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Suvorexant in insomnia: efficacy, safety and place in therapy

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***Abstract*:** Insomnia is a highly prevalent disorder that can occur in conjunction with other medical or psychiatric conditions or can occur in the absence of a coexisting disorder. Regardless, treatment of insomnia is beneficial to the patient and may benefit comorbidities if they exist. Nonpharmacologic modalities such as sleep hygiene and stimulus controls are important mainstays of insomnia therapy, but may not be sufficient to treat the disorder. Dual orexin receptor antagonists (DORAs) are a new class of insomnia medication that target wakefulness-promoting neuropeptides to regulate the sleep–wake cycle. Suvorexant is the first DORA to be approved and has demonstrated efficacy at decreasing both time to sleep onset and increasing total sleep time compared with placebo. Suvorexant has a novel mechanism of action and may represent an alternative for patients who cannot tolerate or do not receive benefit from traditional sleep agents. Suvorexant is generally effective and well tolerated, but has not been compared head to head with traditional sleep agents and being only newly available, lacks a longer-term 'real-world' experience base.

Keywords: dual orexin receptor antagonist, hypocretin, insomnia, suvorexant

Introduction

Orexin receptor antagonists represent a new therapeutic drug class for treating insomnia. Orexins (also called hypocretins) are a group of hypothalamic neuropeptides that promote wakefulness *via* their actions on serotonin, histamine, acetylcholine, and dopamine [de Lecea *et al.* 1998; Sutcliffe and de Lecea, 2000]. Loss of orexin function in humans results in narcolepsy, further lending support to their function in promoting wakefulness [Sakurai and Mieda, 2011]. Orexin receptors OX1R and OX2R are both important in promoting wakefulness with dual receptor blockade [Winrow and Renger, 2014]. Suvorexant (Belsomra; Merck & Co., Inc., Whitehouse Station, NJ, USA) is the first dual orexin receptor antagonist (DORA) to be approved for the treatment of insomnia. Suvorexant improves both sleep latency and sleep maintenance in patients with insomnia [Merck & Co., Inc., 2013].

Suvorexant is a schedule IV controlled substance based on its abuse potential, a determination made by the US Drug Enforcement Administration [Drug Enforcement Administration, Department of Justice, 2014]. The primary adverse effect of suvorexant established during clinical trials was daytime somnolence (including impaired driving). However, concerns have been raised regarding unconscious nighttime activity, sleep paralysis, hypnagogic hallucinations, mild cataplexy, and suicidal ideation with suvorexant use [Farkas 2013]. These adverse effects have a dose-dependent relationship; patients treated with up to four times the maximum recommended dose experienced somnolence twice as frequently as those treated with the recommended dose (10 mg and 20 mg) [Herring *et al.* 2014]. As such, only lower doses of suvorexant are approved for use [Herring *et al.* 2014; Merck & Co., Inc., 2014]. The goals of this review are to highlight the efficacy and safety of suvorexant, and its potential place in therapy.

Pharmacology

Mechanism of action and dosing

Suvorexant works by selectively blocking the binding of neuropeptides orexin A and B to receptors OX1R and OX2R, suppressing wakefulness.

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Suvorexant was studied in humans at doses of 10–80 mg. Based on concerns for adverse events experienced by patients at higher doses (30 and 40 mg), suvorexant is US Food and Drug Administration (FDA) approved at 5 mg, 10 mg, 15 mg, and 20 mg. The labeled starting dose for most patients is 10 mg, which can be increased to 20 mg if 10 mg is tolerated but ineffective. The maximum dose in 24 is 20 mg. Doses should be taken 30 min prior to intended time of sleep and should not be taken if less than 7 h of sleep is expected [Merck & Co., Inc., 2014].

Pharmacokinetics

Suvorexant pharmacokinetics (PK) were characterized using PK data from phase I studies and pooled phase II and III data [FDA, 2013]. Suvorexant peak concentrations occur at a median time at which the maximum serum drug concentration is observed (T_{max}) of 120 min (range 30–360 min). Food ingestion can delay the T_{max} by 90 min, so suvorexant should not be administered with or soon after a meal if faster sleep onset is preferred. Both the area under the curve (AUC) and maximum serum drug concentration (C_{max}) are increased in female patients by 17% and 9%, respectively. Even higher increases in AUC and C_{max} are observed in patients with obesity [body mass index (BMI) $>$ 30 kg/m^2] for which the AUC and C_{max} are increased by 31% and 17%, respectively. Additionally, the average concentration 9 h after a 20 mg dose of suvorexant is 15% higher in patients with obesity compared with those of normal body weight (BMI $\leqslant$ 25 kg/m^2). The PK effects are even more marked in female patients with obesity, with AUC and C_{max} increases of 46% and 25%, respectively. Despite these sex and weight-based differences in suvorexant exposure, no sex-specific or weight-based dosing is recommended other than that caution should be exercised when considering a dose increase in an obese female patient [Merck & Co., Inc. 2014].

