Efficacy and safety of suvorexant for the treatment of primary insomnia among Chinese: A 6-month randomized double-blind controlled study

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Abstract

Background: Insomnia often responds to the orexin receptor antagonist suvorexant. This study aimed to evaluate the efficacy and adverse events of suvorexant for Chinese patients with primary insomnia over 6 months. *Methods:* A total of 120 patients with primary insomnia were assigned randomly to two groups that received placebo or suvorexant (40 mg) for 6 months. The primary outcomes were the total sleep time (sTST), time to sleep onset (sTSO), and sleep quality (sQUAL). The secondary outcomes were the Insomnia Severity Index (ISI) score and adverse events. *Results:* A total of 111 patients completed the study and all of them were included in the final analysis. Suvorexant showed greater efficacy than the placebo in enhancing sTST, sTSO, sQUAL and ISI score at months 1 and 6. Serious adverse events were documented in 2 patients (3.3%) in the suvorexant group and 1 patients (1.7%) in the placebo group. The most common adverse event was somnolence, which occurred in 7 patients (11.7%) in the suvorexant group and 2 patients (3.3%) in the placebo group. No death related to suvorexant treatment was recorded.
Conclusions: Suvorexant was efficacious and well-tolerated in a group of Chinese patients with primary insomnia over 6 months.

Keywords: Suvorexant, insomnia, randomized controlled trial, clinical trial

INTRODUCTION

Patients with insomnia often complain of difficulties with falling asleep and maintaining sleep as well as experiencing non-restorative sleep. Despite a number of available treatments, insomnia is the most common medical complaint in general practice.[1] It has been estimated that approximately one-third of population have at least one symptom associated with insomnia.[2,3] Patients with acute and chronic pain[4-6], hypertension[7,8], pulmonary disease[7,8], urinary disorders[7-10], pressure ulcers[11,12] and gastrointestinal problems[13,14] are more likely to develop insomnia. In addition, insomnia is a major risk factor for anxiety disorders and major depression, which may lead to a decreased quality of life.[3]

Various intervention options are available for insomnia. The most common pharmacological treatments are benzodiazepines (BZD) and non-BZDs[15-26], both of which enhance activity of the widespread central nervous system inhibitory neurotransmitter gamma-aminobutyric acid receptor alpha-1 (GABA). In addition, sedating anti-depressants, melatonin receptor agonists, and histamine H1 receptor antagonists (e.g., doxepin) have been used to treat insomnia.[27-29] However, these therapies often have limited efficacy and unwanted side effects, which limits treatment options for many patients. Therefore, new drugs that are better tolerated are needed to provide broader options to patients with insomnia.

Suvorexant, an orexin receptor antagonist (ORA), is the first in a new class of drugs in development for the treatment of insomnia.[30-32] Suvorexant promotes the natural transition from wakefulness to sleep and improves sleep onset and sleep maintenance.[33-35]

Currently, suvorexant is licensed in the US and Japan. The maximum FDA-approved dose of suvorexant is 20 mg once daily.[36] As per an addendum to Merck's briefing document[37], the original dosing recommendation was to initiate suvorexant therapy at 40 mg for patients < 65 years old, and 30 mg for patients ≥65 years old with a reduction to 20 mg (15 mg in elderly) for patients based on individual tolerability.[35,38] However, limited data are available concerning the efficacy and safety of suvorexant in Chinese

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patients with primary insomnia. Here, we present a 6 months treatment clinical investigation to examine the efficacy and tolerability of suvorexant in Chinese patients younger than 65 years with primary insomnia.

