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Quviviq® (daridorexant): Sweet Dreams in the Setting of Chronic Insomnia

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Chronic insomnia, as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), as a sleep-wake disorder characterized by the inability to get an adequate amount of sleep, in terms of both quality and number of hours slept per night.[1] In contrast to acute insomnia, chronic insomnia is experienced for at least 3+ times per week over a minimum duration of three months.[1] There are worldwide estimates of 10-30% of the human population suffer from some form of insomnia.[2] In addition, chronic insomnia has been shown to both directly and indirectly cost the United States an estimated $100 billion in healthcare costs.[3] The negative economic impact on businesses has led to an estimated $65 billion dollars in decreased job performance, work-related accidents, and higher work absenteeism.[4]

Lack of sleep has been shown to have long-term effects on risk for weight gain, leading to potential comorbidities such as hypertension and diabetes.[5] In fact, there has been studies linking lack of sleep to possible altered hormone concentrations that play a role in regulating food intake and hunger. The endocannabinoid system (eCB) is a one of the key regulators of appetite activation, with 2-arachidonoylglycerol (2-AG) being the abundant agonist for of one of its main receptors, CB1.[6] An increase in 2-AG levels are shown to occur when there is a consistent lack of sleep, with elevated levels of 2-AG extending throughout the day.[6] Other studies have shown further impacts on hormones in different organ systems, displaying a positive correlation between lack of sleep and altered concentrations of the well-known "hunger hormones", leptin and ghrelin[7], and the potential link between recurrent sleep limitations and decreased insulin sensitivity and glucose tolerance.[8]

The diagnosis and clinical recommendations for treating chronic insomnia are split into two subcategories. Isolated sleep onset insomnia is characterized by difficulty in the initiation of sleep whereas sleep maintenance is manifested by difficulty maintaining sleep throughout the night.[9] According to the American Academy of Sleep clinical practice guidelines, the initial use of cognitive behavioral therapy in management carries a strong recommendation in initial treatment of chronic insomnia. The guidelines also state that pharmacological treatments overall for the disease state of insomnia carry a weak recommendation.[9]

Pharmacological treatments, such as benzodiazepines, non-benzodiazepine receptor agonists, melatonin receptor agonists (MRAs), and doxepin should only be considered when cognitive behavioral therapy has had unsatisfactory results and the pharmacological option carry more benefit than risk.[9] γ-Aminobutyric acid, well known as GABA, is a key inhibitory neurotransmitter with an integral role in sleep, playing a key role in the mechanism of actions for both benzodiazepines and non-benzodiazepine BZRAs. These two agents work to improve and prolong GABA's affinity to the GABA-a receptor, which causes sedative effects and eventual sleep.[10] In contrast, MRAs, such as ramelteon, are bind directly to the melatonin receptors, which are responsible for regulation of one's circadian rhythm and sleep enhancing effects.[11] Doxepin, within the class of tricyclic antidepressant medication class, is also used for insomnia due to associated anticholinergic side effects causing increased sedation and eventual recalibration of the circadian rhythm.[12] Furthermore, some of these agents have abuse potential, leading to possible misuse of medications and patient harm.[13]

Orexin-receptor antagonists (ORAs) are a relatively new drug class coming to the market in 2014 with the approval of suvorexant (Belsomra©). Though clinical trials have proven efficacy, ORA use has led to problems with heavy somnolence following administration. While likely the target for insomnia treatment, prolonged sedation is inconvenient to the working individual and poses a problem in the workplace.

Approved in January 2022, Quviviq© is the newest ORA on the market and works both on mitigating wakefulness and initiation of sleep, leading to a more seamless transition into high quality, non-interruptive sleep throughout the night. Unlike other medications in the same drug class, daridorexant was designed with a short half-life, helping patients achieve their goal to sleep throughout the night without feeling drowsy throughout the day.[14]

The purpose of this manuscript is to explore the use of the newest ORA on the market, further discuss relevant pharmacology, pharmacokinetic/pharmacodynamic parameters, clinical studies reviewing safety and efficacy, and its clinical implications.

