Suvorexant for sleep-onset insomnia or sleep-maintenance insomnia, or both

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Suvorexant, FDA-approved to treat insomnia, has demonstrated efficacy in helping patients with insomnia improve their ability to fall asleep and remain asleep (***Table 1***).[1] This first-in-class compound represents a novel mechanism of action to promoting sleep that may avoid some problems associated with other hypnotics.[2]

Clinical implications

Insomnia is among the most common clinical complaints in psychiatry and medicine. The FDA-approved insomnia medications include several benzodiazepine-receptor agonists (zolpidem, eszopiclone, zaleplon), a melatonin-receptor agonist (ramelteon), and a histamine-receptor antagonist (low-dose doxepin). Suvorexant joins these drugs and is an entirely novel compound that is the first orexin- (also called hypocretin) receptor antagonist approved by the FDA for any indication.

Through a highly targeted mechanism of action, suvorexant could enhance sleep for patients with insomnia, while maintaining an acceptable safety profile.[3] The drug should help patients with chronic insomnia, particularly those who have difficulty maintaining sleep—the sleep disturbance pattern that is most challenging to treat pharmacotherapeutically.

Because orexin antagonists have not been used outside of clinical trials, it is too soon to tell whether suvorexant will have the ideal real-world efficacy and safety profile to make it a first-line treatment for insomnia patients, or if it will be reserved for those who have failed a trial of several other treatments.[4]

Table 1

Suvorexant: Fast facts

Brand name: Belsomra
Class: Dual orexin-receptor antagonist
Indication: Insomnia characterized by difficulty with sleep onset or sleep maintenance, or both
FDA approval date: August 13, 2014
Availability date: Early 2015
Manufacturer: Merck
Dosage forms: 5 mg, 10 mg, 15 mg, and 20 mg tablets
Recommended dosage: 10 mg taken only once within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening
Source: Reference 1

In theory, the orexin antagonist approach to treating insomnia could represent a major advance that modulates the fundamental pathology of the disorder.[5] The syndrome of chronic insomnia encompasses not just the nighttime sleep disturbance but also an assortment of daytime symptoms that can include fatigue, poor concentration, irritability, and decreased school or work performance but usually not sleepiness. This constellation of nighttime and daytime symptoms could be conceptualized as a manifestation of persistent CNS hyperarousal. Because the orexin system promotes and reinforces arousal, perhaps an orexin antagonist that dampens the

Suvorexant, an orexin-receptor antagonist, enhances sleep by dampening the arousing wake drive

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Disclosure

Dr. Neubauer is a consultant to Ferring Pharmaceuticals and Vanda Pharmaceuticals.

Table 2

Polysomnographic assessment of sleep maintenance (wake after sleep onset)

	Mean baseline and change from baseline[a] after 1 and 3 months (minutes)		Difference[a] between suvorexant and placebo (minutes)
Study 1			
	Placebo (n = 290)	Suvorexant 15 or 20[b] mg (n = 193)	
Baseline	115	120	
Change from baseline			
Month 1	-19	-45	-26[c]
Month 3	-25	-42	-17[c]
Study 2			
	Placebo (n = 286)	Suvorexant 15 or 20[b] mg (n = 145)	
Baseline	118	119	
Change from baseline			
Month 1	-23	-47	-24[c]
Month 3	-25	-56	-31[c]

[a]Change from baseline and treatment differences based upon estimated means
[b]15 mg in geriatric and 20 mg in non-geriatric patients
[c]$P < .001$

Source: Reference 9

Clinical Point

Suvorexant might be associated with residual sleepiness, but this risk should be minimized when using recommended dosages

level of orexin activity will ameliorate the full spectrum of insomnia symptoms—not simply sedate patients.[6]

How suvorexant works

Suvorexant is a potent and reversible dual orexin-receptor antagonist. The orexin system, first described in 1998, has a key role in promoting and stabilizing wakefulness.[7] Evidence suggests that people with chronic insomnia exhibit a central hyperarousal that perpetuates their sleep difficulty. Accordingly, a targeted pharmaceutical approach that reduces orexin activity should facilitate sleep onset and sleep maintenance for these patients. It is well known that the regulation of sleep and wakefulness depends on the interaction of multiple nuclei within the hypothalamus. Orexinergic neurons in the perifornical-lateral hypothalamic region project widely in the CNS and have especially dense connections with wake-promoting cholinergic, serotonergic, noradrenergic, and histaminergic neurons.[6]

A precursor prepro-orexin peptide is split into 2 orexin neurotransmitters (orexin A and orexin B). These 2 orexins bind with 2 G-protein-coupled receptors (OX1R and OX2R) that have both overlapping and distinct distributions.[7] Suvorexant is highly selective and has similar affinity for OX1R and OX2R, functioning as an antagonist for both.[8] Fundamentally, suvorexant enhances sleep by dampening the arousing wake drive.

