General

Daridorexant for the Treatment of Insomnia

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Purpose of Review

Insomnia is a complex sleeping disorder that affects the lives of many individuals worldwide. Insomnia often occurs in the presence of coexisting comorbidities making it a complex disorder that requires a multifactorial approach to therapy. First-line therapy is cognitive-behavioral therapy for insomnia (CBT-I). Pharmacotherapy for insomnia falls into four classes based on mechanism of action: benzodiazepine receptor agonists (BZRAs), histamine receptor antagonists, melatonin receptor agonists, and dual orexin receptor antagonists (DORAs).

Recent Findings

Daridorexant is a dual orexin type 1 and types 2 (OX_1 and OX_2) receptor antagonist that was recently approved by the US FDA for the treatment of adults suffering from insomnia. It was shown to be effective in reducing insomnia symptoms, increasing daytime functioning, and improving the overall quality of sleep. Daridorexant offers patients relief from insomnia while avoiding the severe side effects and dependency issues of traditional treatments like benzodiazepines and sedatives.

Summary

In this article, we review the most recent data on insomnia treatments and summarize the safety and efficacy of daridorexant in treating insomnia.

INTRODUCTION

Insomnia is a common disorder that affects an individual's sleep hygiene and subsequently the quality of life for a disproportionate number of individuals. Patients typically struggle with initiating sleep, staying asleep, or returning to sleep after waking early in the morning. These difficulties can produce deleterious effects on daily functioning and performance in the form of fatigue, hypersomnolence, mood disturbances, impaired memory, and inattentiveness.[1] The various classifications and subtypes for an insomnia diagnosis have undergone many revisions, which ultimately resulted in inconsistent and unreliable approaches to therapy. This issue was addressed by the committee for the International Classification of Sleep Disorders (ICSD-3) by recategorizing the insomnia subtypes as short-term, chronic, and other for ease of diagnosis. The ICSD-3 and Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-V) require symptoms to appear at least 3 times a week and persist for at least 3 months for a chronic insomnia diagnosis.[1,2] Insomnia often occurs in the presence of coexisting comorbidities making it a complex disorder that requires a multifactorial approach to therapy.

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First-line therapy is cognitive-behavioral therapy for insomnia (CBT-I). Though proven to be effective, the use of short-term pharmacotherapy has also been advised in conjunction with CBTI-I.[3–5] Currently approved medications fall into four mechanisms of action: benzodiazepine receptor agonists (BZRAs), histamine receptor antagonists, melatonin receptor agonists, and dual orexin receptor antagonists (DORAs). Daridorexant, classified as a DORA, was recently approved in January 2022 by the United States Food and Drug Administration (US FDA) for treating insomnia.[6–8] The purpose of this paper is to summarize the safety and efficacy of daridorexant in treating insomnia.

EPIDEMIOLOGY

The prevalence of insomnia is estimated to be 10-15% based on the criteria used to make the diagnosis and results in over five million clinic visits annually in the United States.[9–11] The worldwide prevalence of insomnia is approximated at 30-35% with a one-year incidence of 5%.[9,10,12–14] Insomnia has a higher prevalence in the elderly, female population, those who are disabled, or people who have jobs with irregular shifts.[9] Patients with social factors such as unemployment, marital status (*i.e.,* widowed, divorced, or separated), and low socioeconomic status tend to have higher rates of insomnia.[15] Nearly half of insomnia cases report a coexisting psychiatric disorder and a majority have an accompanying medical condition.[16,17]

PATHOPHYSIOLOGY

The complexity of insomnia creates a problem for understanding its pathophysiology and explains why there is not an accepted model for its disease process.[18] This can be explained in part by the heterogenic nature of insomnia and its presence in comorbid conditions.[18,19] The current literature utilizes different approaches to describe the manifestations of insomnia such as the neurobiological, cognitive, behavioral, and emotional models.[19–21] Regardless of the model, there is a consensus that insomnia is the result of a dysregulation of brain centers containing the circadian rhythm and homeostatic processes that control sleep and wakefulness.[5]

