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Review Article

Suvorexant: A New Drug in the Treatment of Insomnia

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ABSTRACT
Insomnia is classified as a psychiatric disorder where patients complain of difficulty falling asleep, maintaining sleep, or not feeling rested in spite of a sufficient opportunity to sleep. In today's stressful society an increase in complaints of insomnia has been noted. Patients have been found trying to source over the counter sleep aids to help with sleepless nights. It has been noted due to the rise in sleep aid use and complaints of chronic insomniacs that it will be of great interest to identify new more effective / safe treatments as OTC sleep aids are not curative and tend to be habit forming. Suvorexant was recently approved as a prescription drug in August 2014 for the treatment of adults who have trouble falling asleep or staying asleep. This article attempts to present a review on therapeutic profile of this newly approved orexin receptor antagonist.

Key words: New drug update, Insomnia, Suvorexant.

INTRODUCTION

Humans typically have four to six cycles of non-rapid eye movement (NREM) and REM sleep each night, each cycle lasting 70-120 minutes.[1] Usually there is progression through the four stages of NREM sleep before the first REM period.

In REM sleep there is increased electric and metabolic activity, increased cerebral blood flow, muscle atonia, vivid dreaming, poikilothermia and fluctuations in respiratory and cardiac rates.[2] REM sleep is turned on by cholinergic cells. Dopamine has an alerting effect. Neurochemicals involved in wakefulness include norepinephrine and acetylcholine in the cortex and histamine and neuropeptides (e.g. substance P and corticotropin releasing factor) in the hypothalamus.[1,3]

Patients with insomnia complain of difficulty falling asleep, maintaining sleep or experiencing nonrestorative sleep. Transient (two or three nights) and short term (<3weeks) insomnia is common and usually related to a precipitating factor. Chronic insomnia (>1month) may be related to a medical or psychiatric disorder or medication, or it may be psychophysiologic.[4] There are many causes of insomnia. It can be due to medical conditions, use of certain prescription medications and OTC items as well. Insomnia may be a manifestation of an underlying sleep disorder such as restless legs syndrome, periodic limb movements during sleep, or sleep apnea.[5] Finally, insomnia can result from circadian factors associated with jet lag, with alterations of the sleep/wake schedules required by shift work, or with a misalignment between endogenous circadian sleep phase and a person's chosen sleep-wake schedule.[6]

Treatment options for insomnia include cognitive therapy and proper sleep hygiene. However, pharmacotherapy has proven to be the most effective method of alleviating this issue. Medication (prescribed and over-the-counter) is the most common treatment used for insomnia. Only two classes of medications, benzodiazepine-receptor agonists (BRA) and melatonin-receptor agonists, were approved by the Food and Drug Administration of the United States of America for the treatment of insomnia. BRA include the traditional benzodiazepines (e.g., flurazepam, temazepam), and the more recent non-benzodiazepine receptor agonists (e.g., zolpidem, eszopiclone, zaleplon). One of the most recent hypnotics introduced to the market, Ramelteon, is a melatonin-receptor agonist. These agents have all been found effective for the short-term treatment of insomnia. Despite a relative lack of data and no government-approved indication for insomnia, sedating antidepressants, such as the tricyclics, Trazodone and Mirtazapine, are commonly prescribed agents for treating chronic insomnia. There is relatively little efficacy data regarding the use of these agents specifically for insomnia.[7] The role of long-term use of hypnotics, however, is controversial and there is limited evidence at this time to support this clinical practice. Behavioral approaches, alone or combined with brief pharmacotherapy, should be preferred to continuous long-term use of hypnotics to treat chronic insomnia.

Suvorexant, approved in August 2014 by the USFDA is an orexin receptor antagonist. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the orexin receptor suppresses wakefulness.[8] Suvorexant is specifically indicated for the treatment of

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There are two main types of sleep

Non-REM (NREM) Sleep consists of four stages of sleep, each deeper than the last.

REM (Rapid Eye Movement) Sleep is where you do most active dreaming. Your eyes actually move back and forth during this stage, which is why it is called Rapid Eye Movement Sleep.

The Stages Of Sleep[2]

Non-REM Sleep	*REM Sleep*
StageN1 (Transition to sleep) – This stage lasts about five minutes. The eyes move slowly under the eyelids, muscle activity slows down and the person is easily awakened.	REM Sleep (Dream Sleep)- About 70 – 90 minutes after falling asleep, REM sleep starts. In this stage dreaming occurs. Eyes move rapidly, breathing shallows and heart rate and blood pressure increase. Also during this stage arm and leg muscles are paralysed.
Stage N2 (Light Sleep) – This is the first stage of true sleep, lasting from 10-25 minutes. Eye movement stops, heart rate slows and body temperature decreases. Stage N3 (Deep Sleep) - Difficult to awaken and person does not adjust immediately from sleep to wake, often feels groggy and disoriented for several minutes. In this deepest stage of sleep brain wave are extremely slow. Blood flow is directed away from the brain and towards muscles restoring physical energy.	