Suvorexant is extensively protein bound in the plasma. Metabolism of suvorexant occurs predominantly through cytochrome P450 (CYP) 3A4, with a minor contribution from CYP219. The resulting metabolite, hydroxyl suvorexant, is therapeutically inactive. Suvorexant elimination occurs primarily through feces (66%) and less commonly through urine (23%) [Merck & Co., Inc. 2014].

Suvorexant has been evaluated in phase I open-label trials of both renally and hepatically impaired patients. In eight male and female patients with an estimated creatinine clearance (CrCl) of 30 ml/min matched with eight healthy male and female patients (estimate CrCl 80 ml/min) who each received a one-time dose of suvorexant 20 mg, there was no difference in the plasma unbound AUC of suvorexant between groups (90% confidence interval 0.83, 1.67). Suvorexant had a T_{max} of 2 h in the renally impaired group compared with 1 h in the healthy group; the terminal half life ($t_{1/2}$) was 13.5 h in both groups. An analogous study was conducted in hepatically impaired patients whereby 8 male and female patients with a Child–Pugh score of 7–9 were matched with eight healthy male and female patients and each received a one-time dose of suvorexant 20 mg. The geometric mean AUC (unbound) and C_{max} (unbound) ratios were similar between groups but the terminal $t_{1/2}$ was prolonged in patients with hepatic impairment compared with healthy subjects (19 h *versus* 15 h) (Merck & Co., Inc., data on file). Because these PK differences were not clinically impactful, suvorexant does not require any renal- or hepatic-specific dose adjustments [Merck & Co., Inc., 2014].

Efficacy: summary of key studies

Suvorexant has been studied for insomnia in three phase III clinical trials. All three clinical trials compared suvorexant with placebo. Herring and colleagues evaluated the efficacy of suvorexant in two separate trials at 3 months whereas Michelson and colleagues evaluated the safety and tolerability of suvorexant at 1 year. Efficacy for the trials was assessed by a variety of primary and secondary endpoints that included sleep diaries, subjective total sleep time (sTST), subjective time to sleep onset (sTSO), subjective wake after sleep onset (sWASO), wake after sleep onset (WASO), subjective quality of sleep (sQUAL), subjective refreshed feeling on waking (sFRESH), subjective number of awakenings (sNAW), and latency to onset of persistent sleep (LPS) [Herring *et al.* 2014; Michelson *et al.* 2014].

All three trials stratified patients by age category [nonelderly (18–65 years of age) and elderly ($\geqslant$ 65 years of age)] and included patients who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR) criteria for primary insomnia. The trials excluded subjects if they had other sleep disorders, confounding neurologic disorders, current major affective or psychotic psychiatric illness, substance

abuse or an unstable medical condition [Herring *et al.* 2014; Michelson *et al.* 2014].

Herring and colleagues assessed 3-month efficacy of suvorexant in trial 1 and trial 2. Trial 1 had an optional 3-month double-blind extension phase. The two trials randomized 2030 patients to suvorexant 40/30 mg ($n = 770$), suvorexant 20/15 mg ($n = 493$) or placebo ($n = 767$) with doses varying by age category (40 mg or 20 mg for patients < 65 years; 30 mg or 15 mg for patients ≥ 65 years). The primary endpoints evaluated were change from baseline at months 1 and 3 for subjective (sleep diary: sTST, sTSO, sWASO, sNAW, sQUAL, sFRESH) and objective (polysomnography: LPS, WASO) sleep measures. Baseline characteristics were similar for each treatment arm. Baseline sTST in minutes was 322, 316, and 316 in trial 1 and 298, 315, and 310 in trial 1 for suvorexant 20/15 mg, suvorexant 40/30 mg, and placebo, respectively. Baseline sTSO in minutes was 63, 68, and 67 in trial 1 and 86, 74, and 81 in trial 2 for suvorexant 20/15 mg, suvorexant 30/40 mg, and placebo, respectively. Patients were included for the primary endpoint analysis if they took at least one dose of treatment, had at least one post-treatment efficacy measure, and had baseline data. Patients included for the safety analysis were those who received treatment within 14 days of their last dose [Herring *et al.* 2014].