METHODS

Design

The 6-month study was a randomized, double-blind, two-arm parallel-group, placebo-controlled design. Participants who met the inclusion and exclusion criteria were randomized to receive either suvorexant (40 mg) or placebo for 6 months. A total of 120 Chinese patients with primary insomnia were scheduled, including those for screening, baseline evaluation (to determine baseline values and whether the patient met all the inclusion/exclusion criteria), and outcome evaluation at the cessation of the 6-month trial. The trial was conducted between December 2014 and April 2016 at the clinical research centre in China in accordance with the Declaration of Helsinki and the Guidelines for Good Clinical Practice: The People's Hospital of Yanan. The study was approved by the Medical Ethical Committee of The People's Hospital of Yanan. Eligible subjects were randomly allocated to the suvorexant group or the placebo group in a 1:1 allocation ratio. Participants received treatment for 6 months with 1 month of follow-up.

Inclusion and exclusion criteria

Both male and female patients with primary insomnia aged 18–64 years were enrolled in the trial. All patients were required to meet the DSM-IV-TR diagnostic criteria for primary insomnia[39] and were assessed by a clinical interview and a structured sleep diagnostic interview. All pharmacological and non-pharmacological interventions for insomnia were discontinued within 15 days before entry to the study. Moreover, medications such as antipsychotics, antidepressant, mood stabilizers and antihistamine that might affect the outcome measures were also not allowed during the treatment period in this study. In addition, all patients provided written informed consent. Patients were excluded if they were pregnant or breastfeeding; had diabetes mellitus, significant renal, hepatic, gastrointestinal, pulmonary, or endocrine disorders; or other neurological disease. Patients with psychiatric diagnosis such as major depression, bipolar disorder, schizophrenia,

substance abuse/dependence and anxiety disorders were also excluded from the study.

Randomization and blinding

Patients who met all the inclusion/exclusion criteria were assigned to either the suvorexant or the placebo group using a computerized number generator in the stratified block randomization method in SAS (version 8.2; SAS Institute, Inc., Cary, NC, USA). The randomization was performed by a statistician from whom treatment allocation was masked. The treatment allocation was concealed in opaque sequentially numbered sealed envelopes containing the randomization assignments. The patients, investigators, and study site personnel were blinded to the treatment allocation. Individuals who were directly involved in the study (including the trial conduction and data analysis) did not have access to the randomization schedule until the trial was completed.

Participants and recruitment

All patients were new and they were recruited through the clinic of the Clinical Medicine Research Center of The People's Hospital of Yanan. All patients were administered a clinical assessment. After the clinical evaluation, patients were randomized to either the suvorexant or the placebo group. Suvorexant or placebo was administered by the service's therapists, all of whom were trained in its administration. Then, all included patients were offered suvorexant or placebo treatment, and were informed about the research and given an information sheet. Consent was obtained at the next appointment from patients who agreed to participate.

Intervention

Patients assigned to the suvorexant group received suvorexant (40 mg daily) for 6 months. Participants assigned to the placebo group received placebo and the same dose as that with the treatment group.

Efficacy assessments

The primary outcomes were the total sleep time (sTST), time to sleep onset (sTSO), and sleep quality (sQUAL). Those scales were measured with an electronic morning sleep diary completed daily throughout the study by the patient.[40] The electronic diary was based on previously used and validated paper diaries, which was widely accepted by regulators and the academic

community.[40] The secondary outcomes were the Insomnia Severity Index (ISI) score[41] and adverse events. Patient-based sleep assessments were recorded using questionnaires administered through an electronic patient diary. Patients also completed the ISI.

Data collection and analysis

The clinical outcomes included the sTST, sTSO, and sQUAL as well as the ISI score during the intervention period. Data collection also included the number of eligible patients with primary insomnia, the number of patients willing to be randomized, and compliance with the intervention, with the aim of estimating the effect size for a fully powered trial.

Statistical analysis

The sample size was calculated in order that superiority potentially could be claimed on the primary efficacy outcome. The standardized effect size (i.e., delta/common standard deviation) was expected to be 0.35 with $\alpha = 0.05$ (two-sided) and $\beta = 0.20$. The estimated sample size for the suvorexant and placebo groups with a 1:1 ratio was 48 patients in each group. Assuming a 20% dropout rate, this estimate indicated that at least 120 patients needed to be recruited for the study.