Table 1: Polysomnographic Assessment of Time to Sleep Onset in Studies 1 and 2.

	Mean Baseline & Change From Baseline After 1 & 3 Months (minutes)		Difference Between Suvorexant & Placebo (minutes)
STUDY 1			
	Placebo (n=290)	Suvorexant 15-20 mg (n=193) (n=193)	
Baseline	66	69	
Change From Baseline			
Month 1	-23	-34	-10***
Month 3	-27	-35	-8**
STUDY 2			
	Placebo n = 290	Suvorexant 15 – 20mg n =193	
Baseline	66	65	
Change From Baseline			
Month 1	-25	-33	-8*
Month 3	-29	-29	0

↑ Change from baseline & treatment differences based upon estimated means.

↕ 15mg in elderly and 20mg in non-elderly patients

*p < 0.05 ** p< 0.01 ***p <0.001

insomnia characterized by difficulties with sleep onset and/or sleep maintenance.[8]

Indications

Suvorexant is an orexin receptor antagonist indicated for the treatment of insomnia, characterized by difficulties with sleep onset and/or sleep maintenance.

Recommended Dosage and Pre-Medication

Suvorexant is supplied as a tablet for oral administration. The recommended dose is 10 mg, taken no more than once per night and within 30 minutes of going to bed, with at least 7 hours remaining before the planned time of awakening. If the 10 mg dose is well-tolerated but not effective, the dose can be increased. The maximum recommended dose of suvorexant is 20 mg once daily.[9]

Suvorexant is available as tablets in the 5mg, 10mg, 15mg and 20mg strengths.

Clinical pharmacology

Mechanism of action

The mechanism by which suvorexant exerts its therapeutic effect in insomnia is presumed to be through antagonism of orexin receptors. The orexin neuropeptide signaling system is a central promoter of wakefulness. Blocking the binding of wake-promoting neuropeptides orexin A and orexin B to receptors OX1R and OX2R is thought to suppress the wake drive.[9]

Pharmacokinetics

Suvorexant exposure increases in a less than strictly dose-proportional manner over the range of 10-80mg because of decreased absorption at higher doses. Suvorexant pharmacokinetics are similar in healthy subjects and patients with insomnia.[9]

Pharmacodynamics

Table 2: Patient-estimated Time to Sleep Onset in Studies 1 and 22:

	Mean Baseline & Change From Baseline After 1 & 3 Months (minutes)		Difference Between Suvorexant & Placebo (minutes)
STUDY 1			
	Placebo (n=382)	Suvorexant 15-20 mg (n=193) (n=251)	
Baseline	67	64	
Change From Baseline			
Month 1	-12	-17	-5
Month 3	-17	-23	-5*
STUDY 2			
	Placebo n = 369	Suvorexant 15 – 20mg n =231	
Baseline	83	86	
Change From Baseline			
Month 1	-14	-21	-7*
Month 3	-21	-28	-8*

↑ Change from baseline & treatment differences based upon estimated means.
↕ 15mg in elderly and 20mg in non-elderly patients
*p < 0.05 ** p< 0.01 ***p <0.001

Table 3: Polysomnographic Assessment of Sleep Maintenance (Wake after Sleep Onset) in Studies 1 and 2

	Mean Baseline & Change From Baseline After 1 & 3 Months (minutes)		Difference Between Suvorexant & Placebo (minutes)
STUDY 1			
	Placebo (n=290)	Suvorexant 15-20 mg (n=193) (n=193)	
Baseline	115	120	
Change From Baseline			
Month 1	-19	-45	-26***
Month 3	-25	-42	-17***
STUDY 2			
	Placebo n = 286	Suvorexant 15 – 20mg n =145	
Baseline	118	119	
Change From Baseline			
Month 1	-23	-47	-24***
Month 3	-25	-56	-31***

↑ Change from baseline & treatment differences based upon estimated means.
↕ 15mg in elderly and 20mg in non-elderly patients
*p < 0.05 ** p< 0.01 ***p <0.001