IN THIS ISSUE

Pharmacology

Mechanism of Action

Orexin-A and Orexin-B are neuropeptides originating from the lateral hypothalamus that promote arousal responses, and more importantly normal wakefulness, by binding to the OX1 and OX2 receptors.[14] Orexin-A and B deficiency has been connected to narcolepsy and is speculated to have the opposite effect when levels are elevated.[15] Animal trials looking into the role of orexin-A and orexin-B in narcolepsy have demonstrated elevated levels during the normal hours of the day, while seeing a significant reduction in their levels at night. In similarity, human studies mimicked similar results to a much lesser extent.[14]

Development of a synthetic peptides used to block OX1 and OX2 receptors, like Quviviq©, has led to mitigated wakefulness and relief of symptoms of chronic insomnia sufferers.

Pharmacokinetics

With an absolute bioavailability of 62%, daridorexant reaches a peak plasma concentration between 1-2 hours.[16] However, with a highly caloric meal, the peak plasma concentration can be delayed by 1.3 hours and decreased altogether by 16%. Due to this, it is advised to refrain from taking daridorexant with a dense meal if you are going to bed soon after. Daridorexant primarily undergoes metabolism through hepatic CYP3A4 enzyme degradation with more than half of the medication excreted through the feces (58%).[16] With a volume of distribution (Vd) of 31 L, daridorexant is an almost completely plasma protein bound with 99.7% of the drug binding to plasma proteins.[16] The terminal half-life of daridorexant is approximately 8 hour.[16] Refer to **Table 1** for a summarization of daridorexant pharmacokinetic properties.

Table 1 | Select Oral Daridorexant Pharmacokinetics[16]

Absorption	
T_{max}[a]	1-2 hours
Bioavailability	62%
Distribution	
V_{ss}[b]	31 L
Protein Binding	99.7%
Metabolism	
	CYP3A4
Elimination	
$T_{1/2}$[d]	8 hours
Urine	28%
Feces	57%

[a]Time to maximum concentration; [b]Steady state volume of distribution; [c]Half-life

Clinical Trials

The FDA approval of Quviviq© for both sleep initiation and maintenance were based on data from two separate phase III, randomized, placebo-controlled studies. These two studies were intended to assess both safety and efficacy of daridorexant. Researchers Mignot et al. conducted two phase III, multicentered, randomized, double-blind, placebo-controlled trial that grouped 930 and 924 participants, respectively, into three separate groups. In both trials, two of those groups would receive two separate doses of daridorexant to compare to the placebo group.

To measure efficacy, sleep studies were conducted on participants to assess successful sleep initiation and sleep maintenance. A survey called the Insomnia Severity Index was used to assess patient eligibility based on disease severity and inclusion criteria[16] (example in **Appendix Table 1**) while the Insomnia Daytime Symptoms and Impacts Questionnaire (example in **Appendix Table 2**) was a self-reported three domain assessment that focused on the impact of chronic insomnia on alert/cognition, mood, and sleepiness throughout the daytime.[17] Below is a detailed summarization of described studies.

NCT03545191[18]

In order to demonstrate both the safety and efficacy of daridorexant, Mignot et al. conducted a phase III, multicentered, randomized, double-blind, placebo-controlled trial that grouped 930 participants into three equal treatment arms, daridorexant 50 mg, daridorexant 25 mg, or placebo.[18] The study was conducted in 81 different locations, with sites based in 10 different countries.[18] All three groups were to be administered medication in tablet form given once daily 30 minutes before bedtime. Participants were included if they were 18 years or older, had a current diagnosis of chronic insomnia as defined by DSM-5, a Insomnia Severity Index of 15 or greater, a written log signaling a lack of sleep quantity in participant's sleep diary, and a negative pregnancy test.[18] Exclusion criteria included those with a BMI < 18.5 or > 40.0 kg/m^2, a past medical history of another sleep disorder, were undergoing cognitive behavioral therapy for chronic insomnia, had self-reported episodes of daytime napping, had acute or unstable psychiatric diagnoses (history of suicidal ideation or attempt, acute or chronic psychiatric condition not controlled by therapy, severe depression, and/or alcohol or drug misuse), had a Mini Mental State Examination (MMSE) score of less than 25 in participants who were over the age of 50, pregnant, or have any disease or conditions in which it put the participation of the subject at risk.

