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Dayvigo® (lemborexant): Putting unsafe insomnia treatment to bed

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Insomnia is a common sleep disorder that is characterized by the inability to fall asleep or maintain sleep.[1] Short-term, occasional insomnia affects 30% to 50% of the population, while chronic insomnia disorder affects approximately 5-10% of the population in developed nations.[2-4] The prevalence of insomnia increases in the medically and psychiatrically ill and the elderly populations.[5] Causes of insomnia can vary widely and may include stress, poor sleep habits, or inconsistent work and travel schedules. The total cost of insomnia may exceed $100 billion per year, when including cost of treatment, insomnia-related accidents, and loss of productivity.[6] Moreover, insomnia accounts for more than 5.5 million visits to primary care physicians each year, thus it is important to have appropriate and efficacious options for treatment.[7] The goal of insomnia treatment is to improve sleep and alleviate the dysfunction or distress caused by this disorder.[5]

Diagnostic criteria for insomnia disorder, as outlined by The Diagnostic and Statistical Manual of Mental Disorders (DSM-5), includes difficulty initiating, maintaining, or returning to sleep at least three days per week for at least three months or a complaint of clinically significant daytime impairment despite adequate opportunity for sleep.[1] The American Academy of Sleep Medicine (AASM) released a Clinical Practice Guideline for the Pharmacologic Treatment of Chronic Insomnia in Adults in 2017. All the pharmacologic therapies recommended for the treatment of insomnia in this guideline are deemed as a weak recommendation by the authors due to low quality of evidence.[5] Treatment of insomnia should start with cognitive behavioral therapy (CBT) as the primary treatment and should be initiated in all patients. For patients with chronic insomnia who fail to respond to CBT or require adjunct therapy, pharmacologic treatment can be considered.[5]

In general, drugs with a shorter duration of action are used to target sleep-onset insomnia (difficulty falling asleep), while longer-acting medications are used to address sleep-maintenance insomnia (difficulty staying asleep).[8] Drug selection is also impacted by presence of comorbid conditions such as depression, anxiety, or neuropathic pain in which antidepressants, anxiolytics, or antiepileptic medications are used, respectively. First-line treatment includes short-intermediate acting benzodiazepines (temazepam, triazolam), newer benzodiazepine receptor agonists ("Z-drugs" such as zolpidem, eszopiclone, and zaleplon), or ramelteon.[5] No specific agent is recommended over another and selection of the appropriate treatment should be based on patient needs and response. For instance, zaleplon is recommended for sleep onset, while eszopiclone and zolpidem are recommended for both sleep onset and maintenance. Ramelteon is can be used for sleep onset insomnia but does not address sleep maintenance.5 Regardless of the type of therapy, the patient should be clinically reassessed every two to four weeks until insomnia is stable or resolved, and then every six months to assess for relapse or recurrence.[5]

Second-line therapy includes alternate short-intermediate acting benzodiazepine receptor antagonists or ramelteon if the initial agent was unsuccessful.[5] Sedating antidepressants, such as trazadone, amitriptyline, doxepin, and mirtazapine can be used if also treating comorbid depression and anxiety as third-line therapy. There is little evidence that these drugs are efficacious when used alone and other factors such as comorbid conditions, treatment history, side effects, and cost should guide therapeutic decisions. Benzodiazepine receptor agonists or ramelteon can be combined with sedating antidepressants, but patients should be carefully monitored.[5] Anti-epilepsy medications, such as gabapentin or tiagabine, and antipsychotics, such as quetiapine and olanzapine, may be useful in the setting of patients who benefit from the primary action of the drug as well as the sedating effects to treat comorbid insomnia. The guidelines recommend avoiding these drugs alone as primary treatment for insomnia due to side effects. Barbiturates, chloral hydrate, and "non-barbiturate non-benzodiazepine" drugs (such as meprobamate) are FDA-approved for insomnia but are not recommended as treatment due to their adverse effects, narrow therapeutic index, and tendency towards tolerance and dependence.[5]

When a draft of the guidelines was released to the public for comment, the AASM responded to requests to include a recommendation for suvorexant (BELSOMRA), which was the first

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approved drug belonging to a class of medications called dual orexin receptor antagonists (DORAs) in 2014.[5] The guidelines were updated to recommend use of suvorexant for treatment of sleep maintenance insomnia but did not give a recommendation as to its sequence in therapy. DAYVIGO® (lemborexant) is the second FDA approved medication in the DORA drug class and was approved on December 20th 2019. It is indicated for insomnia characterized by difficulties with sleep onset and/or maintenance.[9] The Drug Enforcement Administration (DEA) has deemed both suvorexant and lemborexant as schedule IV.10 The purpose of this article is to review the safety and efficacy of lemborexant for the treatment of insomnia.