The ascending reticular activation system (ARAS) influences wakefulness while the ventrolateral preoptic region (VLPR) drives to sleep. ARAS activates different cerebral nuclei, specifically the orexin system (hypocretin/orexin-containing neurons) that inhibits the VLPR to maintain wakefulness. The opposite occurs when the VLPR inhibits ARAS through two neurotransmitters, γ-aminobutyric acid (GABA) and galanin, effectively creating what is known as the flip flop switch; this model demonstrates how sleep and wakefulness are mutually exclusive events.[18,22,23] The current accepted stance on insomnia is that it is a disorder of hyperarousal and manifests on a cognitive, emotional, and physiological level. Individuals experience excessive worrying, racing thoughts, increased metabolic rate and blood pressure, elevated cortisol levels, and high-frequency electroencephalographic activity whilst asleep.[24,25] The progression of insomnia from its acute to the chronic stage is best described by the 3P model which explains how predisposing, precipitating, and perpetuating factors affect these brain centers for the production and persistence of insomnia.[5,18,26]

RISK FACTORS AND PRESENTATION

Predisposing factors for insomnia include older age, female sex, previous incidences of insomnia, and family history.[9,27,28] Additionally, a genome-wide association study identified several loci providing a genetic basis for insomnia.[29] In 50% of patients, psychiatric comorbidity often coexisted with insomnia such as anxiety, substance use disorders, and post-traumatic stress disorder.[16,25] Approximately 80% of individuals with major depressive disorder had insomnia, and in nearly half of all cases, insomnia preceded a mood disorder.[30]

Patients typically present with trouble initiating sleep, maintaining sleep, or waking in the early morning without an appropriate return to sleep. As a result, patients report a lack of sleep affecting functioning in daily activities, lack of concentration, fatigue, accidents at work, or driving.[1] The hallmark of insomnia that separates it from other causes of sleeplessness is illustrated by the persistence of symptoms despite ample opportunities for sleep.[1,2]

CURRENT TREATMENTS FOR INSOMNIA

Insomnia is a condition characterized by a lack of sleep quality, initiation, or duration resulting in daytime fatigue or impairment.[31] This condition has a complex etiology with causative factors stemming from genetic, social, environmental, behavioral, and psychological elements that converge with one another into the clinical disorder that affects 10-30% of adult populations.[32] Other conditions such as depression and severe medical complications, including heart disease and high blood pressure, are frequently reported in tandem with insomnia. Insomnia's prevalence in the population coupled with the comorbidities associated with its chronic manifestation makes its treatment a priority. Insomnia's complex etiology and many causative factors require multiple treatment options for patients to obtain a higher quality of life and improved daytime alertness and functioning.[32–34]

Treatments are based on the underlying cause identified by both the treating healthcare provider and the patient. In most cases, an individualized treatment plan addressing causes specific to the patient has shown the greatest efficacy and alleviation of symptoms.[35] Cognitive behavioral therapy (CBT) is currently indicated as the first-line therapy for insomnia due to its lack of pharmacological intervention and reduced side effects in comparison with other treatments. Methods currently being utilized by this approach include relaxation techniques, modified sleep restriction therapy, as well as education to inform patients of behaviors that may prevent a good night's sleep.[36] A meta-analysis examining the effect of CBT treatment found significant improvements in insomnia severity, a number of

awakenings, sleep quality, as well as total sleep time.[37] CBT should be considered a low-risk and viable treatment option in most cases of insomnia, including pharmacotherapy-resistant insomnia.[38]

Pharmacotherapy treatments for insomnia include BZRA, histamine receptor agonists, melatonin receptor agonists, and DORA. These treatments have proven short-term efficacies, however, their long-term effectiveness diminishes soon after cessation of therapy.[39,40] Benzodiazepines have traditionally been a mainstay of pharmacological interventions for insomnia, but evidence continues to emerge discouraging the long-term use of this class of drug due to its risk for abuse and myriad of side effects.[41,42] Benzodiazepines and other hypnotics are known to create physical dependence in patients undergoing long-term treatment, and termination of treatment can lead to withdrawal symptoms lasting for months.[43] New treatment options such as DORAs offer relief of patient's insomnia symptoms without the severe side effects and dependency issues of traditional treatments like benzodiazepines and sedatives.[41,44]