The baseline characteristics were equal among all groups with average of 55.4 years old (ranging from 18 to 88 years of age) with ethnic category breakdown of 90% White, 8% African American, 1% Asian, and less than 1% of other race.[18] The primary endpoints in this study were parameters measured through sleep studies assessed by an independent scorer that were collected after months 1 and 3 known as wake time after sleep onset (WASO) and latency to persistent sleep (LPS). WASO measures the degree of wakefulness and includes the period of time that elapses after each waking episode throughout the night.[19] LPS is defined as the amount of time elapsed after the lights have been turned off and the time it takes for the patient to fall asleep.[19]

Secondary endpoints included changes from the baseline in self-reported total sleep time and the sleepiness domain score, known as the Insomnia Daytime Symptoms and Impacts Questionnaire (IDSIQ).[18] These also were collected at months 1 and 3.

Study results indicate both treatment arms had significantly lower WASO and LPS results when compared to the placebo group. The group taking daridorexant 50 mg reported significantly lower mean WASO differences compared with the placebo group at both the 1 month (-18.3 min) and 3rd month (-22.8 min) checkpoints, p<0.0001. The LPS was reported with a mean differences of -11.7 min and -11.4 min, respectively, at the 1 month and 3-month checkpoint, p<0.0001. The group taking daridorexant 25 mg had similar results against the placebo group indicating a statistically significant decreased WASO and LPS.[18] A summary of these findings can be seen in **Table 2.**

When comparing secondary outcomes, there was a difference in the two daridorexant treatment arms regarding self-reported total sleep time and IDSIQ sleepiness domain score.[18]

Table 2 | Primary Outcome Results[18]

Trial		Outcome[a]	Intervention	Result (95% CI)	P-Value
NCT03545191 (n=310 per treatment arm)	WASO[b]	1 month	Daridorexant 50mg Daridorexant 25mg Placebo	-29.0 (-32.7 to –25.3) -18.4 (-22.1 to –14.7) -6.2 (-9.9 to –2.5)	<0.0001
		3 months	Daridorexant 50mg Daridorexant 25mg Placebo	-29.4 (-33.4 to –25.4) -23.0 (-27.0 to –19.0) -11.1 (-15.1 to –7.1)	<0.0001
	LPS[c]	1 month	Daridorexant 50mg Daridorexant 25mg Placebo	-31.2 (-34.5 to –27.9) -28.2 (-31.5 to –24.8) -19.9 (-23.2 to –16.5)	<0.0001 0.0005
		3 months	Daridorexant 50mg Daridorexant 25mg Placebo	-34.8 (-38.1 to –31.5) -30.7 (-34.0 to –27.4) -23.1 (-26.5 to –19.8)	<0.0001 0.0015
NCT03575104 (n=307 per treatment arm)	WASO[b]	1 month	Daridorexant 25mg Daridorexant 10mg Placebo	-24.2 (-28.5 to –19.9) -15.3 (-19.5 to –11.1) -12.6 (-16.8 to –8.3)	0.0001 0.37
		3 months	Daridorexant 25mg Daridorexant 10mg Placebo	-24.3 (-29.0 to –19.5) -16.0 (-20.7 to –11.2) -14.0 (-18.8 to –9.2)	0.0028 0.57
	LPS[c]	1 month	Daridorexant 25mg Daridorexant 10mg Placebo	-26.5 (-30.6 to –22.3) -22.6 (-26.7 to –18.5) -20.0 (-24.1 to –15.9)	0.03 0.38
		3 months	Daridorexant 25mg Daridorexant 10mg Placebo	-28.9 (-33.4 to –24.4) -23.1 (-27.6 to –18.6) -19.9 (-24.4 to –15.4)	0.0053 0.32

[a]Change from baseline; [b]Wake time after sleep onset; [c]Latency to persistent sleep