Pharmacology

Mechanism of Action

The mechanism of action of lemborexant is presumed to be through antagonism of orexin receptors, which play a role in wakefulness.[9] Neuropeptides orexin A and B bind to receptors OX1R and OX2R to promote wake drive, thus blocking the binding of these neuropeptides suppresses the wake drive.[9]

Pharmacokinetics

Lemborexant is a small, orally bioavailable drug which shows good brain penetration with a time to max concentration (Tmax) of approximately one to three hours or three to five hours following a high-fat, high calorie meal.[9] It is 94% protein-bound in vitro and is primarily metabolized in the liver by CYP3A4 and to a lesser extent by CYP3A5. The major circulating metabolite is M10, which is pharmacologically active and binds to orexin receptors with similar affinity as the parent compound. The parent drug is extensively metabolized, with approximately 57% recovered in the feces and 29% in the urine (<1% unchanged). The effective half-life of a 5 mg dose is 17 hours and 19 hours for a 10 mg dose.[9]

Pharmacodynamics

Lemborexant binds to orexin receptors OX1R and OX2R and acts as a competitive antagonist, with IC50 values of 6.1 nM and 2.6 nM, respectively.[9] M10 is a major metabolite of lemborexant and binds to orexin receptors, OX1R and OX2R, with comparable affinity as the parent drug (IC50 values of 4.2 nM and 2.9 nM respectively). Lemborexant has not been shown to prolong the QTc interval in clinical trials, when given at five times the recommended dosage.[9]

Clinical Trials

The FDA approval of lemborexant was based off of two phase III clinical trials, called Sunrise 1 and 2. Two phase I special safety studies were conducted by the manufacturer to evaluate the drug's impact on middle of the night safety, as well as the effect on next-day postural stability, memory, and driving. A phase II study was conducted to examine the dose response to various strengths of lemborexant. Additionally, Kishi et al. conducted a systematic review and network meta-analysis study to compare both approved DORAs, suvorexant and lemborexant. The following section will highlight the results of the two phase III clinical trials, used for the approval of the drug, as well as the results of the various safety studies. The results of the Sunrise 1 and 2 clinical trials will be summarized in **tables 2 and 3**. The clinical implications of these results and comparison to alternate treatment options will be analyzed in the discussion section.

Table 1 | Select Lembexorant Pharmacokinetics[9]

Absorption	
T_{max}[a]	1-3 hours
Distribution	
Vd[b]	1970 L
Proetin binding	94% (in vitro)
Metabolism	
Liver	CYP3A4 (majority), CYP3A5 (lesser extent)
Elimination	
T1/2[c]	17 hours (5 mg); 19 hours (10 mg)
Fecal Excretion	57.4%
Urinary Excretion	29.1% (<1% unchanged)

[a]Time to maximum plasma concentration; [b]Volume of distribution; [c]Half-life

Sunrise 1 Trial

Conducted by the manufacturer Eisai, the Sunrise 1 trial was a phase III, randomized, double-blind, placebo-controlled, multicenter trial conducted at sites across North America and Europe.[11] It was conducted in females aged 55 and older and males 65 and older who met the DSM-5 diagnostic criteria for insomnia disorder. Participants were required to have a history of subjective wake-after-sleep onset (sWASO) of 60 minutes or greater at least three nights a week in the past month, spend 7-9 hours in bed regularly, an Insomnia Severity Index (ISI) score of 13 or greater, have evidence of sleep maintenance insomnia, report a habitual bedtime between 21:00 and 24:00 and habitual waketime between 05:00 and 09:00. Subjective sleep criterion was confirmed by sleep diary. The ISI is a validated tool that is used to assess the severity of subjective insomnia symptoms; The total score ranges from 0-28 with a score of 0-7 indicating no insomnia, 8-14 sub-threshold insomnia, 15-21 moderate insomnia, and 22-28 severe insomnia. Objective WASO was also required for inclusion and was defined as at least 60 minutes of WASO on two consecutive polysomnograpy (PSG) tests. Participants were excluded with obstructive sleep apnea, clinically significant COPD, CV disease, severe renal or hepatic impairment, narcolepsy, females of childbearing potential (premenopausal), excessive caffeine use, history of alcohol or drug dependency, HIV positive, prolonged QTc interval, a Beck Depression Inventory score >19, a Beck Anxiety Index score >15, history of sleep-eating or violent sleep behaviors, people that habitually napped more than three times per day, or failed treatment with suvorexant.

A total of 1006 participants underwent randomization and were assigned to placebo, zolpidem tartrate ER 6.25 mg (active comparator), lemborexant 5 mg, or lemborexant 10 mg once nightly in a 4:5:5:5 ratio.11 The zolpidem 6.25 mg dose was chosen based on prescribing recommendations for elderly patients 65 years and older. Participants were treated for 30 days and followed up for 14-18 days after treatment completion. The participants were comprised of 86.4% women, median age of 63 years old, 72% White, 25% African American, and 45% ≥65 years of age. Based on the ISI, insomnia severity was moderate at baseline across all treatment groups and all other with baseline characteristics between the treatment arms well balanced.