In a direct comparison, CBT was found to benefit young and middle-aged patients significantly more than pharmacotherapy. Benefits and symptom alleviation lasted much longer in the CBT treatment group when compared with the pharmacotherapy group, and a combination of pharmacotherapy and CBT treatments showed no greater efficacy than CBT alone.[36] This coupled with the greater safety of CBT in comparison with pharmacological intervention suggests CBT will likely continue its role as the first-line therapy for insomnia into the immediate future.

DARIDOREXANT INFORMATION

Daridorexant was patented in 2013 and received its first approval for use in treating adult insomnia in the US on January 7, 2022.[45] It is available in 25 to 50 mg once daily oral doses.[46] Daridorexant's recommended administration is within 30 minutes of going to bed with at least 7 hours before planned awakening. Daridorexant was found to help patients fall asleep faster and stay asleep longer in comparison with a placebo, and 50 mg doses were found to be more effective and had longer-lasting effects than 25 mg doses.[47] Daridorexant is contraindicated in patients with narcolepsy and is considered a central nervous system depressant. It should not be used in conjunction with other central nervous system depressants as this may exacerbate its effects. Daridorexant's controlled substance schedule will be decided pending a review by the Drug Enforcement Agency.[48]

Daridorexant belongs to a relatively new class of drugs called DORAs, which act on different brain pathways than other treatments currently available to the public. These drugs were developed as an alternative treatment option to positive allosteric gamma-aminobutyric acid (GABA) A receptor modulators, which have traditionally been a mainstay in treating insomnia. Daridorexant's development was the result of a research program seeking to find a medication with sleep-promoting properties that did not affect next-morning alertness, cognition, or memory. It does this by binding orexin receptors inhibiting the action of the neuropeptide orexin, which is secreted primarily in the lateral hypothalamus and exhibits its effects by activating two G protein-coupled receptors, orexin receptors type one and type two. Orexin functions to promote daytime wakefulness and is largely inactive during sleep. Daridorexant helps patients get to sleep and stay asleep longer by competitively binding both orexin receptors, preventing the downstream effects of orexin.[47,49–51] An added benefit seen in rodent models over traditional hypnotics is that efficacy is maintained over time without tolerance development, and while DORAs still need long-term clinical evaluation, they are an exciting new class of drugs that offer effects unique from anything currently available to treat insomnia.[52–54]

MECHANISM OF ACTION OF DARIDOREXANT/ DARIDOREXANT DRUG INFO

Daridorexant (Quviviq™) has been specifically developed to act on orexin receptors OX1 and OX2, and antagonize their effects, promoting sleep.[45] Daridorexant (ACT-541468) has been recently approved by the FDA for the treatment of insomnia and has been sub-grouped under a fairly novel class of drugs known as DORAs as it selectively and potently exhibits its effects on both OX1 and OX2 receptors.[55–59] Orexinergic neurons which are notably found in the hypothalamus have a well-connected system projecting their axons to several wake-promoting neuronal regions such as dorsal raphe, ventral tegmental area, locus ceruleus, tuberomammillary nuclei centers, and laterodorsal tegmental nuclei where the abundance of serotonergic, dopaminergic, noradrenergic, histaminergic, and cholinergic neuronal projections are found to exist.[60–66] Classic hypnotics targeting the aforementioned receptors including GABA-A have been commonly used until now to combat insomnia, but these newly developed specific DORA agents such as daridorexant exhibit its effect in a distinct manner, leading to lesser side effects and does not affect the sleep-wake architecture.[55,67]