The effects of suvorexant on the QTc interval were evaluated in a randomized, placebo- and active controlled (moxifloxacin 400mg) crossover study in healthy subjects (n=53). The upper bound of the one sided 95% confidence interval for the largest placebo-adjusted, baseline-corrected QTc interval was below 10ms based on analysis of suvorexant doses up to 240mg, 12 times the maximum recommended dose. Suvorexant thus does not prolong the QTc interval to any clinically relevant extent.[9]

Absorption

Suvorexant peak concentrations occur at a median Tmax of 2 hours (range 30 minutes to 6 hours) under fasted conditions. The mean absolute bioavailability of 10 mg is 82%. Ingestion of suvorexant with a high-fat meal resulted in no meaningful change in AUC or Cmax but a delay in Tmax of approximately 1.5 hours. Suvorexant may be taken with or without food; however for faster sleep onset, suvorexant should not be administered with or soon after a meal.[9]

Distribution

The mean volume of distribution of suvorexant is approximately 49 liters. Suvorexant is extensively bound (>99%) to human plasma proteins and does not preferentially distribute into red blood cells. Suvorexant binds to both human serum albumin and α1-acid glycoprotein.[9]

Metabolism

Suvorexant is mainly eliminated by metabolism, primarily by CYP3A with a minor contribution from CYP2C19. The major circulating entities are suvorexant and a hydroxy-suvorexant metabolite. This metabolite is not expected to be pharmacologically active.[9]

Table 4: Patient-estimated Total Sleep Time in Studies 1 and 2

	Mean Baseline & Change From Baseline After 1 & 3 Months (minutes)		Difference Between Suvorexant & Placebo (minutes)
STUDY 1			
	Placebo (n=290)	Suvorexant 15-20 mg (n=193) (n=193)	
Baseline	115	120	
Change From Baseline			
Month 1	-19	-45	-26***
Month 3	-25	-42	-17***
STUDY 2			
	Placebo n = 286	Suvorexant 15 – 20mg n =145	
Baseline	118	119	
Change From Baseline			
Month 1	-23	-47	-24***
Month 3	-25	-56	-31***

↑ Change from baseline & treatment differences based upon estimated means.
↕ 15mg in elderly and 20mg in non-elderly patients
*p < 0.05 ** p< 0.01 ***p <0.001

Table 5: Patient-estimated Total Sleep Time in Studies 1 and 2

	Mean Baseline & Change From Baseline After 1 & 3 Months (minutes)		Difference Between Suvorexant& Placebo (minutes)
STUDY 1			
	Placebo (n=382)	Suvorexant 15-20 mg (n=193) (n=251)	
Baseline	315	322	
Change From Baseline			
Month 1	23	39	16***
Month 3	41	51	11*
STUDY 2			
	Placebo n = 369	Suvorexant 15 – 20mg n =145	
Baseline	307	299	
Change From Baseline			
Month 1	22	43	21***
Month 3	38	60	22***

↑ Change from baseline & treatment differences based upon estimated means.

↕ 15mg in elderly and 20mg in non-elderly patients

*p < 0.05 ** p< 0.01 ***p <0.001

Elimination

The primary route of elimination is through the feces, with approximately 66% of radiolabeled dose recovered in the feces compared to 23% in the urine. The systemic pharmacokinetics of suvorexant are linear with an accumulation of approximately 1- to 2-fold with once-daily dosing. Steady-state is achieved by 3 days. The mean t1/2 is approximately 12 hours (95% CI: 12 to 13).[9]

Specific populations

Age and race are not predicted to have any clinically meaningful changes on suvorexant pharmacokinetics; therefore, no dose adjustment is warranted based upon these factors. Suvorexant exposure is higher in females than in males. In females, the AUC and Cmax are increased by 17% and 9%, respectively, following administration of suvorexant 40 mg. The average concentration of suvorexant 9 hours after dosing is 5% higher for females across the dose range studied (10-40mg). Dose adjustment of suvorexant is generally not needed based on gender only.

Apparent oral clearance of suvorexant is inversely related to body mass index. In obese patients, the AUC and Cmax are increased by 31% and 17%, respectively. The average concentration of suvorexant approximately 9 hours after a 20 mgdose is 15% higher in obese patients (BMI > 30

kg/m^2) relative to those with a normal BMI (BMI ≤ 25 kg/m^2).

In obese females, the AUC and Cmax are increased by 46% and 25%, respectively, compared to non-obese females. The higher exposure to suvorexant in obese females should be considered before increasing dose. The effects of renal and hepatic impairment on the pharmacokinetics of suvorexant were evaluated in specific pharmacokinetic studies. Suvorexant exposure after a single dose was similar in patients with moderate hepatic insufficiency (Child-Pugh category 7 to 9) and healthy matched control subjects; however, the suvorexant apparent terminal half-life was increased from approximately 15 hours (range 10 - 22 hours) in healthy subjects to approximately 19 hours (range 11 - 49 hours) in patients with moderate hepatic insufficiency Suvorexant exposure (expressed as total and unbound concentrations) was similar between patients with severe renal impairment (urinary creatinine clearance ≤30 mL/min/1.73m^2) and healthy matched control subjects.