Table 2 | Sleep Onset Endpoints from Sunrise Trials[11,12]

Trial	Primary Outcome	Intervention	Result (SD[a])	LSGM[b] treatment ratio versus placebo (95% CI[c])	LSGM treatment ratio vs zolpidem (95% CI)
Sunrise 1 Trial NCT02783729	Mean change from baseline to end of treatment (days 29/30) in LPS[d]	Placebo	-7.9 (32.0)	-	-
		Lemborexant 5 mg	-19.5 (33.1)	0.77 (0.67 to 0.89)	0.63 (0.57 to 0.72)
		Lemborexant 10 mg	-21.5 (32.4)	0.72 (0.63 to 0.83)	0.59 (0.52 to 0.68)
		Zolpidem ER 6.25 mg	-7.5 (35.1)	1.22 (1.06 to 1.40)	-
Sunrise 2 Trial NCT02952820	Mean change from baseline to six-months in subjective sSOL[e]	Placebo	-11.43	-	-
		Lemborexant 5 mg	-21.81	0.732 (0.636 to 0.843)	-
		Lemborexant 10 mg	-28.21	0.701 (0.607 to 0.810)	-

[a]Standard deviation; [b]Least squares geometric mean; [c]Confidence interval; [d]Latency to persistent sleep (defined as the number of minutes from lights off to the first 10 consecutive minutes of non-wakefulness as measured by overnight polysomnography (PSG) monitoring; functioned as a measurement of sleep onset); [e]Subjective sleep onset latency (defined as the estimated minutes from when a patient attempted to sleep until sleep onset as measured by a patient-reported sleep diary)

The primary efficacy endpoint was the mean change in latency to persistent sleep (LPS) from baseline to end of treatment (days 29/30) for lemborexant vs placebo, which functioned as a measurement of sleep onset.11 LPS was defined as the number of minutes from lights off to the first 10 consecutive minutes of non -wakefulness and was measured by overnight PSG monitoring. The key secondary efficacy endpoints were changes from baseline to end of treatment in sleep efficiency (SEF) and wake after sleep onset (WASO) compared to placebo. Additional secondary endpoints included subjective patient-reported measures of sleep onset and maintenance as recorded by sleep diaries. Other prespecified exploratory endpoints included change from baseline to one month in LPS for lemborexant 5 mg and 10 mg vs zolpidem ER.

For the purpose of these results, the treatment effect refers to the ratio of [Day 29/30 LPS / Baseline LPS] for lemborexant versus placebo, where a smaller ratio corresponds to a greater improvement. For objective sleep onset, measured as LPS, the treatment effect was 0.8 for lemborexant 5 mg and 0.7 for lemborexant 10 mg.[10]

The results of the study demonstrated both lemborexant 5 mg and 10 mg were statistically significant in achieving objective changes in time to sleep onset.[11] When comparing baseline to after one month of therapy, the average LPS (minutes) was decreased by approximately eight minutes in the placebo group, 7.5 minutes in the zolpidem group, 19.5 minutes in the lemborexant 5 mg group, and 21.5 minutes in the lemborexant 10 mg group.[11] After one month of treatment, (Least Squares Geometric Mean (LSGM) treatment ratio vs placebo for lemborexant 5 mg was 0.77; 95% CI: 0.67-0.89; $P < 0.001$ and for lemborexant 10 mg was 0.72; 95% CI: 0.63-0.83; $P < 0.001$). In comparison to zolpidem therapy: (LSGM treatment ratio vs zolpidem for lemborexant 5 mg was 0.63; 95% CI: 0.56-0.72; $P < 0.001$ and for lemborexant 10 mg was 0.59; 95% CI: 0.52-0.68; $P < 0.001$).

For objective sleep maintenance, both doses of lemborexant (5 mg, 10 mg) therapy reduced WASO by greater than 45 minutes as compared to baseline.[11] WASO at nights 29 and 30 was also significantly improved in lemborexant 5 mg group at -24.0 min (95% CI: −30.0 to −18.0 min; $P < 0.001$), lemborexant 10 mg group at - 25.4 min (95% CI: −31.4 to −19.3 min; $P < 0.001$), and zolpidem 6.25 mg group -16.3 minutes (95% CI: -22.3 to -10.2 min; $P < 0.001$) compared to placebo. In terms of comparing lemborexant to the active comparator, zolpidem, the WASO LSM treatment difference for lemborexant 5 mg vs placebo was a reduction of 7.7 min (95% CI: −13.4 to −2.1 min; $P = .007$) and for lemborexant 10 mg there was a reduction of 9.1 min (95% CI: −14.8 to −3.5 min; $P = .002$). Both doses of lemborexant lead to an increase in SEF, which translates into greater than 60 minutes more sleep per night as compared to baseline ($p<0.001$). The LSM treatment difference for lemborexant 5 mg vs placebo was 7.1% (95% CI: 5.6-8.5; $P < 0.001$) and for lemborexant 10 mg it was 8.0% (95% CI: 6.6-9.5; $P < 0.001$). The LSM treatment difference for lemborexant 5 mg vs zolpidem was 3.9% (95% CI: 2.5-5.3; $P < 0.001$) and for lemborexant 10 mg it was 4.9% (95% CI: 3.5-6.3; $P < 0.001$).

