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Suvorexant (Belsomra®): A New Treatment Option for Insomnia

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Insomnia is characterized by patient-reported difficulty in falling or staying asleep. Approximately 50-70 million U.S. adults report at least one symptom of insomnia, such as difficulty falling asleep, difficulty staying asleep, poor sleep quality, and waking up too early; of these, approximately 20 million Americans (30%) diagnosed with insomnia have chronic insomnia.[1] Chronic insomnia is associated with decreased health-related quality of life (HRQOL): patients who suffer from insomnia have a decrease in physical functioning similar to that of heart failure patients and a decrease in mental health that is 60% of that observed for clinical depression.[2]

Approximately 10% of patients in the U.S. who suffer from insomnia also suffer from daytime symptoms including fatigue, sleepiness, mood disturbances, and cognitive difficulties.[3] These symptoms can lead to motor vehicle accidents, and drowsy drivers are responsible for about 16.5% of fatal car crashes in the U.S.[4] Patients with insomnia are also more likely to have decreased work productivity as evidenced by increased rates of absenteeism, decreased concentration, and difficulty performing tasks.[5] Additionally, mean total healthcare expenditure is estimated to be 60% higher for patients with insomnia compared to patients without insomnia.[6]

Current first-line pharmacologic treatment options for insomnia include short-to-intermediate acting benzodiazepines, non-benzodiazepine sedative-hypnotics, and melatonin receptor agonists. Benzodiazepines and non-benzodiazepine sedative hypnotics decrease objective measures of sleep latency and wake after sleep onset, and increase objective total sleep time.[7] Ramelteon, the only melatonin receptor agonist approved for use for insomnia in the U.S., decreases subjective sleep latency and improves subjective sleep quality.[8] However, these agents are associated with significant side effects including daytime drowsiness, somnolence, and other central nervous system effects.[9] Benzodiazepines and non-benzodiazepine sedative hypnotics are also associated with potential abuse and dependence. If the first-line agents are unsuccessful, sedating antidepressants, antiepileptics, or antipsychotics may be considered especially if the patient has comorbid conditions that can be treated with these agents. However, the efficacy of these agents for insomnia have not been evaluated rigorously.[10]

Orexin is a peptide found in the lateral hypothalamus that also promotes wakefulness.[11] Suvorexant is a novel drug that promotes sleep, presumably via its effects as an orexin receptor antagonist.[12] Suvorexant recently received an FDA-approved indication for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance, and is marketed under the trade name Belsomra® by Merck & Co., Inc. The purpose of this manuscript is to review the pharmacology, efficacy, adverse events, and administration of suvorexant.

CLINICAL PHARMACOLOGY

Orexin A and B are neuropeptide ligands for the G-protein coupled orexin 1 and 2 receptors. When stimulated by orexin A and B, the orexin neurons send projections to the nuclei involved in sleep and wakefulness regulation which promotes wakefulness.[12] Antagonism of these receptors by suvorexant is believed to block the binding of the wake-promoting molecules, orexin A and B.[12]

Pharmacodynamics and Pharmacokinetics

Suvorexant is administered orally and reaches its maximum concentration (C_{max}) in two hours under fasting conditions.[12] Ingestion of a high fat meal delays the time to maximum concentration (T_{max}) by 1.5 hours, but does not have an effect on the area under the curve (AUC) or C_{max}. Suvorexant is highly protein bound to albumin and α_1-acid glycoprotein. Metabolism of suvorexant occurs in the liver, primarily by CYP3A to inactive metabolites. Suvorexant is primarily eliminated in the feces with some metabolites excreted in the urine.[12] Additional pharmacokinetic parameters are listed in **Table 1**.

Suvorexant exposure is higher in women compared to men: mean AUC is 17% greater and C_{max} is 9% greater after a 40-mg dose. However, the clinical significance of this finding is unknown and dosage adjustments are not recommended based on sex alone. The average concentration of

suvorexant 9 hours after a 10-mg to 40-mg dose is 5% higher in women compared to men.[12] Similarly, the clearance of suvorexant is decreased in obese patients: the mean AUC is 31% greater and C_{max} is 17% greater in obese compared to non-obese patients. The average concentration of suvorexant 9 hours after a 20-mg dose is 15% higher in obese compared to non-obese patients.[12]