The two trials demonstrated that suvorexant 40/30 mg was superior to placebo by improving sleep maintenance, measured by sTST and WASO, at months 1 and 3 ($p < 0.001$ for both). Changes from baseline for sTST were 19.7 and 25.1 min for trials 1 and 2, respectively. Trial 1 showed suvorexant 40/30 mg improved sleep onset, measured by sTSO and LPS, at months 1 and 3 ($p < 0.01$ and $p < 0.001$, respectively), whereas trial 2 did not find LPS of suvorexant 40/30 mg to be significantly different at month 3. Changes from baseline for sTSO were –8.4 and –13.2 min for trials 1 and 2, respectively. Additionally, suvorexant 40/30 mg improved subjective endpoints at month 3 for sWASO and sQUAL. Similarly, suvorexant 20/15 mg was more effective than placebo in improving sleep maintenance, measured by sTST and WASO, at months 1 and 3 ($p < 0.001$). Changes from baseline in sTST were 10.7 and 22.1 min for trials 1 and 2, respectively. It was superior to placebo for improving sleep onset, measured by LPS at 1 month; however, this did not differ at month 3. The numbers of adverse events between the treatment groups were similar. Percent differences in reports of somnolence *versus* placebo with 95% confidence interval were as follows: trial 1: 20/15 mg = 1.7 (–1.4, 5.5), 40/30 mg = 7.3 (3.8–11.1); trial 2: 20/15 mg = 5.2 (1.6–9.7), 40/30 mg = 7.2 (3.8–10.9). Reports of somnolence decreased after the first 3 months and appeared to be dose related, with suvorexant 40/30 mg having more reports of somnolence [Herring *et al.* 2014].

Michelson and colleagues evaluated suvorexant 30 mg (elderly patients) and 40 mg (nonelderly patients) *versus* placebo for 1 year. The primary objectives were to assess safety and tolerability of suvorexant at 1 year. Secondary objectives assessed the efficacy through patient-reported sTST and sTSO. After 1 year, a 2-month discontinuation phase was completed for patients who received suvorexant during the 1-year study to assess rebound insomnia and withdrawal [Michelson *et al.* 2014].

A total of 781 patients were randomly assigned to receive suvorexant ($n = 522$) or placebo ($n = 259$). For the discontinuation phase, 484 patients entered the discontinuation phase with 156 randomized to the suvorexant–suvorexant group, 161 to the suvorexant–placebo group, and 157 to the placebo–placebo group. Baseline sTST and sTSO for suvorexant and placebo were similar (320.4 min *versus* 330.1 min and 65.9 min *versus* 64.9 min, respectively). Of the 781 patients, 484 completed the 1-year phase. Three hundred twenty-two (62%) and 162 (63%) patients who received suvorexant and placebo, respectively, completed the 1-year phase. During the 1-year treatment period, 362 (69.5%) patients in the suvorexant arm experienced adverse events compared with 164 (63.6%) in the placebo arm. The most common adverse effect reported was somnolence [reported by 69 (13%) patients who received suvorexant *versus* 7 (3%) patients who received placebo]. Medication discontinuation due to adverse events were similar between suvorexant and placebo groups [61 (11.7%) and 22 (8.5%), respectively].

At 1 month, suvorexant improved sTST (38.7 min) *versus* placebo (16 min), $p < 0.0001$. sTSO was also improved with suvorexant (–18 min) *versus* placebo (–8.4 min), $p = 0.0002$. Analysis of rebound insomnia and withdrawal found no statistically significant differences between the suvorexant–placebo group and placebo–placebo group [Michelson *et al.* 2014].

Table 1. Efficacy of suvorexant *versus* placebo in patients with insomnia.

Study	Intervention	*N*	Female (%)	*N* < 65 years (%)	Baseline sTST (min)	Baseline sTSO (min)	Change in sTST at month 3 (min)	Change in sTSO at month 3 (min)
Herring [2014] Trial 1	Suvorexant 20/15 mg	254	162 (63.8)	147 (57.9)	322	63	10.7*	−5.2*
	Suvorexant 30/40 mg	383	230 (60.1)	222 (58)	316	68	19.7$	−8.4‡
	Placebo	384	245 (63.8)	223 (58.1)	316	67	–	–
Herring [2014] Trial 2	Suvorexant 20/15 mg	239	157 (65.7)	144 (60.3)	298	86	22.1$	−7.6*
	Suvorexant 30/40 mg	387	267 (69)	229 (59.2)	315	74	25.1$	−13.2$
	Placebo	383	247 (64.5)	226 (59)	310	81	–	–

*$p < 0.05$; $^{\$}p < 0.001$; $^{‡}p < 0.01$.
sTSO, subjective time to sleep onset; sTST, subjective total sleep time.