Lemborexant 5 mg provided statistically significant benefit compared to zolpidem therapy with regards to subjective sleep onset at the end of month 1, 0.88; 95% CI: 0.80-0.98; $P = 0.02$) and lemborexant 10 mg therapy 0.81; 95% CI: 0.73 to 0.90; $P < 0.001$ vs zolpidem. However, neither doses of lemborexant provided a statistically significant benefit compared with zolpidem therapy on subjective SEF or subjective WASO.

Overall, lemborexant was well tolerated with 2 [1.0%] in the placebo group, 6 [2.3%] in the zolpidem group, 2 [0.8%] in the lemborexant 5 mg group, and 3 [1.1%] in the lemborexant 10 mg group discontinuing the study as a result of adverse events.[11] None of the serious adverse events reported were treatment related and all adverse effects reported were transient according to the investigators. Mild sleep paralysis was reported in one patient in the lemborexant 5 mg group and three patients in the lemborexant 10 mg group. Falls were reported by four participants but none were related to the treatment according to the investigator. Additionally, there was no evidence of rebound insomnia in the two weeks following the end of the trial with either lemborexant or zolpidem therapies.[9,11]

Sunrise 2 Trial

Sunrise 2 was a phase III multicenter, randomized, placebo-controlled, double blind, global trial conducted in Japan, North America, South America, Europe, Asia, and Oceania. It was conducted in adults ages 18 and older who met the DSM-5 criteria for insomnia disorder.[12] Participants included in the study must have a history of subjective Sleep Onset Latency (sSOL), defined as the estimated minutes from when a patient attempted to sleep until sleep onset, of ≥30 minutes on at least three nights per week in the previous four weeks and/or sWASO ≥ 60 minutes on at least three nights per week in the previous four weeks, spend seven to nine hours in bed regularly, have a regular bedtime between 21:00 and 01:00, a regular wake time, and get out of bed for the day between 05:00 and 10:00, and Insomnia Severity Index (ISI) score ≥15. The subjective sleep measures were confirmed by a sleep diary. Similar exclusion criteria from the Sunrise 1 Trial was applied to the Sunrise 2 Trial. More detailed inclusion and exclusion criteria can be found on clinicaltrials.gov (NCT02952820).[13]

The Sunrise 2 trial lasted 12 months (longer than Sunrise 1) and examined the safety and efficacy of lemborexant in 971 participants aged 18-88 with insomnia disorder.[12] The median age of participants was 55 years old, 68% were female, and 28.5% were non-white. Approximately 28% of the patients that were randomized and treated were 65 years of age or older. The study design included a six-month placebo-controlled treatment period, with a six-month parallel-group extension period, and a 14-day follow-up period. Therefore, all participants received lemborexant for at least six months and also received placebo at some point during the study but were not told when the medication was changed. During the first six months of the trial, patients were randomized to receive either lemborexant 5 mg, lemborexant 10 mg, or placebo. The primary outcome was the mean change from baseline in sSOL. The secondary endpoints were change from baseline in subjective SEF (sSEF), defined as the proportion of time spent asleep per time in bed, and sWASO after 6 months. The primary and secondary efficacy outcomes were assessed using a patient-reported sleep diary.

For the purpose of these results, treatment effect refers to the ratio of [Month six sSOL / Baseline sSOL] for lemborexant vs placebo, such that a smaller ratio corresponds to a greater improvement. The treatment effect was 0.7 for lemborexant 5 mg and 0.7 for lemborexant 10 mg.10 Lemborexant resulted in statistically significant improvements compared to placebo in sSOL, which was reduced from baseline by 21.81 minutes for lemborexant 5 mg, 28.21 minutes for lemborexant 10 mg, and 11.43 minutes for placebo; $p<0.0001$ for both treatment group comparisons.[14] Additionally, the study showed statistically significant improvements in sSEF where the least squares mean (LSM) change for lemborexant 5 mg was 14.19% ($p=0.0001$), for lemborexant 10 mg was 14.31% ($p<0.0001$), as compared to placebo which was 9.64%. Moreover, there was statistically significant improvements in sWASO where lemborexant 5 mg reduced this endpoint by 46.75 minutes ($p=0.0005$) , lemborexant 10 mg reduced it by 41.95 minutes ($p=0.0105$), as compared to placebo which reduced it by 29.28 minutes.[12]

Adverse events reported during the trial were mostly mild to moderate in severity.[14] Serious or severe adverse events related to treatment were similarly low, occurring in less than 4% of subjects in each group. As summarized in table 4, the most common adverse effects that occurred in over 5% of both lemborexant treatment groups were somnolence, influenza, and headache. These adverse effects occurred at a higher rate than in the placebo group. Discontinuation rates due to adverse events were similar between placebo and lemborexant 5 mg (3.8% and 4.1%, respectively), and higher for lemborexant 10 mg (8.3%).[14]