The clinical outcome data were analyzed using an "intention to treat" (ITT) approach and were assessed over the first and sixth months with a mixed-effects model that included terms for the baseline value of the response variable, sex, treatment, time (as a categorical variable), and a treatment by time interaction. For the discontinuation phase, responders were defined as those patients with a 6-month ISI score ≤14, which suggests no or subthreshold insomnia, and a degree of improvement in sTST from study entry to Month 6 using thresholds ≥20%, ≥10%, and ≥5%. For the ISI responders at Month 6, relapse was defined as a return to moderate or severe insomnia (i.e., ISI >14). For the sTST responders at Month 6, relapse was defined as a worsening in sTST that crossed back over the specified threshold value relative to baseline. Data analysis was performed by a study statistician who was blind to the treatment allocation.

Safety

Safety was evaluated by clinical review of adverse effects (AEs) after the last dose of treatment, laboratory values and vital signs, and physical examinations. AEs were documented by an investigator at each visit date, and clinically significant changes in clinical and laboratory measurements were recorded. Withdrawal effects were measured using the Tyrer Withdrawal Symptom Questionnaire (TWSQ). If the summed TWSQ≥3, the patient was considered to have withdrawal effects. Safety data for all the treated patients were included in the analysis.

RESULTS

A total of 214 patients were initially screened and entered the study (Figure 1). Of these 214 Chinese patients, 82 did not meet the study criteria and 12 declined to participate. Therefore, 120 patients were randomized into the study groups. All included participants received study medication, and 111 patients completed the efficacy assessment of the primary outcomes (sTST, sTSO, and sQUAL). Nine patients withdrew from the study. The major reasons for withdrawal included adverse events, withdrawal of consent, loss to follow-up, and other reasons (Figure 1).

The patient characteristics and the baseline symptom severity of the study population are shown in Table 1. The two groups did not differ significantly in the majority of characteristics and clinical variables at the baseline visit. At baseline, the mean age (SD) was 50.6 (11.9) years in the suvorexant group and 51.4 (12.2) years in the placebo group. All the patients were Chinese (100.0%, both groups). The sTST, sTSO, and sQUAL was 331.5 (67.1), 62.9 (36.8), and 1.9 (0.4), respectively, in the suvorexant group and 334.7 (69.2), 59.2 (35.1), and 2.0 (0.4), respectively, in the placebo group at baseline. In addition, the ISI score was 14.3 (4.0) in the suvorexant group and 14.1 (3.9) in the placebo group at baseline.