A recent study demonstrated that daridorexant functionally crosses the blood-brain-barrier (BBB) and works by competitively binding to the active site of OX1 and OX2 receptors with K_b values of 0.52 nM at OX1R and 0.78 nM at OX2R, in humans, while not affecting any GABA receptors or centers of the brain involved in abuse potentiality.[67] A study conducted on rodents and Beagle dogs revealed that daridorexant decreases the latency time to non-rapid eye movement (REM) and REM sleep, decreases wakefulness, and increases the time spent in non-REM and REM cycles, but it did not affect the overall total time spent in these cycles, indicating the maintenance of normal sleep architecture (*i.e.,* non-REM/total sleep and REM/total sleep ratio).[68,69]

Though daridorexant was detected in plasma upon awakening, it did not result in any sleep or cognitive effects (impairment in memory or attention) such as can be seen with diazepam and eszopiclone, but daridorexant has been shown to help induce and promote sleep throughout an 8 hour (h) period, with its highest effects exhibited when

orexin neuronal activity is at its peak.[55,58,70–72] Additionally, it has been shown to preserve muscle coordination and strength and the natural ability to wake up and react to auditory/aversive/visual/threat stimuli; in comparison to GABA-A receptor modulators where psychomotor abilities are impaired.[55,69,73–76] Unlike benzodiazepines or other sleep-promoting agents, daridorexant does not affect attention, memory, learning, and cognition.[77–80] Daridorexant was recently shown to improve daytime performance in concordance with the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ).[81] Most importantly, DORAs have not shown to have any abuse/additive potentials or withdrawal phenomena, in comparison to benzodiazepines or other sleep-inducing drugs such as zolpidem acting via GABA-A or GABA-B.[55,82–85]

PHARMACOKINETICS/PHARMACODYNAMICS OF DARIDOREXANT

Daridorexant is an orally administered drug that at the 25 mg dosage has a half-life (t½) of ~ 8 h.[57,86] It is primarily metabolized in the liver by the cytochrome P450 3A4 (CYP3A4) enzyme, and its metabolites are excreted in the urine (~28%) and feces (~57%).[57,87] The inhibition constants (Kb) were found to be 0.52 nM and 0.78 nM on human orexin receptors-OX1 and OX2 in in-vitro experiments, respectively.[67] In human trials, 25 mg and 50 mg of daridorexant declined to baseline levels after 3-6 h and 6-8h, respectively, and it reached its maximum effective capacity around ~1.5-2 h post administration for dosages up to 100 mg.[58,86] In a randomized, double-blind human abuse potential clinical trial conducted in users with the addictive potential for sedatives (n = 63), daridorexant was found to be associated with drug-inclination effects, with drug-liking visual analog scale (VAS) E_{max} of 73.2, 79.1 and 81.3 at 50, 100, and 150 mg respectively; however, in comparison to zolpidem 30mg and suvorexant 150 mg, daridorexant 50 mg had a significantly lower VAS E_{max} ($p \leqslant 0.0007$).[82] Furthermore, daridorexant was not associated with any prolongation of QT intervals between the dosage of 25-200 mg.[88]

In two placebo-controlled crossover trials in patients with mild-moderate obstructive sleep apnea (OSA) not requiring continuous positive airway pressure (CPAP), administration of daridorexant 50 mg was associated with 0.74 (90% CI – 1.43 to 2.92) apnea-hypopnea events/h mean treatment difference in the index during total sleep time (TST) compared to placebo; while in moderate chronic obstructive pulmonary disease (COPD), there was no statistical difference in peripheral oxygen saturation during TST.[89]

The peak plasma concentration of daridorexant occurs at t_{max} of 1-2 h, and its pharmacokinetic (PK) properties remain the same with single-dose and multiple-dose administrations.[58] It is highly bound to plasma proteins (99.7%), its volume of distribution (Vd) is 31 L, and the total area under the curve (AUC) is not hindered by a high-fat meal but does reduce its C_{max} by 16% and increases the t_{max} by 1.3 h.[58]