Postural Instability, Auditory Awakening, and Cognitive Performance

Eisai conducted a phase I study to compare the effect of lemborexant versus zolpidem or placebo on postural instability, auditory awakening, and cognitive performance in the middle of the night and in the morning. It was a randomized, double-blind, placebo-controlled and active-comparator, four-period crossover study that included women over 55 and men over 65 years old.[15] Participants were given either lemborexant 5 mg, lemborexant 10 mg, zolpidem ER 6.25 mg or placebo and a 14-day washout followed all four treatments. Overall the change from baseline in mean overnight body sway, which is a measure of postural stability, was significantly higher in zolpidem as compared to both strengths of lemborexant. The results of the study were summarized in a press release from Eisai, which noted the the average change from baseline for middle-of-the-night body sway was -1.1 units for placebo, 5.8 units for lemborexant 5 mg, 8.1 units for lemborexant 10 mg, and 20.4 units for zolpidem ER 6.25 mg; ($p<0.0001$ vs. zolpidem ER for both lemborexant 5 mg and 10 mg).[16]

There was no significant difference on body sway in the morning from baseline in body sway between the groups with -2.2 units for placebo, 0.4 units for lemborexant 5 mg, -0.4 units for lemborexant 10 mg, and 5.0 units for zolpidem ER 6.25 mg ($p=$NS [not significant] for both doses of lemborexant vs. placebo, $p=0.01$ for zolpidem ER vs. placebo).15 Lemborexant 5 mg did not demonstrate any statistically significant changes as compared to placebo when examining cognitive performance. However, lemborexant 10 mg and zolpidem demonstrated worse performance on some attention and memory tests. No serious adverse events occurred during this trial.[15]

Morning Driving Performance

Eisai conducted a phase I study to assess the potential impact of lemborexant on next-morning driving performance. It was a randomized, double-blind, double-dummy, placebo and active-controlled, four period incomplete crossover study in 48 active volunteers.[17] About half the volunteers were female (n=22) and the participants were aged 23-78 years old. Inclusion criteria was a valid driver's license, driving experience of 3,000 km/year on average with the last three years, BMI between 18-30 kg/m2, and normal vision. Exclusion criteria were any clinically significant neurological, physical, sleep, or psychiatric disorders, alcoholism or drug abuse, medication known to affect driving performance or hepatic drug metabolism, SBP >140 mmHg or >150 mmgHg (elderly) or DBP >90 mmHg (all ages), resting HR <50 or ≥100 beats per minute; major surgery, blood donation or participation in any other clinical trial within four weeks before screening; smoking >six cigarettes per week; alcohol consumption >14 (females) or >21 (males) drinks per week; caffeine consumption greater than three cups per day.

Participants were treated at bedtime for eight nights in a row with various dose levels of lemborexant (2.5, 5, or 10 mg), zopiclone 7.5 mg (on the first and last night with placebo on intervening nights), or placebo.17 Volunteers were randomized to one of 12 treatment sequences in a 1:1 ratio. Driving performance was assessed in the morning on days two and nine using a standard-

ized highway driving test in normal traffic, measuring standard deviation of lateral position (SDLP). Volunteers were assessed 9 hours after receiving various strengths of lemborexant at bedtime. If the SDLP increased more than 2.4 cm, this indicated impairment. For all strengths of lemborexant, the average changes in SDLP scores from placebo were less than 0.75 cm on days two and nine of testing. However, even though zopiclone did show a statistically significant increase in SDLP vs lemborexant, it too was not above the 2.4 cm mark indicated for impairment.[17] Doses of lemborexant 10 mg were well tolerated with the exception of elderly patients taking the 10 mg dose who had a greater nonsignificant average ΔSDLP on day 2: 0.82, 95% CI [−1.11 to 2.75] and ΔSDLP on day 9: 0.65 [−1.2 to 2.55]. This same effect was seen to a greater statistically and clinically significant extent in the elderly zopiclone group (ΔSDLP Day 2: 2.57, 95% CI [0.89 to 4.25]; ΔSDLP Day 9: 1.98 [0.33 to 3.63].[17]

Dosing Safety Study

Eisai conducted a phase II study to identify the dose(s) of lemborexant that would maximize efficacy in treating insomnia while minimizing next morning residual sleepiness. It also served to evaluate the effects of lemborexant on PSG measures such as sleep efficiency (SE), latency to persistent sleep (LPS), and wake after sleep onset (WASO) at baseline and the end of treatment. This was a multicenter, randomized, double-blind, placebo-controlled, Bayesian, adaptive, parallel-group study, in which patients received lemborexant (1, 2.5, 5, 10, 15, 25 mg) or placebo for 15 nights.[18]

Study participants were 19-80 years of age and met the DSM -5 criteria for insomnia. Inclusion criteria were on two consecutive screening/baseline PSGs: LPS average of ≥ 30 minutes with neither night < 15 minutes; and/or WASO average of ≥ 30 minutes with neither night < 20 minutes; and an SE average of ≤ 85% with neither night > 87.5%.18 The average age of participant was 49 years and 63% were female; the baseline characteristics were well matched.