Pharmacokinetics

Suvorexant is available as an immediate-release tablet with pharmacokinetic properties that offer benefits for sleep onset and maintenance.[9] Ingestion under fasting conditions results in a median time to maximum concentration (T_{max}) of approximately 2 hours, although the T_{max} values vary widely from patient to patient (range 30 minutes to

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Table 3

Polysomnographic assessment of time to sleep onset

	Mean baseline and change from baseline[a] after 1 and 3 months (minutes)		Difference[a] between suvorexant and placebo (minutes)
Study 1			
	Placebo (n = 290)	Suvorexant, 15 or 20[b] mg (n = 193)	
Baseline	66	69	
Change from baseline			
Month 1	-23	-34	-10[c]
Month 3	-27	-35	-8[d]
Study 2			
	Placebo (n = 286)	Suvorexant 15 or 20 mg (n = 145)	
Baseline	69	65	
Change from baseline			
Month 1	-25	-33	-8[e]
Month 3	-29	-29	0

[a]Change from baseline and treatment differences based upon estimated means
[b]15 mg in geriatric and 20 mg in non-geriatric patients
[c]$P < .001$
[d]$P < .01$
[e]$P < .05$

Source: Reference 9

Clinical Point

Efficacy and safety studies mostly were performed at dosages considerably higher than those approved by the FDA

6 hours). Although suvorexant can be taken with food, there is a modest absorption delay after a high-fat meal, resulting in a further T_{max} delay of approximately 1.5 hours.

Suvorexant is primarily metabolized through the cytochrome P450 (CYP) 3A pathway, with limited contribution by CYP2C19. There are no active metabolites. The suvorexant blood level and risk of side effects will be higher with concomitant use of CYP3A inhibitors. The drug should not be administered with strong CYP3A inhibitors; the initial dosage should be reduced with moderate CYP3A inhibitors. Concomitant use of strong CYP3A inducers can result in a low suvorexant level and reduced efficacy.

Suvorexant has little effect on other medications, although a person taking digoxin might experience intestinal P-glycoprotein inhibition with a slight rise in the digoxin level. In a patient taking both medications, monitoring of the digoxin level is recommended.

The elimination half-life of suvorexant is approximately 12 hours, with a steady state in approximately 3 days. Because the half-life of suvorexant is moderately long for a sleep-promoting medication, use of the drug might be associated with residual sleepiness the morning after bedtime dosing. The risk for next-morning sleepiness or impairment should be minimized, however, when using the recommended dosages. Elimination is approximately two-thirds through feces and one-third in the urine.

Suvorexant metabolism can be affected by sex and body mass index. Females and obese people have a modestly elevated exposure to suvorexant, as reflected by the area under the curve and maximum concentration (C_{max}). These patients might not require dosage adjustments unless they are obese *and* female, in which case they should take a lower dosage.

Age and race have not been shown to influence suvorexant metabolism to a signifi-

Clinical Point

Suvorexant is a Schedule IV controlled substance; studies have shown that the likeability rating is similar to that of zolpidem

cant degree. Patients with renal impairment and those with mild or moderate hepatic impairment do not need dosage adjustment. Suvorexant has not been evaluated in patients with severe hepatic impairment.

Efficacy

Suvorexant showed significant evidence of improved sleep onset and sleep maintenance in patients with insomnia in clinical trials. The key efficacy clinical trials with insomnia patients included a phase-IIb dose-finding study,[10] 2 similar 3-month phase-III studies,[11] and one 12-month phase-III safety study that incorporated efficacy outcomes.[12] All these trials included subjective sleep measures and all except for the long-term safety study also incorporated polysomnographic assessment. The specific sleep laboratory outcomes were latency to persistent sleep (LPS), wake after the onset of persistent sleep (WASO), total sleep time (TST), and sleep efficiency (SE). Subjective sleep outcomes were time to sleep onset (sTSO), wake after sleep onset (sWASO), and total sleep time (sTST). Other exploratory endpoints also were assessed. These efficacy and safety studies mostly were performed at dosages considerably higher than those approved by the FDA.

The dose-finding (phase-IIb) trial was conducted with non-geriatric (age 18 to 64) patients with insomnia in a randomized, double-blind, crossover design of two 4-week periods with subjects given a nightly placebo or suvorexant (10 mg, 20 mg, 40 mg, or 80 mg).[10] Each of the 4 groups included approximately 60 subjects. The 2 co-primary endpoints were SE at Night 1 and the end of Week 4; secondary endpoints were LPS and WASO. Suvorexant was associated with dosage-related improvements in SE and WASO compared with placebo at both time points. Carryover effects from the period-1 active drug group complicated the analysis of LPS.

The phase-III efficacy and safety trials were performed with 40 mg high dosage (HD) and 20 mg low dosage (LD) groups for adults and with 30 mg HD and 15 mg LD groups for geriatric (age ≥65) patients.[11] Two similarly designed 3-month randomized, double-blind, placebo-controlled pivotal efficacy studies assessed objective and subjective sleep measures in 4 groups with non-geriatric (HD and LD) and geriatric (HD and LD) insomnia patients.