In pharmacokinetic modelling studies, AUC for daridorexant escalated by 240% and > 400% when used concomitantly with moderate CYP3A4 inhibitor diltiazem and strong CYP3A4 inhibitor itraconazole, respectively; whereas AUC decreased by ~ 30% and > 50% when used with moderate CYP3A4 inducer efavirenz and strong CYP3A4 inducer rifampin, respectively.[59,90] There were no interactions or changes in the pharmacokinetic profile of daridorexant 50 mg when used with famotidine, citalopram, or rosuvastatin.[90–92] However, concomitant administration of ethanol and daridorexant hindered psychomotor functioning and prolonged the t_{max}.[59,93] Moreover, studies found a reduction in attention and vigilance, postural instability, and impaired visual-motor coordination when used in advancing doses and used with other CNS depressants.[93] There has been evidence that the t½ is prolonged in patients with moderate liver failure (Child-Pugh B stage), and the maximum recommended dose in these patients is 25 mg.[94] While there has been no data in patients with severe liver failure and the usage of daridorexant, there has been studies which demonstrated no changes in the pharmacokinetic properties of daridorexant in relation to mild liver failure (Child-Pugh A stage), mild-to-severe renal failure (Cockcroft-Gault < 30 ml/min, not on dialysis), age, sex, ethnicity, or obesity.[94,95]

CLINICAL STUDIES: SAFETY AND EFFICACY

Symptoms of insomnia have been self-reported in nearly 30% of the general population and can lead to a wide variety of daytime effects such as fatigue, reduced energy, mood alteration, and cognitive difficulties.[96,97] Daridorexant is a generally safe, well-tolerated DORA that has been studied to improve the symptoms of insomnia and mitigate the negative impact it could have on a patient's daily life. The potential side effects of daridorexant are considered relatively mild and may include headache, gait disturbance, fatigue, and nasopharyngitis.[72] In the trials described (Table 1), the safety and efficacy of daridorexant were assessed for the treatment of insomnia in a wide variety of populations.

EFFICACY OF DARIDOREXANT

Prior to administering daridorexant to patients for the treatment of insomnia, it is important to determine whether it will be effective when compared to a placebo. Two multicenter randomized, double-blind, placebo-controlled phase 3 trials assessed the efficacy of daridorexant. Both trials consisted of a screening period for 7-18 days, a single-blind placebo run-in period for 13-24 days, a double-blind treatment period for 3 months, and a single-blind placebo run-out period for 7 days followed by a safety follow-up period for 23 days or a 9-month placebo-controlled extension trial.[97] Participants were included if they were over the age of 18 who fit the criteria of insomnia under the DSM-V and were considered mild to moderate severity based on an Insomnia Severity Index (ISI) of > 15.[97] Patients were randomized to take 25 mg of daridorexant, 50

Table 1. Studies demonstrating the clinical efficacy and safety of daridorexant.