Table 2. Efficacy and safety of suvorexant versus placebo in patients with insomnia.

Study	Intervention	*N*	Female (%)	*N* < 65 years (%)	Baseline sTST (min)	Baseline sTSO (min)	⩾1 AE (%)	Discontinuation due to AE (%)	sTST at 1 year	sTSO at 1 year
Michelson [2014]	Suvorexant	521	287 (55)	213 (41)	320.4	65.9	362 (69.5)	61(11.7)	60.5*	−26.6$
	Placebo	258	149 (58)	107 (42)	330.1	64.9	164 (63.6)	22 (8.5)	33	−17

*$p < 0.0001$; $^{\$}p < 0.0055$.
AE, adverse event; sTSO, subjective time to sleep onset; sTST, subjective total sleep time.

Across the three phase III suvorexant studies in patients with insomnia, suvorexant demonstrated efficacy compared with placebo and was generally well tolerated. The patient characteristics and outcomes are displayed in Tables 1 and 2.

Safety considerations

Contraindications

The only population specifically contraindicated for use of suvorexant is patients with narcolepsy [Merck & Co., Inc., 2014]. As many as 90% of patients with narcolepsy with cataplexy are orexin ligand deficient and further antagonizing their orexin receptors could propagate their condition [Zeitzer *et al.* 2006].

General adverse events

In clinical trials, the most common adverse event experienced in patients who received suvorexant was somnolence (7% *versus* 3% for placebo). Other commonly reported adverse events (⩾2% incidence and greater than placebo) were diarrhea, xerostomia, upper respiratory tract infections, headache, dizziness, abnormal dreams, and cough [Herring *et al.* 2014]. In an extended study of patients over a 1-year treatment phase, the most frequent adverse events were similar and included somnolence, fatigue, xerostomia, dyspepsia, and peripheral edema [Michelson *et al.* 2014].

Precautions of special note include daytime impairment (e.g. falling asleep while driving), additive central nervous system (CNS) depression when coadministered with other CNS depressants, abnormal thinking and behavioral changes, worsening depression or increases in suicidal ideation, sleep paralysis, hypnagogic and hypnopompic hallucinations, and cataplexy-like

symptoms [Herring *et al.* 2014]. These adverse effects were dose related, prompting the FDA to request that the drug manufacturer decrease the starting dose of suvorexant. It is important to note that the doses studied in clinical trials were oftentimes higher than the doses that were approved by the FDA [Neubauer, 2015].

Female patients

In clinical trials of suvorexant, somnolence occurred more frequently in female than male patients who received the 15 mg and 20 mg dose (8% for female patients *versus* 3% for male patients; no *p* value reported). Also more common in female patients were headache, abnormal dreams, xerostomia, cough, and upper respiratory tract infection [Herring *et al.* 2014; Merck & Co., Inc., 2014]. There were two specific safety studies conducted in healthy elderly and nonelderly patients to assess nighttime administration of suvorexant and its next-day effects on driving performance. Patients were randomized to either suvorexant or placebo and the driving test was conducted after one night of drug therapy and again after eight consecutive nights of drug therapy. In the nonelderly group who received either 20 mg or 40 mg of suvorexant or placebo, four female patients taking suvorexant stopped their driving test prematurely due to somnolence. Because of this result, patients taking suvorexant 20 mg should be cautioned about next-day driving impairment [Merck & Co., Inc., 2014].

Elderly patients

Suvorexant has been studied in both elderly (age $\geqslant$ 65 years) and nonelderly (age 18–64 years) patients and there were no significant efficacy or safety differences noted between these two groups. In the two specific safety studies conducted in healthy elderly and nonelderly patients to assess nighttime administration of suvorexant and its next-day effects on driving performance, elderly patients received either 15 mg or 30 mg of suvorexant or placebo. The only elderly patient who stopped her driving test prematurely owing to somnolence was randomized to placebo [Merck & Co., Inc., 2014]. Elderly patients were also evaluated for the effects of suvorexant on next-day memory and balance as well as middle-of-the-night safety. Balance was evaluated by body sway test and memory was assessed by a word recall test. There were no significant effects on next day memory or balance in elderly subjects, but there was a noted impairment in balance in elderly patients 90 min after they were given suvorexant 30 mg [Merck & Co., Inc., 2014].