We examined the least squares mean change from baseline (95% CI) by treatment and the difference (95% CI) between suvorexant and placebo to evaluate the efficacy of suvorexant. The results for the other efficacy endpoints at month 1 and month 6 are summarised in Table 2. Suvorexant improved all subjective sleep measures as well as the ISI score compared with placebo at month 1 and month 6. After the first month, the suvorexant group exhibited significant improvements in sTST, sTSO, and the ISI score compared with the placebo group (Table 2). These improvements were maintained throughout the endpoint at 6 months.
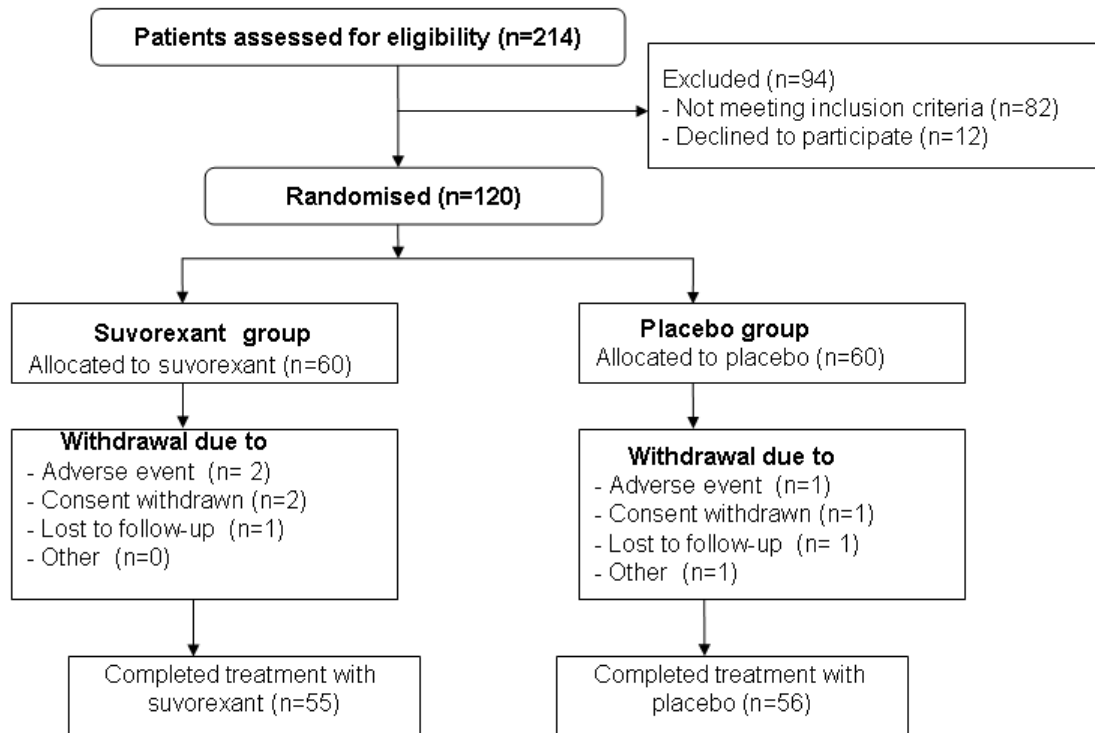
Figure 1. Flow of participants through the trial

Of the 120 participants who received medication during the 6-month double-blind intervention phase, 9 patients withdrew from the study. Three patients (5.0 % of all patients) withdrew due to AEs (such as somnolence and headache). Three, two and one patients withdrew from the study because of the consent withdrawn, lost to follow-up and others respectively. More patients from the suvorexant group (8.3%; 5 of 60 participants) than the placebo group (6.7%; 4 of 60 participants) withdrew from the study. The most frequent AEs in both groups are shown in Table 3. No significant difference in withdrawal rate between both groups was found. However, there was significant difference in the AEs of somnolence between two groups. The severe AEs were somnolence and fatigue. However, no fatality of any life threatening condition was reported.

Table 1: Baseline characteristics of participants at trial entry

	Variable	Suvorexant (n=60)	Placebo (n=60)
Age, yrs: mean (±SD)		50.6 (11.9)	51.4 (12.2)
Sex, n (%)	Male	35 (58.3%)	37 (61.7%)
	Female	25 (41.7%)	23 (38.3%)
Race	Asian (Chinese)	60 (100.0%)	60 (100.0%)
Diary measure score mean (±SD)	sTST, min	331.5 (67.1)	334.7 (69.2)
	sTSO, min	62.9 (36.8)	59.2 (35.1)
	sQUAL	1.9 (0.4)	2.0 (0.4)
Rating scales	ISI	14.3 (4.0)	14.1 (3.9)

Note: sTST, total sleep time; sTSO, time to sleep onset; sQUAL, quality of sleep (1-4 scale); ISI, Insomnia Severity Index (0-28 scale).