Author (year)	Groups Studied and Intervention	Results and Findings	Conclusions
Zammit et al. (2020)[72]	Elderly patients between 65-85 years old with insomnia were randomly allocated to receive 5 treatments of 5, 10, 25, and 50 mg daridorexant and placebo during 5 treatment periods that lasted 2 nights followed by a washout period of 5-12 days.	WASO and LPS were dose-dependently reduced after daridorexant administration ($p < 0.0001$, $p < 0.004$). Reductions were statistically significant for daridorexant doses ^{3} 10 mg ($p < 0.025$) when compared to placebo. Adverse events were similar to placebo, with the most common being fatigue, nasopharyngitis, gait disturbance, and headache.	Daridorexant is well tolerated in the elderly population for the use of insomnia.
Mignot et al. (2022)[97]	Two randomized, double-blind, placebo-controlled phase 3 trials in adults 18 years old were randomly assigned to 25 or 50 mg of daridorexant or placebo in study 1 and 10 or 25 mg of daridorexant or placebo in study 2.	Study 1: WASO and LPS were significantly reduced in patients taking 50 mg daridorexant compared to the placebo group after month 1 ($p < 0.0001$, $p < 0.0001$) and 3 ($p < 0.0001$, $p < 0.0001$). Additionally, 50 mg daridorexant had improved self-reported sleep time at month 1 and 3 ($p < 0.0001$, $p < 0.0001$) and IDSIQ sleepiness domain scores at month 1 and 3 ($p < 0.0001$, $p < 0.0002$) compared to placebo. Participants taking 25 mg daridorexant had improved self-reported TST at months 1 and 3 ($p < 0.0013$, $p < 0.033$), but not in IDSIQ sleepiness domain Study 2: WASO was significantly reduced in patients taking 25 mg daridorexant after month 1 ($p < 0.0001$) and 3 ($p < 0.0028$), but no differences in LPS were observed. Additionally, patients reported improvement in TST but not in IDSIQ sleepiness domain scores. There were no significant differences between 10 mg daridorexant and placebo for WASO, LSP, TST, or IDSIQ sleepiness domain scores.	50 mg daridorexant improved sleep outcomes and daytime functioning, while 25 mg daridorexant improved sleep outcomes in patients with insomnia disorder when compared to placebo.
Boof et al. (2021)[98]	Randomized, double-blind, placebo-controlled, two-period crossover study involving 28 patients > 18 years old that were randomized to receive 50 mg daridorexant followed by placebo or vice versa.	There was no effect of 50 mg daridorexant on AHI during TST when compared to placebo with a 90% CI of 0.74 (-1.43, 2.92). Time spent with SpO2 < 90%, < 85%, and < 80% with 50 mg daridorexant was comparable to placebo. Daridorexant significantly increased TST by 39.6 minutes ($p < 0.007$) after a single dose. There was no significant difference in total arousal indices when compared to placebo. Additionally, repeated administration of daridorexant 50 mg significantly increased SEI by 8.04% ($p = 0.0002$), reduced WASO by 31 minutes ($p = 0.004$), and shortened LPS by 19.8 minutes that was not considered statistically significant ($p = 0.12$).	Single and repeated doses of 50 mg daridorexant do not impair nighttime respiratory function in patients with mild to moderate COPD.
Schilling et al. (2021)[99]	Randomized, double-blind, placebo-controlled, four-period crossover study involving 36 healthy subjects who received 50 or 200 mg daridorexant, 400 mg moxifloxacin, or placebo to investigate the effect on QT interval duration.	Baseline and placebo corrected QT interval was > 5 ms following moxifloxacin administration ($p < 0.01$). When daridorexant was administered, QT interval was 1.40 ms with the 50 mg dose and 1.84 ms with the 100 mg dose. Lack of QT prolongation with daridorexant was further confirmed using secondary by-time point analysis and categorical outlier analysis.	Daridorexant does not impair cardiac repolarization via absence of QT prolongation, making it well tolerated for individuals with insomnia.
Muehlan et al. (2020)[100]	Double-blind, placebo-controlled, randomized, single-ascending dose study in elderly patients aged 65-80 years old. Patients were randomly assigned to take 5, 15, or 25 mg of daridorexant or placebo in the morning and an additional 10 subjects received 25 mg daridorexant in the evening to assess the pharmacokinetics, pharmacodynamics, and tolerability of daridorexant in elderly patients.	Median time to maximum concentration of daridorexant was found to be about 1 h and the elimination half-life was 8.5-9.8 hours. No pharmacodynamic effects were noted with the 5 mg dose when compared to placebo. The 15 mg dose of daridorexant reduced the saccadic peak velocity while all other variables were similar to placebo. All pharmacodynamic parameters were observed with the 25 mg dose of daridorexant when compared to placebo, however there was no difference to placebo 8-12 hours after administration.	Daridorexant is well-tolerant in the elderly population for the use of insomnia and have very little next-day effects that are a common complaint with other insomnia medications.