While the group receiving the 50 mg dose was able to report a significantly increased self-reported total sleep time at 1 month (22.1 min) and 3 months (19.8 min), as well as an improved IDSIQ sleepiness domain score at the 1 month (-1.8) and 3 month point (-1.9), the 25 mg dosed group did not fare the same. The 25 mg dose group did report a significantly increased self-reported total sleep time at 1 month (12.6 min) and 3 months (9.9 min) but did not achieve an improved IDSIQ score (-0.8 at 1 month and -1.0 at 3 months) compared to the placebo group.[18] A summary of these findings can be seen in **Table 3.**

NCT03575104

Similar to the previously conducted study, Mignot et al. conducted another phase III, multicentered, randomized, double-blind, placebo-controlled trial that grouped 924 participants into three equal treatment arms, daridorexant 25 mg, daridorexant 10 mg, or placebo.[18] All of the inclusion and exclusion criteria were kept the same as the previous study.

Results in relation to the primary and secondary endpoints varied from the previous study conducted. The daridorexant 25 mg treatment group was still able to produce statistically significant WASO scores with a 95% CI compared to the placebo group at the 1-month (-11.6 min, p<0.0001) and 3rd month (-10.3 min, p=0.0028) checkpoints. However, this treatment group was not able to produce the same statistically significant LPS results, as there was no significant differences in comparison to the placebo group at the 1-month (-6.5 min, p=0.030) and 3rd month (-9.0 min p=0.0053) checkpoints. Furthermore, the daridorexant 10 mg treatment arm was not able to produce any significantly different results in comparison the placebo group, with the WASO scores at both the 1 month (-2.7 min, p<0.37) and 3rd month (-3.2 min, p=0.57) deemed too small of a deviation from placebo. The LPS results fared the same, with the 1-month (-2.6 min, p=0.38) and 3-month (-3.2 min, p=0.32) resulting in no significant difference for proof of efficacy.[18] A summary of these findings can be seen in **Table 2**.

Secondary endpoints results further support daridorexant 20 mg as efficacious therapy, while further revealing the 10 mg treatment dose inability to deliver benefit in comparison to the placebo group. The 25 mg dose arm was able to repeat results from the previous study, generating significantly increased self-reported total sleep time at 1 month (16.1 min, p<0.0001) and 3 months (19.1 min, p<0.0001), but did not achieve an improved IDSIQ score (-0.8, p=0.073 at 1 month and -1.3, p=0.012 at 3 months) compared to the placebo group.[13] In addition, the daridorexant 10 mg treatment group was not able to produce results of big enough scale compared to the placebo group, with the self-reported total sleep time at 1 month (13.4 min, p=0.0009) and 3 months (13.6 min, p=0.0028).[13] The IDSIQ sleepiness domain scores for the daridorexant 10 mg treatment arm was also not able to produce scores of statistical significance (-0.8, p=0.073 at 1 month and -1.3, p=0.012 at 3 months).[18] A summary of findings can be seen in **Table 3.**

Adverse Effects and Precautions

Headache was reported in 6% of patients taking the 25 mg and 7% reported when taking the 50 mg. Also reported was somnolence, stated to effect 6% of patients taking the 25 mg and 5% reported when taking the 50 mg.[16] Out of all the adverse events reported, nasopharyngitis was the highest reported adverse reaction in all treatment arms, including placebo. Refer to **Table 4** for a detailed summary of all adverse reactions reported.

Daridorexant is contraindicated in patients who have narcolepsy. A 50 mg dose of daridorexant administration with a blood alcohol level of greater than or equal to 0.6 g/L led to compounding effects on impairment of bodily function, leading to a reduced ability to maintain postural stability and mental awareness.[16] Daridorexant should also be used cautiously when operating heavy machinery. There were signs of impairment after initial usage, however impairment eventually went away after day 5 of repeated use.[20]

Table 3 | Secondary Outcome Results[18]

