studies confirm the lack of short-term and long-term serious side effects when using it. [12]

Worth noting is the fact that daridorexant prolongs the REM phase of sleep. [8] The consequence may be a higher incidence of nightmares reported by patients.[8] Other, rarely reported, side effects were sleep paralysis and increased depression, which could potentially be related to low orexin levels. [8][16][17] However, the number of studies showing a statistically significant increase in the frequency of the above is still insufficient.[8]

The elderly are more likely to develop chronic insomnia. [21] The etiology is multidirectional - polyphagia, the burden of multiple chronic diseases, and a lower physiological need for sleep. [21] Previous studies do not indicate that daridorexant has adverse effects on the cardiovascular or respiratory systems during sleep, making it safer in geriatric patients. [12] Safety and tolerability assessments in studies did not differ between age groups, indicating that no dose reduction is necessary in older patients. [10] [17] [21] In addition, daridorexant has been shown not to adversely affect postural stability or mobility, so it does not increase the risk of falls and thus injuries, a common cause of hospitalization among people over 65. [15] Studies confirm the preservation of responsiveness to external stimuli, keeping patients alert to suprathreshold sounds while at rest. [15]

DISCUSSION

Chronic insomnia represents a widespread and multifactorial clinical issue with profound implications for patients' physical, psychological, and social functioning. While benzodiazepines and Z-drugs have long dominated pharmacotherapy, their unfavorable safety profiles - particularly in elderly populations - necessitate the evaluation of alternative strategies.

Daridorexant, a dual orexin receptor antagonist (DORA), emerges as a promising agent with a favorable pharmacokinetic profile and reduced risk of next-day impairment, addiction, and falls. Available data indicate that daridorexant improves both objective and subjective sleep parameters, particularly latency to persistent sleep (LPS) and wake after sleep onset (WASO), while enhancing next-day functioning. [22]

Table 4 compares insomnia pharmacological treatments including Daridorexant and their safety information.

Table 4. Comparative Overview of Pharmacological Treatments for Chronic Insomnia

Drug Class	Example Agents	Mechanism of Action	Risk of Dependence	Suitable for Elderly	Common Adverse Effects
Benzodiazepines	Diazepam, Lorazepam	GABA-A receptor agonists	High	No	Sedation, falls, cognitive impairment
Z-drugs	Zolpidem, Zopiclone	Selective GABA-A a1 receptor binding	Moderate	Caution	Dizziness, dependence, next-day drowsiness
Antidepressants	Trazodone, Doxepin	Serotonin/ norepinephrine modulation	Low	Yes (low- dose)	Dry mouth, weight gain, hypotension
Antihistamines	Diphenhydramine	H1 receptor antagonists	Low	No	Confusion, dry mouth, urinary retention
Melatonin receptor agonists	Ramelteon	MT1 and MT2 receptor agonists	None	Yes	Headache, dizziness
DORAs (Orexin Antagonists)	Daridorexant, Suvorexant	Dual orexin receptor antagonists	Low	Yes	Somnolence, headache, rare parasomnias

For example, in phase III studies, daridorexant was associated with a significantly lower incidence of next-day somnolence and impaired psychomotor function compared to traditional hypnotics. [23]

In one trial, the incidence of next-morning sleepiness was 10% in patients taking daridorexant, compared to 22% in those receiving zolpidem [24]. Moreover, daridorexant did not increase the rate of nighttime falls among geriatric participants, which is a key safety consideration. Highlighting such outcomes through numerical data or effect sizes would provide stronger support for its clinical advantages over benzodiazepines and Z-drugs [21].

Despite encouraging findings, evidence remains limited by short study durations and a lack of real-world long-term data. Additional research is warranted to determine daridorexant's effectiveness across diverse patient groups and comorbid conditions.

CONCLUSION

Given how common the problem of insomnia today, the search for new methods and techniques to treat or at least alleviate it is an extremely important task for scientists and doctors. It should be remembered that sleep is one of the key elements of the physical and mental well-being of every human being, regardless of age, so we should also make the best use of existing solutions to this problem, since a sleep-deprived body is an inefficient body.

However, each doctor should judiciously select pharmacological agents, especially those that cause serious side effects and associated with high addictive potential or increased risk of falls and consequent injuries. Hence the importance of awareness about new insomnia drugs, especially among geriatric care professionals.

In conclusion, daridorexant provides an effective addition to the therapeutic instruments for chronic insomnia, particularly in populations for whom traditional hypnotics pose substantial risk. A personalized, evidence-based approach that incorporates both pharmacological and behavioral therapies remains essential to optimize outcomes in insomnia management.

PRACTICAL RECOMMENDATIONS FOR CLINICIANS

- 1. Patient selection: Consider daridorexant as a first-line pharmacological treatment in elderly patients, those with polypharmacy, or individuals at risk of falls.
- 2. Dosing guidance: Begin with the 50 mg dose, as it appears to provide the best balance between efficacy and tolerability, with no need for dose adjustment in older adults.
- 3. Safety considerations: Monitor for rare adverse events such as vivid dreams or transient mood changes, especially in patients with psychiatric comorbidities.
- 4. Adjunctive strategies: Encourage concurrent implementation of non-pharmacological interventions such as cognitive behavioral therapy for insomnia (CBTI) and sleep hygiene education.

AUTHORS' CONTRIBUTIONS

Conceptualization: Magdalena Cyrkler; methodology: Aleksandra Drabik; analysis and investigation: Aleksandra Śledziewska; Magdalena Cyrkler; Resources: Aleksandra Zagajewska; data curation: Kamila Sieradocha; writing - original draft: Magdalena Cyrkler, Aleksandra Śledziewska, Aleksandra Drabik, Kamila Sieradocha, Aleksandra Reda; writing - review and editing: Aleksandra Giba, Dorota Słupik, Aleksandra Zagajewska; Aleksandra Krygowska: supervision: Magdalena Cyrkler; project administration: Michał Wąsik, Dorota Słupik

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