Table 2: Primary and secondary outcomes at 1 and 6 month after treatment

	Month 1				Month 6			
	Suvorexant (n=60)	Placebo(n=60)	Difference	P value	Suvorexant (n=60)	Placebo (n=60)	Difference	P value
Diary measure score								
sTST, min	37.9(32.2, 40.5)	16.1 (10.9, 21.4)	21.7 (13.5, 28.7)	<0.01	48.1(40.9, 51.7)	23.8 (16.0,29.4)	24.3 (15.9, 31.5)	<0.01
sTSO, min	-18.5(-23.1, -15.5)	-8.7 (-12.3, -4.6)	-9.4 (-14.8, -4.3)	<0.01	-23.1 (-26.8, -19.1)	-12.9(-18.1, -9.9)	-10.2 (-15.1, -3.5)	<0.01
sQUAL	0.3(0.2, 0.4)	0.1(0.1, 0.2)	0.2 (0.1, 0.2)	<0.01	0.4 (0.3, 0.4)	0.2 (0.2, 0.3)	0.2 (0.1, 0.2)	<0.01
Rating scales								
ISI	-3.5(-3.7, -2.9)	-2.1(-2.4, -1.6)	-1.4 (-2.3, -0.8)	<0.01	-5.5 (-6.0, -5.1)	-4.5(-5.1, -3.6)	-0.9 (-2.1, -0.5)	<0.01

Note: sTST, total sleep time; sTSO, time to sleep onset; sQUAL, quality of sleep (1-4 scale); ISI, Insomnia Severity Index (0-28 scale).

DISCUSSION

blind, placebo-controlled trial provide data that warrant the further evaluation of suvorexant in patients with primary insomnia. The clinical outcomes identify trends in the reduction of primary insomnia symptoms within the intervention period. The study demonstrated acceptability by subjects with suvorexant, randomization and participation in the trial. Compliance and follow-up were all acceptable.

Our results demonstrated that 40 mg/day of suvorexant is safe and effective in reducing the symptoms of primary insomnia in Chinese patients. Suvorexant improved primary insomnia symptomatology to a significantly greater extent than placebo, as measured by the study's primary and secondary efficacy outcomes, including sTST, sTSO, sQUAL, and the ISI score.

Suvorexant also had a favourable safety profile. The overall frequency of AEs was similar in both groups, and most side effects were judged to be of minor severity. The frequency of both drug-related AEs and AEs of severe intensity was higher in the suvorexant group than the placebo group.

The study had several strengths. First, the trial was randomized, which reduced selection bias. Second, the fixed dose of suvorexant administered in this trial was an acceptable intervention for primary insomnia in Chinese patients. Further studies with a larger sample size and a longer duration of intervention are needed to confirm the results of this study.

The primary limitations of this study are that this study failed to use more convincing scales, such as Clinical Global Impression (CGI) to evaluate the outcomes; and the duration of treatment was relatively short. Further clinical trials should more fully characterize the clinical profile of suvorexant.

In conclusion, the results of this study provide evidence to support the hypothesis that suvorexant is efficacious and safe in reducing the symptoms of Chinese patients with primary insomnia. However, larger studies with a longer duration of treatment are warranted.

DISCLOSURE

Conflicts of interest: None

REFERENCES

1. Dopp J, Phillips B. Sleep disorders. In: DiPiro J, Talbert R, Yee G, et al., eds: Pharmacotherapy: A pathophysiologic approach, 8th ed. New York: McGraw-Hill; 2011; 621-3.

Table 3: Adverse events

	Suvorexant (n= 60)	Placebo (n= 60)
≥1 adverse event (n, %)	31 (51.7)	32 (53.3)
≥1 drug-related adverse event* (n, %)	28 (46.7)	10 (16.7)
≥1 serious adverse event (n, %)	2 (3.3)	1 (1.7)
Discontinued owing to adverse event (n, %)	3 (5.0)	2 (3.3)
Common adverse events (≥2%) (n, %)		
Somnolence	7 (11.7)	2 (3.3)
Headache	4 (6.7)	3 (5.0)
Dizziness	6 (10.0)	5 (8.3)
Fatigue	2 (3.3)	1 (1.7)
Dry mouth	1 (1.7)	0 (0)

*Number (%) of patients included in the analysis.