After baseline assessment, patients took nightly bedtime doses of placebo; suvorexant, 40 mg or 20 mg (non-geriatric individuals); or suvorexant, 30 mg or 15 mg (geriatric individuals). All subjects kept a daily electronic diary and had polysomnographic recordings performed on Night 1, at the end of Month 1, and at the end of Month 3. Both the individual studies and combined analyses (2,030 subjects) showed that, in non-geriatric and geriatric patients, HD suvorexant resulted in significantly greater improvement in key subjective and objective measures throughout the study (***Table 2,***[9] ***page 20,*** and ***Table 3,***[9] ***page 21***), with the exception of a single LPS outcome in 1 study, compared with placebo. The LD dosages also demonstrated efficacy, but to a reduced extent.

Subjective sleep outcomes were assessed in a 1-year randomized, placebo-controlled trial with nightly placebo, suvorexant, 40 mg, for non-geriatric, or suvorexant, 30 mg, for geriatric insomnia patients.[12] The 1-year phase was completed with 484 subjects. Key efficacy outcomes were sTST and sTSO changes from baseline during the first month of treatment. Compared with placebo, suvorexant dosages demonstrated significantly greater efficacy, improvements that were sustained throughout the year.

Clinical trials found suvorexant to be generally safe and well tolerated.[13] However, specific safety concerns led the FDA to approve the medication at dosages lower than those assessed in the phase-III studies.[1]

Somnolence was the most common adverse event in clinical trials. In the phase-IIb dose-finding study, somnolence was reported in <1% in the placebo group, but was associated with suvorexant in 2% of the 10 mg group, 5% with 20 mg, 12% with 40 mg, and 11% with 80 mg.[9] In the phase-III combined analysis of the 3-month

studies, somnolence was reported by 3% in the placebo group and 7% of non-geriatric patients taking 20 mg or geriatric patients taking 15 mg. Somnolence was reported in 8% of women and 3% of men taking the 15 mg or 20 mg dosage in these studies. The 1-year study was performed only with higher suvorexant dosages (30 mg and 40 mg), in comparison with placebo. In this long-term trial, somnolence was reported by 13% of subjects taking suvorexant and 3% taking placebo.

Additional safety issues in trials included excessive daytime sleepiness, impaired driving, suicidal ideation, sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms.[9] Occurrences of these events are rare but have been reported more often among patients taking suvorexant than among those taking placebo.

Unique clinical issues

The U.S. Drug Enforcement Agency has categorized suvorexant as a Schedule IV controlled substance. Although there is no evidence of physiological dependence or withdrawal symptoms with suvorexant, studies with recreational substance abusers have shown that the likeability rating is similar to that of zolpidem.[13]

Contraindication

Suvorexant is contraindicated in patients with narcolepsy.[9] The underlying pathology of narcolepsy involves a marked reduction in orexin functioning with corresponding excessive sleepiness and related symptoms, such as cataplexy, hypnagogic hallucinations, and sleep paralysis. Although suvorexant has not been evaluated in patients with narcolepsy, the drug

Clinical Point

Suvorexant should be taken no more than once a night, within 30 minutes of bedtime and at least 7 hours before the planned wake time

Related Resources

- Jacobson LH, Callander GE, Hoyer D. Suvorexant for the treatment of insomnia. Expert Rev Clin Pharmacol. 2014; 7(6):711-730.
- Neubauer DN. New and emerging pharmacotherapeutic approaches for insomnia. Int Rev Psychiatry. 2014;26(2): 214-224.

Drug Brand Names

Doxepin • Silenor
Digoxin • Lanoxin
Eszopiclone • Lunesta
Ramelteon • Rozerem
Suvorexant • Belsomra
Zaleplon • Sonata
Zolpidem • Ambien, Edluar, Intermezzo

Clinical Point

There are no specified limitations on duration of suvorexant use and no evidence of withdrawal effects when discontinued

might, hypothetically, put patients at higher risk of the full spectrum of narcolepsy symptoms.

There are no other contraindications for suvorexant.

Dosing

Suvorexant should be taken no more than once a night within 30 minutes of bedtime and with at least 7 hours before the planned wake time.[9] The recommended starting dosage is 10 mg. If this dosage is well tolerated but insufficiently effective, the dosage can be increased to a maximum of 20 mg. The 5-mg dosage is recommended for individuals taking a moderate CYP3A inhibitor. Generally, patients should take the lowest effective dosage.

There are no specified limitations on the duration of suvorexant use. There is no evidence of withdrawal effects when discontinuing the medication. Patients taking suvorexant should be educated about possible next-day effects that might impair driving or other activities that require full mental alertness, especially if they are taking the 20-mg dosage.

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Bottom Line

Suvorexant is FDA-approved for treating sleep onset and sleep maintenance insomnia. The drug is a dual orexin-receptor antagonist, which targets persistent CNS hyperarousal. In clinical trials, suvorexant improved the ability to fall asleep and remain asleep in patients with insomnia. It is generally safe and well tolerated. However, these studies evaluated dosages higher than those approved by the FDA.