In patients with moderate hepatic insufficiency (Child-Pugh category 7 to 9) the half-life of suvorexant is 19 hours compared to 15 hours in healthy subjects after a single dose. Suvorexant has not been studied in patients with severe hepatic impairment and the drug should generally be avoided in these patients.[12]

Suvorexant exposure is similar between healthy subjects and patients with severe renal impairment (creatinine clearance ≤30 mL/min). Thus, no dose adjustments are recommended in patients with renal impairment.[12]

Clinical Trials

Clinical trials assessing the efficacy and safety of suvorexant are summarized in **Table 2**. Two multicenter, randomized, double-blind, placebo-controlled, superiority trials were conducted to compare suvorexant to placebo.[14,15] These studies included 2,030 patients who were ≥18 years of age with a diagnosis of primary insomnia. Patients were randomly assigned to one of three treatment arms: high-dose suvorexant (40 mg for patients <65 years or 20 mg for patients aged ≥65 years), low-dose suvorexant (20 mg for patients aged <65 years or 15 mg for patients aged ≥65 years), or matching placebo. Although the studies utilized multiple doses of suvorexant, the primary outcomes – measured at 1 month and 3 months after starting treatment – focused on comparing the efficacy of high-dose suvorexant to placebo. The efficacy outcomes studied were mean subjective total sleep time (sTST), mean subjective time to sleep onset (sTSO), wakefulness after persistent sleep onset (WASO), and latency to onset of persistent sleep (LPS). A statistically significant difference was found between high-dose suvorexant and placebo for all of the aforementioned efficacy outcomes except for LPS at month 3 in one of the studies.[15] The efficacy results are summarized in **Table 2**.

A third multicenter, randomized, double-blind, placebo-controlled, parallel-group trial evaluated the efficacy and safety of suvorexant compared to placebo.[16] This study included 771 patients who were ≥18 years of age and met the DSM-IV-TR criteria for primary insomnia. Patients were randomly assigned to one of three treatments: 40 mg of suvorexant nightly for patients aged <65 years; 30 mg of suvorexant nightly for patients aged ≥65 years; or, matching placebo. Patients continued the study drug for one year, at which time patients abruptly discontinued the drug in a randomized fashion. The efficacy of the study medication was assessed via patient reporting of several subjective measures in an electronic morning sleep diary. The primary objective was to assess the safety and tolerability of suvorexant. Prespecified secondary objectives were change in subjective total sleep time (sTST) and subjective time to sleep onset (sTSO) during the first month of treatment. The sample size in the study had 99% power to detect a 20 minute difference in change in sTST, comparing treatments, and 97% power to detect a 10 minute difference in change in sTSO, comparing treatments. Over the first month, patients who were treated with suvorexant reported an average increase, from baseline to 1 month, of 38.7 minutes sTST per night compared to 16.0 minutes in the placebo group (p<0.001). Additionally, patients who were treated with suvorexant reported an average decrease, from baseline to 1 month, of 18.0 minutes sTSO per night compared to 8.4 minutes in the placebo group (p=0.0002) over the first month of therapy. These improvements in sleep outcomes continued for the duration of the study. Abrupt discontinuation of suvorexant after one year of treatment was associated with the return of insomnia symptoms similar to that of the placebo group; however, discontinuing suvorexant was not associated with any adverse events when compared to patients who continued to receive suvorexant.

Table 1 | Pharmacokinetics of suvorexant.[12]

Parameter	Measurement
T_{max}	2 hours (fasting)
Elimination $t_{1/2}$	12 hours
Bioavailability	82% (for 10-mg tablet)
Metabolism	CYP3A (major); CYP2C19 (minor)
V_d	49 L
Elimination	66% in feces; 23% in urine
Protein Binding	>99%

$t_{1/2}$ = half-life; T_{max} = time to maximum concentration; V_d = volume of distribution.

These clinical trials show that suvorexant is more effective than placebo for treatment of primary insomnia.[14-16] Although the outcome measures show statistically significant improvements in sleep duration and quality, the clinical significance of these results appears to be relatively modest, though generally consistent with other treatments for insomnia. Patients reported an improvement in sTSO of 19.1 minutes, 26.9 minutes, and 18.0 minutes less per night compared to baseline in phase 3 clinical trials.[14,15,16] Patients also reported an improvement in WASO of 45.0 minutes and 51.9 minutes less per night compared to placebo in phase 3 clinical trials.[14,15] The primary outcomes in all of the clinical trials compared high-dose suvorexant to placebo. The doses of suvorexant used in these trials were higher than the FDA recommended maximum dosage of 20 mg daily.