2. Ohayon MM. Epidemiology of insomnia: what we know and what we still need to learn. *Sleep Med Rev* 2002; 6: 97-111.
3. Briefing Materials from Peripheral and Central Nervous System Advisory Committee (2013) Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/PeripheralandCentralNervousSystem-DrugsAdvisoryCommittee/UCM352969.pdf. (Accessed January 1, 2015).
4. Sun ZR, Yue JH, Tian HZ, Zhang QH. Acupuncture at Houxi (SI 3) acupoint for acute neck pain caused by stiff neck: study protocol for a pilot randomised controlled trial. *BMJ Open* 2014; 4(12):e006236.
5. Zhang Q, Yue J, Lu Y. Acupuncture treatment for chronic knee pain: study by Hinman *et al.* underestimates acupuncture efficacy. *Acupunct Med* 2015; 33(2):170.
6. Sun ZR, Yue JH, Zhang QH. Electroacupuncture at Jing-jiaji points for neck pain caused by cervical spondylosis: a study protocol for a randomized controlled pilot trial. *Trials* 2013; 14:360.
7. Taylor DJ, Mallory LJ, Lichstein KL, Durrence HH, Riedel BW, Bush AJ. Comorbidity of chronic insomnia with medical problems. *Sleep* 2007; 30:213-8.
8. Yue JH, Golianu B, Zeng XX, *et al.* Acupuncture for urinary retention after stroke: a protocol for systematic review. *Eur J Bio Med Res* 2015; 1(2): 7-11.
9. Taylor DJ, Lichstein KL, Durrence HH, Reidel BW, Bush AJ. Epidemiology of insomnia, depression, and anxiety. *Sleep* 2005; 28:1457-64.
10. Zhang Q, Sun Z, Yue J. Research progress of electroacupuncture treatment on neurogenic bladder dysfunction after spinal cord injury. *Journal of Clinical Acupuncture and Moxibustion* 2011; 9:41-4.
11. Zhang QH, Sun ZR, Yue JH, *et al.* Traditional Chinese medicine for pressure ulcer: a meta-analysis. *Int Wound J* 2013; 10(2):221-31.
12. Zhang Q, Yue J, Sun Z. Massage therapy for preventing pressure ulcers. *Cochrane Database of Systematic Reviews* 2015; (6): CD010518.
13. Schurman JV, Friesen CA, Dai H, *et al.* Sleep problems and functional disability in children with functionalgastrointestinal disorders: an examination of the potential mediating effects of physical and emotional symptoms. *BMC Gastroenterol* 2012; 12:142.
14. Jansson C, Nordenstedt H, Wallander MA, *et al.* A population-based study showing an association between gastroesophageal reflux disease and sleep problems. *Clin Gastroenterol Hepatol* 2009; 7(9):960-5.
15. Roehrs T, Roth T. Insomnia pharmacotherapy. *Neurotherapeutics* 2012; 9: 728-38.
16. Mieda M, Sakurai T. Orexin (hypocretin) receptor agonists and antagonists for treatment of sleep disorders: rationale for development and current status. *CNS Drugs* 2013; 27(2):83-90.
17. Krystal AD, Benca RM, Kilduff TS. Understanding the sleep-wake cycle: sleep, insomnia, and the orexin system. *J Clin Psychiatry* 2013; 74(Suppl 1): 3-20.
18. De Lecea L, Kilduff TS, Peyron C, *et al.* The hypocretins: hypothalamus-specific peptides with neuroexcitatory activity. *Proc Natl Acad Sci USA* 1998; 95:322-7.
19. Kilduff TS, Peyron C. The hypocretin/orexin ligandreceptor system: implications for sleep and sleep disorders. *Trends Neurosci* 2000; 23:359-65.
20. Sakurai T. The neural circuit of orexin (hypocretin): maintaining sleep and wakefulness. *Nat Rev Neurosci*. 2007; 8:171–81.
21. Scammell TE, Saper CB. Orexins: looking forward to sleep, back at addiction. *Nat Med* 2007; 13:126-8.
22. Ohno K, Sakurai T. Orexin neuronal circuitry: role in regulation of sleep and wakefulness. *Front Neuroendocrinol* 2008; 29:70-87.
23. Roecker AJ, Coleman PJ. Orexin receptor antagonists: medicinal chemistry and therapeutic potential. *Curr Top Med Chem* 2008; 8:977-87.
24. Scammell TE, Winrow CJ. Orexin receptors: pharmacology and therapeutic opportunities. *Annu Rev Pharmacol Toxicol* 2011; 51:243-66.
25. Hoever P, Dorffner G, Benes H, *et al.* Orexin receptor antagonism, a new sleep-enabling paradigm: a proof-of-concept clinical trial. *Clin Pharmacol Ther* 2012; 91:975-85.
26. Bettica PU, Lichtenfeld U, Squassante L, *et al.* The orexin receptor antagonist SB-649868 promotes and maintains sleep in healthy volunteers and in patients with primary insomnia. *Sleep* 2009; 32(suppl):A252.