Drug–drug interactions

Effects on suvorexant

In clinical trials, suvorexant was coadministered with ketoconazole, diltiazem, and rifampin. Coadministration of suvorexant with both ketoconazole and diltiazem resulted in a higher systemic exposure to suvorexant. Patients receiving a single dose of suvorexant 4 mg in period 1 and 11 daily doses of ketoconazole 400 mg with suvorexant 4 mg on day 2 during period 2. Patients treated with concomitant suvorexant and ketoconazole experienced an almost threefold increase in AUC and a prolonged $t_{1/2}$ of 19.4 h (compared with 11.2 h with suvorexant alone) (Merck & Co., Inc., data on file). When a single dose of suvorexant 20 mg was administered with multiple daily doses of diltiazem 240 mg, the AUC increased approximately twofold and the $t_{1/2}$ increased from 12.4 to 16.1 h. Because the inhibitory effect was stronger with ketoconazole than diltiazem, the manufacturer recommends avoiding suvorexant use in patients taking strong CYP3A4 inhibitors (e.g. ketoconazole) and to use a reduced dose of 5 mg in patients concurrently receiving moderate CYP3A4 inhibitors (e.g. diltiazem) [Merck & Co., Inc., 2014].

Rifampin and suvorexant coadministration was studied by providing patients with a single dose of suvorexant 40 mg and multiple doses of rifampin 600 mg. Coadministration of the two decreased the $t_{1/2}$ by almost 5 h (from 12.9 h to 7.7 h) and produced significant reductions (87%) in AUC, a decrease that likely renders suvorexant ineffective [Merck & Co., Inc., 2014; FDA, 2014].

Coadministration of suvorexant and alcohol does not affect the PK profile of suvorexant. However, coadministration of suvorexant and alcohol produces additive impairment on sustained attention/vigilance, balance, and working memory (Merck & Co., Inc., data on file).

Effects of suvorexant on other drugs

Suvorexant is unlikely to perpetrate any clinically relevant drug–drug interactions. Suvorexant has been co administered with midazolam, combined oral contraceptives (ethinyl estradiol/norgestimate), warfarin, and digoxin and has

caused no meaningful interactions with any of these medications [FDA, 2014]. However, due to the slight increase in digoxin concentrations that occurred with coadministration and the narrow therapeutic index observed with digoxin, monitoring of digoxin concentrations is recommended in patients receiving concomitant suvorexant [Merck & Co., Inc., 2013; FDA, 2014].

Place in therapy

Suvorexant is orally available, offers a different mechanism of action than other approved agents, and has side effects similar to other sleep agents, with somnolence being the most common. Based on clinical trials, suvorexant may be considered in patients whose condition fails to respond to treatment with benzodiazepines and nonbenzodiazepine hypnotics. Suvorexant has a longer half life, similar to other sedative hypnotics, and would be useful in patients with sleep maintenance insomnia while also providing benefit for sleep onset. The beneficial effects of suvorexant are likely to outweigh any potential harm from use of the medication [Citrome, 2014]. Like benzodiazepines and nonbendiazepine hypnotics, suvorexant is a controlled substance. Since it is a new agent, it is more expensive than other sleep agents, such as zolpidem, with an average wholesale price (AWP) of approximately $315 for 30 tablets [Merck & Co., Inc., 2014]. This medication provides an alternative for patients with insomnia who do not tolerate benzodiazepine or nonbenzodiazepine hypnotics or in whom these agents are ineffective. Real-world experience with the medication is lacking and there may be safety and efficacy considerations that are borne out with more widespread use that were not identified during clinical trials of suvorexant.

Future therapies

Currently, there are no future medications of this class being studied. Merck and GlaxoSmithKline both developed orexin antagonists; however, neither drug made it through the development phases. If suvorexant is tolerated and found to be beneficial for patients with insomnia, this may spur on the development of more DORA agents.

Conclusion

Suvorexant is the first in a new class of insomnia agents targeted at orexin antagonism. Suvorexant is effective at decreasing sleep latency and increasing total sleep time, much like traditional sleep agents. In general, suvorexant is well tolerated, with somnolence reported as the most significant adverse effect. Suvorexant is an exciting new option for the treatment of insomnia, but longer-term safety and efficacy considerations are unknown until more data on the clinical experience with suvorexant are available.

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