A total of 291 subjects were randomized and a Bayesian dose -response adaptive design with response adaptive randomization (RAR) was used to fully explore the dose-response curve of lemborexant.[18] This primary objective was to identify the dose of lemborexant that would maximize efficacy while reducing residual morning sleepiness; this was evaluated using a utility function of safety and efficacy that combined SE ([total sleep time / time in bed] × 100%) as measured by PSG with residual morning sleepiness as rated on the Karolinska Sleepiness Scale (KSS).[18]

The study was stopped early due to early success. It was found that doses of 5, 10, 15, and 25 mg met the utility index and KSS criteria for success, with 15 mg identified as the maximum dose for functionality without unacceptable residual sleepiness.[18] There was no significant residual morning sleepiness (measured at 15 min, one hour, and two hours after waking) with doses between 1-10 mg. There was no evidence of rebound insomnia after

Table 3 | Sleep Maintenance Endpoints from Sunrise Trials[11,12]

Trial	Primary Outcome	Intervention	Mean change from baseline (SD[a])	LSM[b] treatment difference versus placebo/zolpidem (95% CI[c])
Sunrise 1 Trial NCT02783729	Mean change from baseline to end of treatment (days 29/30) in objective SE[d] (%)	Placebo	5.4 (9.9)	-/-
		Lemborexant 5 mg	12.9 (9.7)	7.1 (5.6 to 8.5)/3.9 (2.5 to 5.3)
		Lemborexant 10 mg	14.1 (10.5)	8.0 (6.6 to 9.5)/4.9 (3.5 to 6.3)
		Zolpidem ER 6.25 mg	9.1 (11.2)	3.2 (1.7 to 4.6)/-
	Mean change from baseline to end of treatment (days 29/30) in sWASO[e] (minutes)	Placebo	-18.6 (41.9)	-/-
		Lemborexant 5 mg	-43.9 (39.3)	-24.0 (-30.0 to -18.0)/-7.7 (-13.4 to -2.1)
		Lemborexant 10 mg	-46.4 (39.6)	-25.4 (-31.4 to -19.3)/ -9.1 (-14.8 to -3.5)
		Zolpidem ER 6.25 mg	-36.5 (43.4)	-16.3 (-22.3 to -10.2)/-
Sunrise 2 Trial NCT02952820	Mean change from baseline to six-months in subjective SE (%)	Placebo	9.64 (0.84)	-
		Lemborexant 5 mg	14.19 (0.86)	4.55 (1.18)
		Lemborexant 10 mg	14.31 (0.87)	4.67 (1.17)
	Mean change from baseline to six-months in sWASO(minutes)[e]	Placebo	-29.28 (3.61)	-
		Lemborexant 5 mg	-46.75 (3.66)	-17.47 (5.01)
		Lemborexant 10 mg	-41.95 (3.69)	-12.67 (4.95)

[a]Standard deviation; [b]Least squares mean; [c]Confidence interval; [d]Sleep efficacy; [e]Subjective wake after sleep onset

treatment had concluded.[18]

Lemborexant vs Suvorexant

Kishi et al. conducted a random-effects model network meta-analysis to evaluate differences between lemborexant and suvorexant in safety and efficacy outcomes for treating patients with insomnia.[19] They conducted their search on Embase, MEDLINE, and CENTRAL. Four double-blind, randomized controlled trial were identified for their analysis (n = 3237; 72.4% female; mean age 58.0 years). The meta-analysis included the Sunrise 1 and 2 Trials and the selected article for suvorexant included two double-blind, randomized controlled trials.[20]

The primary endpoints were subjective time to sleep onset (sTSO), subjective total sleep time (sTST), and sWASO at week 1. The standard mean difference (95% CIs): sTSO at week 1: for lemborexant 10 mg was -0.51 (-0.63 to -0.39), lemborexant 5 mg -0.48 (−0.60, −0.36), and suvorexant 20 mg/15 mg −0.21 (−0.33, −0.10); sTST for lemborexant 10 mg was −0.58 (−0.70, −0.45), lemborexant 5 mg −0.33 (−0.46, −0.21), and suvorexant 20 mg/15 mg −0.34 (−0.46, −0.23); sWASO for lemborexant 10 mg was −0.42 (−0.57, −0.28), lemborexant 5 mg −0.26 (−0.40, −0.11), and suvorexant 20 mg/15 mg −0.18 (−0.32, −0.05). Notably, lemborexant 5 mg and 10 mg outperformed suvorexant 20 mg/15 mg in terms of sTSO while, while lemborexant 10 mg outperformed lemborexant 5 mg, suvorexant 20 mg/15 mg in sTST and sWASO at week 1.[19]

Discontinuation due to adverse events was not significantly different between the active treatment drugs and placebo. Lemborexant 10 mg and suvorexant 20 mg/15 mg resulted in a higher rate of somnolence in comparison to placebo. Lemborexant had a greater risk of somnolence than suvorexant, but the size of the effect was not large. The results of this trial demonstrated that lemborexant is more effective than suvorexant for patients that have nighttime awakenings or sleep less time.[19]