Trial		Outcome[a]	Intervention	Result (95% CI)	P-Value
NCT03545191 (n=310 per treatment arm)	STST[b]	1 month	Daridorexant 50mg Daridorexant 25mg Placebo	43.6 (38.2 to 49.1) 34.2 (28.7 to 39.6) 21.6 (16.1 to 27.0)	<0.0001 0.0013
		3 months	Daridorexant 50mg Daridorexant 25mg Placebo	57.7 (51.2 to 64.2) 47.8 (41.3 to 54.3) 37.9 (31.4 to 44.4)	<0.0001 0.033
	IDSIQ[c]	1 month	Daridorexant 50mg Daridorexant 25mg Placebo	-3.8 (-4.3 to –3.2) -2.8 (-3.3 to –2.2) -2.0 (-2.6 to –1.5)	<0.0001 0.055
		3 months	Daridorexant 50mg Daridorexant 25mg Placebo	-5.7 (-6.4 to –5.0) -4.8 (-5.5 to –4.1) -3.8 (-4.5 to –3.1)	0.0002 0.053
NCT03575104 (n=307 per treatment arm)	STST[b]	1 month	Daridorexant 25mg Daridorexant 10mg Placebo	43.8 (38.1 to 49.4) 41.0 (35.4 to 46.6) 27.6 (22.0 to 33.3)	<0.0001 0.0009
		3 months	Daridorexant 25mg Daridorexant 10mg Placebo	56.2 (49.8 to 62.5) 50.7 (44.4 to 57.0) 37.1 (30.8 to 43.5)	<0.0001 0.0028
	IDSIQ[c]	1 month	Daridorexant 25mg Daridorexant 10mg Placebo	-3.5 (-4.1 to –2.9) -3.2 (-3.8 to –2.6) -2.8 (-3.3 to –2.2)	0.073 0.30
		3 months	Daridorexant 25mg Daridorexant 10mg Placebo	-5.3 (-6.0 to –4.6) -4.8 (-5.4 to –4.1) -4.0 (-4.7 to –3.3)	0.012 0.14

[a]Change from baseline; [b]Wake time after sleep onset; [c]Latency to persistent sleep

Vigilance is needed in prescribing daridorexant, as it is metabolized by CYP3A4. Metabolic inducers and inhibitors will affect the exposure to daridorexant, which increase the risk of adverse reactions and decrease the efficacy of the drug.[16]

Special Populations

Renal & Hepatic Impairment

In patients who have severe renal dysfunction, it was found that no dose adjustments were needed. The same cannot be said about patients who are hepatically impaired. Due to the hepatic metabolism of the drug, the reduction of dose is needed in patients with moderate hepatic impairment (Child-Pugh Score 7-9). Severely hepatic impairment has not been studied and it is not recommended in patients seeking to take daridorexant.[16]

Pregnancy & Lactation

Animal studies in pregnant rats and rabbits at doses 8-10 times the maximum normal dose has shown no abnormalities or fetal toxicity in offspring. Breastfeeding rats were given a dose 9 times the maximum dose of daridorexant while breastfeeding, with the offspring showing no stunted developmental growth or injury.[16] Caution is advised in pregnant females due to limitations with available data.

Geriatric Patients

Trials showed that there is an increased risk of fall with patients who take this medication, however dosing considerations must be taken due a proven lack of adjustment needed in patients over the age of 65. Elderly patients should be cautioned about the side effects and the potential risks.[16]

Dosage and Administration

Daridorexant is available as a 25 mg and 50 mg tablet. It is recommended that it be taken 30 minutes before bed, with enough time in between falling asleep and waking up (preferably 7 hours).[21] If one forgets to take before bed, take the medication as soon as you remember, however it is preferable to not take daridorexant if there is less than a full night worth of sleep (greater than or equal to 7 hours) left due to potential side effects the next morning.[16]

Cost and Availability

According to the manufacturer, Quviviq© has been ready to give to patients since May 2022, with the FDA classifying it as a Schedule IV controlled substance. According to online sources, a 30-day supply of either dose ranges from $456-$483.[22] Using the same sources, a 30 day supple of suvorexant, the most common ORA prescribed, ranges between $404-$475.[23] According to the manufacturer's company website, daridorexant does have a patient assistance program that allows a patient to receive a 30 day supply for as little $0 and every refill for as little as $25.[24] Due to the drug just getting into the market in May 2022, pharmacy service providers are currently working with insurance companies to verify coverage.[25]