27. Deak MC, Winkelman JW. Insomnia. *Neurol Clin* 2012; 30: 1045-66.

28. Buysse DJ. Insomnia. *JAMA* 2013; 309(7):706-16.

29. Neubauer DN. New and emerging pharmacotherapeutic approaches for insomnia. *Int Rev Psychiatry* 2014; 26: 214-24.

30. Winrow CJ, Gotter AL, Cox CD, *et al*. Promotion of sleep by MK-4305: a novel dual orexin receptor antagonist. *J Neurogenet* 2011; 25:52-61.

31. Sun H, Kennedy W, Lewis N, *et al*. Dose effects of MK-4305, a dual orexin receptor antagonist for insomnia, in healthy male subjects. *J Sleep Res* 2010; 19(suppl 2):199-200.

32. Sun H, Kennedy WD, Lewis N, *et al*. The single dose pharmacokinetic and pharmacodynamic profiles of suvorexant (MK-4305), a dual orexin receptor antagonist, in healthy male subjects. *Sleep Biol Rhythms* 2011; 9:332.

33. Herring WJ, Snyder E, Budd K *et al*. Orexin receptor antagonism for treatment of insomnia: a randomized clinical trial of suvorexant. *Neurology* 2012; 79: 2265-74.

34. Sun H, Kennedy WP, Wilbraham D, *et al*. Effects of suvorexant, an orexin receptor antagonist, on sleep parameters as measured by polysomnography in healthy men. *Sleep* 2013; 36(2):259-67.

35. Michelson D, Snyder E, Paradis E *et al*. Safety and efficacy of suvorexant during 1-year treatment of insomnia with subsequent abrupt treatment discontinuation: a phase 3 randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2014; 13: 461-71.

36. Merck Sharp & Dohme Corporation. BELSOMRA (suvorexant) tablets, for oral use. Prescribing information. Revised August 2014. http://www.accessda ta.fda.gov/drugsatfda_docs/label/2014/204569s000l bledt.pdf (accessed 15 May 2015).

37. Merck Sharp & Dohme Corporation. Suvorexant advisory committee meeting briefing document addendum. 22 May 2013. http://www.fda.gov/downloads/advisorycommittees/ committeesmeeting materials/drugs/peripheralandcentralnervoussystem drugsadvisorycommittee/ucm352971.pdf (accessed 15 May 2015).

38. Merck Sharp & Dohme Corporation. Suvorexant advisory committee meeting briefing document. 22 May 2013. http://www.fda.gov/downloads/advisory committees/committeesmeetingmaterials/drugs/peripheralandcentralnervoussystemdrugsadvisory committee/ucm352970.pdf (accessed 15 May 2015).

39. American Psychiatric Association. Diagnostic and statistical manual of mental disorders, 4th ed. Washington, DC: American Psychiatric Association. 2000.

40. Ott H, Oswad I, Fichte K, *et al*. Collegium Internationale Psychiatria-Scalarum. Weinheim: Beltz Test GmbH. 1996.

41. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. *Sleep Med* 2001; 2: 297-307.