Author (year)	Groups Studied and Intervention	Results and Findings	Conclusions
Dauvilliers et al. (2020)[101]	Randomized, double-blind, placebo-controlled, and active-controlled dose-response phase 2 study involving patients aged 18-64 who met the DSM-V criteria for insomnia disorder. Patients received placebo, 5, 10, 25, or 50 mg daridorexant, or 10 mg zolpidem and LSO, WASO, and adverse effects were recorded.	Significant dose-response relationship ($p < 0.011$) was found in reduction of WASO and LASP from baseline to days 1 and 2 with daridorexant when compared to placebo. Incidence of adverse events was 35%, 38%, 38%, and 34% in subjects treated with 5, 10, 25, and 50 mg daridorexant, respectively, compared with 30% for placebo and 40% for 10 mg zolpidem.	When compared to placebo and zolpidem, daridorexant showed significant improvement in sleep induction and maintenance with a minimal side effect profile and insignificant potential for residual next-morning sleepiness.
Ufer et al. (2022)[96]	Randomized, double-blind, double-dummy, placebo- and active-controlled 6 period crossover study that included healthy patients aged 18-55 who reported being a recreational user of sedatives defined by at least 10 lifetime recreational uses and at least one occasion within 12 weeks prior to screening. Patients were randomly given 50, 100, or 150 mg of daridorexant, 150 mg suvorexant, 30 mg zolpidem, or placebo and the drug-liking VAS was assessed after over 24 hours.	The drug-liking VAS of 50 mg daridorexant was significantly lower when compared to suvorexant and zolpidem ($p < 0.0001$). However, 100 mg and 150 mg daridorexant had similar drug-liking VAS when compared to suvorexant and zolpidem and increased with each dose when compared to placebo.	Higher doses of daridorexant are comparative to suvorexant and zolpidem concerning the potential for abuse, making it an important factor to consider when considering daridorexant for the use of insomnia.
Muehlan et al. (2020)[102]	Randomized, placebo- and active-controlled, 4-way crossover study including 60 healthy patients aged 50-79. Participants were randomized to receive 50 or 100 mg daridorexant, 7.5 mg zopiclone, or placebo and then SDLP was assessed to determine drug effect on driving performance.	SDLP was significantly increased with 7.5 mg zopiclone when compared to placebo on day 2 and day 5. SDLP was significantly increased by 2.19 with 50 mg daridorexant and 4.43 with 100 mg daridorexant on day 2 when compared to placebo. In contrast, SDLP values for both doses were significantly below the threshold of impairment (2.6 cm) and similar to the placebo.	Daridorexant can potentiate impaired driving performance after initial dose but not after repeated dosing; therefore, patients should be cautioned about driving when using daridorexant for insomnia.

Abbreviations: apnea/hypopnea index: AHI; total sleep time: TST; sleep efficiency index: SEI; wake after sleep onset: WASO; latency to persistent sleep: LPS; latency to sleep onset: LSO; standard deviation for lateral position: SDLP.

mg of daridorexant, or placebo during the double-blind treatment phase of study 1, and polysomnography was recorded for 2 consecutive nights at the end of months 1 and 3. Study 2 had a similar procedure; however, patients were randomized to receive 10 mg daridorexant, 25 mg daridorexant, or a placebo. In study 1 with 50 mg of daridorexant, wake time after sleep onset (WASO) and latency to persistent sleep (LPS) were significantly reduced after months 1 and 3.[97] Additionally, patients expressed a notable improvement in self-reported total sleep time and their IDSIQ sleepiness domain score had significantly decreased. Furthermore, results with 25 mg of daridorexant were the same in study 1 when compared to placebo, except for an insignificant difference in the IDSIQ sleepiness domain score. In study 2, results for 25 mg of daridorexant were slightly different than study 1. Although there was a significant improvement in WASO and self-reported sleep time, LPS and IDSIQ sleepiness domain scores were statistically insignificant when compared to the placebo.[97] Throughout both trials, patients reported mild adverse effects such as nausea, headache, dizziness, and fatigue. It was concluded that daridorexant was a well-tolerated medication that increased with efficacy with increasing dosages when compared to placebo. Another double-blind clinical trial assessed the efficacy and incidence of adverse effects with daridorexant.[72] Of the 1,005 subjects screened, 359 were randomized to receive 5, 10, 25, or 50 mg of daridorexant, 10 mg of zolpidem, or placebo for a period of 29 days.[72] When compared to placebo, all doses of daridorexant had significantly improved WASO and LPS.[72] Furthermore, the incidence of adverse events including headache, somnolence, diarrhea, and fatigue was 35%, 38%, 38%, and 34% in subjects treated with 5, 10, 25, and 50 mg of daridorexant, respectively; this was notably less than the incidence of 40% seen with zolpidem.[72]