Clinical Implications

According to the American Academy of Sleep Medicine, 2-6 percent of people who have some degree of insomnia will likely use medication to aid them throughout the night.[26] Although not as favored over cognitive behavioral therapy, the shortage of medical sleep specialists and sleep medical centers has led to a lack of resources and education for those suffering from varying degrees of insomnia.[27] The lack of resources to an individual's disposal can lead to prescribing of sleep aiding medications that can help, but may also lead to undesired side effects. The approval of daridorexant, the newest orexin-receptor antagonist, has the potential to surpass its predecessors with data backing its favorable side effect profile while still maintaining efficacy. Orexin receptor antagonists have had problems with somnolence issues that were

Table 4 | Incidence Rate of Common Adverse Effects with Daridorexant[18]

Adverse Effect	Quviviq® 50mg (n=310)	Quviviq® 25mg (n=619)	Quviviq® 10mg (n=306)	Placebo (n=615)
Nausea	7	4	3	6
Fall	1	5	4	11
Dizziness	7	12	4	6
Headache	19	31	12	26
Nasopharyngitis	20	34	32	36

usually associated with other drug classes used to treated chronic insomnia. Both reviewed clinical trials displayed promising results in Quviviq© ability to improve the initiation of sleep and maintenance throughout the night. In the first clinical trial, when compared to the placebo group, both treatment arms (50 mg and 25 mg dosing 30 mins before bedtime) had statistically significant lower primary endpoint results. Secondary endpoints further bolstered the case for daridorexant use, with participants self-reporting improved total sleep times at both dosages tested against the placebo groups, however the 25 mg dose 30 mins before bedtime group was not able to show a significantly improved IDSIQ score compared to the placebo group. The second study was able to further support the efficacy of the 25 mg dose of daridorexant by again highlighting statistically significant WASO score, however, was not able to produce an LPS signifying anything statistically significant. Study 2 was also able to establish the 10 mg dose inability to significantly improve sleep when compared to the placebo group. These two studies were able to establish both the 50 mg and 25 mg doses of daridorexant as viable options to improved sleep outcome, with the 50 mg dose also displaying a potential impact on improved daily productivity.

Daridorexant has shown potential of having less abuse risk compared to other therapies.[28] A study comparing its abuse potential to zolpidem and suvorexant was conducted in which daridorexant demonstrated a significantly lower "drug-liking" rating than comparators. However, the rating was still higher than the placebo, prompting caution for abuse potential.[28] Nevertheless, in later placebo-controlled phase 3 clinical studies, daridorexant use for up to 12 months did not display any indication of abuse liability.[28]

Conclusion

Quviviq© (daridorexant) is the latest orexin receptor antagonist developed for the management of chronic insomnia that assists with the initiation and maintenance of sleep. As displayed by the clinical trials, as well as studies comparing its abuse potential to other agents, daridorexant is a viable option for insomnia due to continued efficacy while maintaining a shorter half-life compared to other alternatives. Although promising, more evidence comparing it to other agents is needed in order to give a definite recommendation over other sleep-aiding medications, specifically in efficacy and side effect profile.

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Drug Update:
New Indications and Dosage Forms
September 2022

Relyvrio® (sodium phenylbutyrate/taurursodiol) Oral Suspension
New Compound: Indicated for the treatment of amyotrophic lateral sclerosis (ALS) in adults; mechanism of action unknown

Omlonti® (oomidenpag isopropyl) Ophthalmic Solution
New Compound: Approved for the use in patients with glaucoma or ocular hypertension working to reduce elevated intraocular pressure

Terlivaz® (terlipressin) Injection
New Molecule: Vasopressin receptor agonist indicated to improve kidney function in adults with hepatorenal syndrome with rapid reduction in kidney function; limited use in patients with SCr>5mg/dL

Sotyktu® (deucravacitinib) Oral Tablets
New Compound: Tyrosine kinase 2 (TYK2) inhibitor indicated for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy; not recommended in combination with other immunosuppressants