Clinical trials studying the efficacy of other pharmacologic sleep agents showed an improvement in sTSO of 19.6 minutes less per night compared to baseline for patients treated with benzodiazepines, and 17.0 minutes less per night compared to baseline for patients treated with non-benzodiazepine sedative-hypnotics.[17] These trials also reported an improvement in WASO of 39.9 minutes less per night compared to baseline for patients treated with benzodiazepines and 15.0 minutes less per night compared to baseline for patients treated with non-benzodiazepine sedative hypnotics.[17] With the exception of WASO for non-benzodiazepine sedative-hypnotics, the improvements in sleep parameters obtained with these agents are similar to

those obtained with high-dose suvorexant.

Adverse Events & Precautions

Suvorexant has been studied at various doses in several clinical trials; however, the drug has been approved for use with a maximum dose of 20 mg daily.[12] Adverse events during 3 months of daily use of suvorexant are summarized in **Table 3**.

No formal statistical analysis has been published comparing adverse events for suvorexant and placebo. The most common adverse events associated with suvorexant 20 mg use in clinical trials were nasopharyngitis (3.7%), headache (7.3%), and somnolence (6.7%).[14,15] Similarly, the most common adverse events associated with suvorexant 40 mg use in clinical trials were nasopharyngitis (4.2%), headache (7.1%), and somnolence (10.5%).[14,15] Headache and somnolence occurred more frequently in the suvorexant group compared to placebo. Only somnolence occurred in at least twice as many suvorexant-treated patients as placebo-treated patients, and appeared to be dose-related.

Serious adverse events were reported in 3 of 493 (0.6%) patients in the 20-mg suvorexant group. These events included atrial fibrillation, ankle fracture, and pneumonia. No patients in the placebo group experienced these adverse events.[14,15] Serious adverse events were reported in

Table 2 | Summary of suvorexant clinical trials.[14-16]

Study	Treatments	Outcomes[a]
Unpublished NCT01097616[14]	• Suvorexant low-dose (N=254): ◦ 15 mg for age ≥65 years ◦ 20 mg for age <65 years • Suvorexant high-dose (N=383): ◦ 30 mg for age ≥65 years ◦ 40 mg for age <65 years • Placebo (N=384)	• Subjective total sleep time (minutes): ◦ Suvorexant high-dose: 42.6 ◦ Placebo: 23.1 ◦ p<0.0001 • Subjective time to sleep onset (minutes): ◦ Suvorexant high-dose: -19.1 ◦ Placebo: -11.7 ◦ p=0.003 • Wake after persistent sleep onset (minutes): ◦ Suvorexant high-dose: -45.0 ◦ Placebo: -18.7 ◦ p<0.0001 • Latency to onset of persistent sleep (minutes): ◦ Suvorexant high-dose: -34.5 ◦ Placebo: -23.3 ◦ p<0.0001
Unpublished NCT01097629[15]	• Suvorexant low-dose (N=239): ◦ 15 mg for age ≥65 years ◦ 20 mg for age <65 years • Suvorexant high-dose (N=387): ◦ 30 mg for age ≥65 years ◦ 40 mg for age <65 years • Placebo (N=383)	• Subjective total sleep time (minutes): ◦ Suvorexant high-dose: 48.7 ◦ Placebo: 22.4 ◦ p<0.0001 • Subjective time to sleep onset (minutes): ◦ Suvorexant high-dose: -26.9 ◦ Placebo: -14.1 ◦ p<0.0001 • Wake after persistent sleep onset (minutes): ◦ Suvorexant high-dose: -51.9 ◦ Placebo: -22.5 ◦ p<0.0001 • Latency to onset of persistent sleep (minutes): ◦ Suvorexant high-dose: -36.7 ◦ Placebo: -24.6 ◦ p<0.0001
Michelson, et al.[16]	• Suvorexant (N=517): ◦ 30 mg for age ≥65 years ◦ 40 mg for age <65 years • Placebo (N=254)	• Subjective total sleep time (minutes): ◦ Suvorexant: 38.7 ◦ Placebo: 16.0 ◦ p<0.0001 • Subjective time to sleep onset (minutes): ◦ Suvorexant: -18.0 ◦ Placebo: -8.4 ◦ p=0.002

Negative numbers indicate a decrease from baseline.
[a]Average daily values for least squares mean change from baseline over the first month of treatment.