Dosing and Administration

Lemborexant is available as 5 and 10 mg tablets. The recommended dosage is 5 mg at bedtime, with at least seven hours remaining before awakening time. Dosage may be increased to the maximum daily dose of 10 mg based on clinical response. Lemborexant doses of either 5 mg or 10 mg provided efficacy for the treatment of insomnia while minimizing next-morning residual sleepiness.[18] There are no adjustments indicated for renal impairment, however lemborexant should be limited to 5 mg in people with moderate hepatic impairment (Child-Pugh Class B) and it is not recommended in severe hepatic impairment.[9] When using lemborexant in the elderly, the prescriber should use caution when giving doses greater than 5 mg in patients over 65 years of age, as higher doses are associated with increased adverse effects. There is insufficient data for this drug in the setting of pregnancy and lactation, thus it is not recommended.[9]

Dosing and Administration

The most common adverse effect that was observed in clinical trials was somnolence (≥5%), which occurred in double the amount of participants versus placebo.[9] Other adverse effects include sleep paralysis, hallucinations, cataplexy-like symptoms and complex sleep behaviors. Patients should be warned that this drug is a CNS depressant and should not be combined with other drugs such as benzodiazepines, opioids, TCA's, or alcohol. This medication can cause drowsiness, especially in the elderly, which places them at a higher risk for falls. Lemborexant has not been studied in moderate-severe obstructive sleep apnea or COPD, so caution should be used if prescribing this drug to patients with compromised respiratory function. The single contraindication to use is in patients with narcolepsy.[9]

Table 4 | Common Adverse Events[9]

Event	Incidence
Somnolence or fatigue	6.9-9.6%
Headache	4.5-5.9%
Nightmare or abnormal dreams	0.9-2.2%

Lemborexant relies on the liver for metabolism which introduces the potential for drug interactions. Specifically, when patients are on concurrent weak CYP3A4 inhibitors the dose should be limited to 5 mg daily and it is recommended to avoid concomitant use with strong CYP3A4 inhibitors and inducers. Lemborexant also has a weak potential to induce CYP2B6 substrates, however this is still considered clinically significant.[9]

Cost

Dual orexin receptor antagonists are more costly than generic alternatives for insomnia such as zolpidem. For example, for a patient on Medicare, zolpidem is a tier 2 drug, trazadone is tier 1, while DORAs are not covered. The cost to a patient with Medicare for a tier 1 or 2 drug ranges from free to 10 dollars for a 30-day supply. On the other hand, if a patient is paying out of pocket or uninsured the cost of medication is around $9 for 30 tablets of zolpidem (10 mg). The cost of suvorexant is approximately ~$369 for 30 tablets (20 mg) and lemborexant is approximately ~$279 for 30 tablets (10 mg) if out of pocket or uninsured.

Clinical Implications

Prescribing Practices

In a NHANES Survey that examined frequency of insomnia medication usage from 1999-2010, there has been a 1.5% increase in medications prescribed over the decade. Zolpidem was the most commonly prescribed medication (1.23% of population), followed by trazadone (0.97%), BZD's (0.4%), quetiapine (0.32%), and doxepin.[21] There are concerns surrounding the potential for tolerance and dependency with benzodiazepine use, yet physicians increasingly prescribed sedating antidepressants "off label," especially trazodone, despite the lack of efficacy studies.[5] This indicates that many drugs are often prescribed despite lack of proven efficacy, possibly due to lack of cost effective or efficacious options on the market. Although they are a relatively new class of medications, DORAs have the potential to change practice guidelines in the setting of more evidence as it becomes available.

Efficacy

Lemborexant was adequately studied in terms of comparison to alternatives on the market. For example, the Sunrise 1 trial compared lemborexant to not only placebo but also to an active comparator (zolpidem). Demonstrating lemborexant's efficacy in comparison to both placebo and zolpidem was a strength of the study. Subjective and objective efficacy outcomes were included

in the two Sunrise trials. A mixture of both measures is not only required for approval by health officials, but also strengthens the results of the study as the perspective of both the patient and provider are being taken into consideration. However, subjective outcomes are also prone to reporting bias and may influence the results of the study.

In the Sunrise 1 trial participants were able to fall asleep in under 20 minutes when taking lemborexant and gained 60 more minutes of sleep per night. Additionally, treatment with lemborexant on days 1-2 and 29-30 were effective, which demonstrates the drug's ability to work quickly and continuously over one month. Within this trial, zolpidem became less effective over time. This contrasts a previous randomized, double-blind, placebo-controlled trial conducted by Walsh et al., in which nightly zolpidem proved to be efficacious in treating chronic insomnia for eight months as measured by PSG.[22] However, the study by Walsh et al. also demonstrated that zolpidem did not show efficacy in comparison to placebo when self-reported subjective measures on sleep improvement were considered. Similarly, when examining subjective sleep onset latency in the Sunrise 1 Trial, lemborexant showed significant benefit over zolpidem. In summary, when examining objective measures of sleep, zolpidem and lemborexant both appear to work well over time; When examining subjective measures of sleep, lemborexant may have greater benefit on outcomes than zolpidem.