SAFETY OF DARIDOREXANT

It is important to determine the safety of daridorexant in all individuals prior to the administration for the treatment of insomnia, including those with comorbidities such as obstructive sleep apnea (OSA) or the elderly. A randomized double-blind crossover study of 28 subjects found that single and repeated doses of 50 mg daridorexant do not result in impairment of respiratory function during and improves sleep in patients with mild and moderate OSA, but further studies must be completed to determine safety in patients with severe OSA who require the use of a CPAP.[103] There are multiple studies assessing the safety of daridorexant in the elderly including a clinical trial which found that doses greater than 10 mg had significantly reduced WASO and LPS compared to placebo with only minor adverse effects including headache, nasopharyngitis, fatigue, and gait disturbance.[101] A double-blind, placebo-controlled randomized trial evaluating 24 subjects between 65-80 years of age revealed that 5-25 mg of daridorexant was well-tolerated, and there was no difference between placebo or next-day effects 8-12 hours following the dose.[100]

In addition to safety in all individuals, daridorexant must be assessed for potentially dangerous adverse effects. A randomized, double-blind, four-period crossover study was performed to investigate the effect of daridorexant on QT prolongation and cardiac repolarization at therapeutic and subtherapeutic doses and demonstrated that daridorexant does not impair cardiac repolarization by inducing prolongation of QT.[99] The potential for abuse was investigated in healthy participants between 18-55 years old who were reported using sedatives for recreational use. Patients were randomly assigned 50, 100, or 150 mg of daridorexant, 150 mg of suvorexant, 30 mg of zolpidem, or placebo, and potential for abuse was measured via the drug-liking visual analog scale (VAS) E_{max}.[96] It was determined that the 50 mg dose of daridorexant had a significantly lower VAS E_{max} and a lower risk of abuse compared to suvorexant and zolpidem; however, the 100 mg and 150 mg doses were similar.[96] Finally, daytime driving performance following bedtime administration of daridorexant was investigated due to a high association between motor vehicle accidents and the use of hypnotics. Sixty participants were randomized to receive 50 or 100 mg of daridorexant, 7.5 mg of zopiclone, or placebo in the evening, and the standard deviation of the lateral position (SDLP) was measured on day 2 and day 5.[102] As expected, zopiclone significantly increased SDLP on both days indicating poor driving performance, and after day 2 of 50 mg or 100 mg of daridorexant, SDLP was significantly increased by 2.19 and 4.43 cm, respectively.[102] However, the increase in SDLP was not statistically significant on day 5 when compared to the placebo, indicating that driving is not as impaired after repeated dosing. As previously mentioned, it is also important to note that the incidence of adverse events in the highest dose of daridorexant was still considerably lower than the incidence of adverse events in zolpidem.[104]

CONCLUSION

Insomnia is a complex sleeping disorder that affects the lives of many individuals worldwide. It often occurs in the presence of psychiatric disorders and medical illnesses, which requires a tailored therapeutic approach. There are currently four approved categories of medications: DORAs, BZRAs, histamine receptor antagonists, and melatonin receptor agonists. Daridorexant is a DORA that was recently approved by the US FDA for the treatment of adults suffering from insomnia.

The FDA granted the approval for daridorexant after phase III trials demonstrated its safety and efficacy. However, some common adverse events observed in these trials were nasopharyngitis, headache, fatigue, dizziness, nausea, and somnolence. Nevertheless, daridorexant was effective in reducing insomnia symptoms, increasing daytime functioning, and improving the overall quality of sleep.

AUTHOR CONTRIBUTIONS

All authors were involved in the writing and editing of the manuscript.

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DISCLOSURES

There is no conflict of interest with the authors.

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