Use in specific populations[9]

Pregnancy

Pregnancy Category C

There are no adequate and well-controlled studies in pregnant women. Suvorexant should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether this drug is secreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when suvorexant is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

No clinically meaningful differences in safety or effectiveness were observed between geriatric patients and younger patients at the recommended doses

Patients with Compromised Respiratory Function

Effects of suvorexant on respiratory function should be considered if prescribed to patients with compromised respiratory function.

Obstructive Sleep Apnea

Suvorexant has not been studied in patients with severe obstructive sleep apnea.

Chronic Obstructive Pulmonary Disease

Suvorexant has not been studied in patients with severe COPD.

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild and moderate hepatic impairment. Suvorexant has not been studied in patients with severe hepatic impairment and is not recommended for these patients

Patients with Renal Impairment

No dose adjustment is required in patients with renal impairment.

Clinical Studies[9,10]

Suvorexant was evaluated in three clinical trials in patients with insomnia characterized by difficulties with sleep onset and sleep maintenance. Two similarly designed, 3-month, randomized, double-blind, placebo-controlled, parallel-group studies were conducted (Study 1 and Study 2). In both studies, non-elderly (age 18-64) and elderly (age ≥ 65) patients were randomized separately. For the studies together, non-elderly adults (mean age 46 years; 465 females, 275 males) were treated with suvorexant 20 mg (n=291) or placebo (n=449). Elderly patients (mean age 71 years, 346 females, 174 males) were treated with suvorexant 15 mg (n=202) or placebo (n=318).

In Study 1 and Study 2, suvorexant 15 mg or 20 mg was superior to placebo for sleep latency as assessed both objectively by polysomnography (Table 1) and subjectively by patient-estimated sleep latency (Table 4). Suvorexant15 mg or 20 mg was also superior to placebo for sleep maintenance, as assessed both objectively by polysomnography (Table 5) and subjectively by patient-estimated total sleep time (Table6). The effects of suvorexant at night 1 (objective) and week 1 (subjective) were generally consistent with later time points. The efficacy of suvorexant was similar between women and men and, based on limited data, between Caucasians and non-Caucasians. Twenty seven percent of patients treated with suvorexant 15 mg or 20 mg in Study 1 and Study 2 were non- Caucasians. The majority (69%) of the non-Caucasian patients was Asian.

In the 1-month crossover study (Study 3), non-elderly adults (age 18-64 years, mean age 44 years) were treated with placebo (n=249) and suvorexant at a dose of 10 mg (n=62), 20 mg (n=61), or up to 80 mg.

Suvorexant 10 mg and 20 mg were superior to placebo for sleep latency and sleep maintenance, as assessed objectively by polysomnography.

Suvorexant was also evaluated at doses of 30 mg and 40 mg in the 3-month placebo-controlled trials (Study 1 and Study 2). The higher doses were found to have similar efficacy to lower doses, but significantly more adverse reactions were reported at the higher doses.

Adverse Effects

The most common adverse reaction (reported in 5% or more of patients treated with suvorexant and at least twice the placebo rate) with suvorexant was somnolence.[9]

Contraindications, Cautions and Precautions

*Daytime somnolence***:** Risk of impaired alertness and motor coordination, including impaired driving; risk increases with dose; caution patients taking 20 mg against next-day driving and other activities requiring complete mental alertness,

Nighttime "sleep-driving" and other complex behaviors while out of bed and not fully awake: Risk increases with dose, with use of CNS depressants, and with alcohol.

Depression: Worsening of depression or suicidal thinking may occur. Risk increases with dose. Immediately evaluate any new behavioral changes.

Compromised respiratory function: Effect on respiratory function should be considered.

Sleep paralysis, hypnagogic/hypnopompic hallucinations, and cataplexy-like symptoms: Risk increases with dose.

Do not use in patients with narcolepsy.

Drug interactions[9]

*Cyp3a inhibitors***:** Recommended dose is 5 mg when used with moderate CYP3A inhibitors. Dose can be increased to 10 mg once daily if the 5 mg dose is not effective. Not recommended for use in patients taking strong CYP3A inhibitors.
Strong CYP3A inducers: Efficacy may be reduced.
Digoxin: Monitor digoxin concentrations

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