6 of 770 (0.8%) patients in the 40-mg suvorexant group. These events included Meniere's disease, autoimmune thyroiditis, compression fracture, fall, ulna fracture, and musculoskeletal chest pain. Patients in the placebo group did not experience these adverse events.[14,15]

Suvorexant is known to depress the central nervous system (CNS) and should be used cautiously with other CNS depressants. Suvorexant may also impair daytime activities including driving. Suvorexant should be used with caution in patients with depression, as this medication may increase suicidal ideations. Sleep paralysis and mild cataplexy have also been reported with the use of suvorexant. Suvorexant has not been studied in patients with compromised respiratory function including obstructive sleep apnea and chronic obstructive pulmonary disease. Suvorexant is contraindicated in patients with narcolepsy.[12]

Suvorexant is schedule federally as a class IV drug indicating a low risk of abuse and dependence. Suvorexant should be used cautiously in patients with a history of substance abuse.[12] Clinical trials have not shown withdrawal symptoms associated with the abrupt discontinuation of suvorexant.[16]

Dosing and Administration

Suvorexant is administered orally and is available as 5-mg, 10-mg, 15-mg, and 20-mg tablets. The recommended dose is 10 mg nightly administered within 30 minutes of going to bed, with at least 7 hours before the planned waking time. If insomnia is not relieved, the dose may be increased to a maximum of 20 mg nightly. The lowest effective dose should be used to minimize adverse effects. When used concomitantly with moderate CYP3A inhibitors, the recommended dose of suvorexant is 5 mg nightly. Suvorexant should not be used in conjunction with strong CYP3A inhibitors.[12] Suvorexant has been used for up to one year before discontinuation in clinical trials; thus long-term data are unavailable at present with this agent.[16]

Summary

Suvorexant is a newly-approved drug that promotes sleep, presumably, via its novel effects as an orexin receptor antagonist. At a usual dose of 10 mg to 20 mg (maximum) nightly, this agent is currently indicated for the treatment of insomnia characterized by difficulties with sleep onset and/or sleep maintenance. In clinical trials, suvorexant modestly improved objective and subjective measures of sleep efficacy compared to placebo. Adverse events were similar between suvorexant and placebo with the exception of increased somnolence and headache with suvorexant treatment. Additional studies comparing suvorexant to other insomnia therapies may further elucidate the role of suvorexant in the treatment of primary insomnia.

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Table 3 | Adverse events in suvorexant trials of 3 month duration.[14,15]

Adverse Effect	Suvorexant 15-20 mg[a] (N=493)	Suvorexant 30-40 mg[b] (N=770)	Placebo (N=767)
Any adverse event	229 (46.5%)	387 (50.3%)	358 (46.7%)
Discontinued drug due to adverse event	15 (3%)	36 (4.7%)	40 (5.2%)
Serious adverse event	3 (0.6%)	6 (0.8%)	16 (2.1%)
Most common adverse events			
Nasopharyngitis	18 (3.7%)	32 (4.2%)	34 (4.4%)
Headache	36 (7.3%)	55 (7.1%)	45 (5.9%)
Somnolence	33 (6.7%)	81 (10.5%)	25 (3.3%)

Data represent n (%).
[a]15 mg for age ≥65 years; 20 mg for age <65 years.
[b]30 mg for age ≥65 years; 40 mg for age <65 years.

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Controversy in Cardiology

Recent study:
Mauri L, Kereiakes DJ, Yeh RW, et al. Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents. N Engl J Med 2014;371:2155-66.

Dual antiplatelet therapy past 1 year of a drug-eluting stent placement, as compared with aspirin monotherapy, reduced the risk of major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%; p<0.001) but was associated with an increased risk of bleeding. (2.5% vs. 1.6%, P = 0.001).

Conflicting evidence:
Valgimigli M, Campo G, Monti M, et al. Short- versus long-term duration of dual-antiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation. 2012 Apr 24;125(16):2015-26.

Twenty-four months of clopidogrel therapy in patients who received a balanced mixture of drug-eluting or bare-metal stents was not significantly more effective than 6 months in reducing the composite outcome of any cause death, myocardial infarction, or cerebrovascular accident.

See also:
Park SJ, Park DW, Kim YH, et al. Duration of dual antiplatelet therapy after implantation of drug-eluting stents. N Engl J Med. 2010 Apr 15;362 (15):1374-82.

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