Lemborexant is a schedule IV drug but did not produce evidence of withdrawal upon discontinuation or physical dependence through one year of use. Compared to zolpidem, lemborexant seems to have less propensity for physical dependence and misuse, making it a more attractive treatment option for those with a history of drug abuse or addiction.[23] Additionally, Sunrise 1 and 2 trials demonstrated a lack of rebound insomnia when discontinuing the drug.9 This is an important benefit to consider when comparing to other alternatives for insomnia, such as benzodiazepines, which have a risk for dependence and withdrawal.

Lemborexant vs. market alternatives

Although suvorexant and lemborexant are both reversible competitive antagonists at OX1R and OX2R, lemborexant has a stronger inhibition effect on OX2R and is predicted to increase non-REM sleep. It also rapidly binds to receptors which is more effective at promoting onset of sleep. Additionally, lemborexant rapidly dissociates from receptors, unlike suvorexant which is typically slower to dissociate and therefore could promote more somnolence the next morning.[24] This was congruous with the results of the meta-analyses study, which found lemborexant to be superior to suvorexant and zolpidem in terms of falling asleep and had greater efficacy for patients who sleep less time and wake during the night.

When comparing the two drugs approved in the DORA class, lemborexant's safety data was studied over a 12-month period which allowed for more time to observe adverse effects if they were to occur. Conversely, suvorexant's safety data was only studied over a three-month period. Longitudinal safety data becomes especially important in light of the FDA placing boxed warnings on Z-drugs in 2019 after recent adverse event reporting showed that serious injuries and death have occurred due to sleep driving, sleepwalking, falls, accidental overdoses, burns, near-drowning, and other unsafe activities that resulted after a lack of wakefulness.[25]

The manufacturer's additional safety studies demonstrated that lemborexant had no meaningful differences on next-day postural stability and did not significantly impair driving the next morning. These safety studies are inherently useful in addressing these ancillary scenarios. Postural instability is thought to be a good singular predictor of falls.[26] In Eisai's safety trial on postural instability, "zolpidem ER increased body sway at a magnitude almost three times greater than the increase in body sway associated with a blood alcohol content (BAC 0.05 percent) near the legal driving limit."[16] Comparatively, lemborexant did not show any meaningful differences in postural stability at either time of day. Since elderly patients are already at an increased risk for falls, a drug that limits postural instability would be beneficial. However, residual sleepiness was limited to a 15-day treatment duration and was an eight-day treatment period. These short study durations may not have allowed long-term side effects or tolerance to be observed. Further studies would be useful in determining if these safety benefits are maintained over longer treatment periods.

Many of the trials included a large majority of elderly (50+), female, Caucasian women. Insomnia affects women approximately 1.4 times more than men, so a large female population in the trials is representative of this.3 The generalizability may be limited when applying data from these trials to other populations such as African Americans, Asians, Hispanics, and American Indians. These groups individually experience more insomnia than Caucasians according to the CDC.[27]

Place in Therapy

Dual orexin receptor antagonists have not specifically been recommended over other insomnia agents in the guidelines. Rather, the AASM has recognized suvorexant and recommended its use for sleep maintenance insomnia. Lemborexant has not yet received a recommendation in these guidelines. Currently, zolpidem is generic and much cheaper but did not perform as well as lemborexant in terms of safety and efficacy outcomes according to the trials discussed here. The authors of the network meta-analyses mention the need for a cost-effective analysis to be performed in order to make a more informed clinical decision. The cost of DORAs is likely going to be a barrier to access.

Lemborexant is not recommended to be used in patients with sleep breathing disorders, COPD, circadian rhythm disorder, patients with a history of complex sleep behaviors, restless leg syndrome, or moderate-severe symptoms of anxiety or depression, which could limit applicability in practice. It is also not recommended for use in severe hepatic impairment but does not require dose adjustment in renal impairment. Moreover, it is contraindicated for use in patients with narcolepsy. Lemborexant has been studied in patients with major depressive disorder, generalized anxiety disorder, hypertension, diabetes, migraines, and menopause so it may be used in these populations.[10] More head to head trials would be useful to determine the place of lemborexant in the treatment of insomnia. Eisai is looking to extend indications to Alzheimer's dementia patients for falls and night-walking in the future.[14]

Conclusion

DAYVIGO® (lemborexant) is a novel DORA that achieved FDA approval in December 2019 for the treatment of insomnia in adults 18 years and older, experiencing difficulties with sleep onset and/or sleep maintenance. Lemborexant has not been given a definitive place in therapy but may be considered given its good safety and efficacy data. The AASM guidelines do not make recommendations about the use of specific drug over another, but

rather provides a general sequence in which to trial medications. More head-to-head trials are needed between DORAs and traditional sedative drugs/hypnotics before a recommendation can be made regarding their place in therapy.

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