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

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Summary

Background Suvorexant (MK-4305) is an orexin receptor antagonist shown to be efficacious for insomnia over 3 months. We aimed to assess its clinical profile during and after 1 year of treatment.

Methods We did a randomised, placebo-controlled, parallel-group trial at 106 investigational centres in the Americas, Australia, Europe, and South Africa from December, 2009, to August, 2011. Patients aged 18 years or older with primary insomnia by DSM-IV-TR criteria were assigned using a computer-generated randomised allocation schedule to receive nightly suvorexant (40 mg for patients younger than 65 years, 30 mg for patients aged 65 years or older) or placebo at a 2:1 ratio for 1 year with a subsequent 2-month randomised discontinuation phase in which patients on suvorexant either continued suvorexant or were abruptly switched to placebo while patients on placebo remained on placebo. Treatment assignment was masked from patients and investigators. The primary objective was to assess the safety and tolerability of suvorexant for up to 1 year. Secondary objectives were to assess the efficacy of suvorexant for improving patient-reported subjective total sleep time (sTST) and time to sleep onset (sTSO) over the first month of treatment. Efficacy endpoints over the first month were assessed with a mixed model with terms for baseline value of the response variable, age, sex, region, treatment, time, and treatment by time interaction. This trial is registered with ClinicalTrials.gov, number NCT01021813.

Findings 322 (62%) of 522 patients randomly assigned to receive suvorexant and 162 (63%) of 259 assigned to receive placebo completed the 1-year phase. Over 1 year, 362 (69%) of 521 patients treated with suvorexant experienced any adverse events compared with 164 (64%) of 258 treated with placebo. Serious adverse events were recorded in 27 patients (5%) who received suvorexant and 17 (7%) who received placebo. The most common adverse event, somnolence, was reported for 69 patients (13%) who received suvorexant and seven (3%) who received placebo. At month 1, suvorexant (517 patients in the efficacy population) showed greater efficacy than placebo (254 in the efficacy population) in improving sTST (38·7 min *vs* 16·0 min; difference 22·7, 95% CI 16·4 to 29·0; p<0·0001) and sTSO (–18·0 min *vs* –8·4 min, difference –9·5, –14·6 to –4·5; p=0·0002).

Interpretation Our findings show that suvorexant was generally safe and well tolerated over 1 year of nightly treatment in patients with insomnia, with efficacy noted for subjective measures of sleep onset and maintenance.

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Introduction

Although many patients chronically use drugs to treat insomnia,[1,2] most randomised, controlled drug trials have been shorter than 3 months in duration. To our knowledge, no study has assessed the value of nightly treatment for a full year and the outcome of stopping chronic pharmacotherapy with a method in which patients previously taking an active treatment were randomly assigned either to remain on the active treatment or to be switched to placebo (table 1).

Benzodiazepine receptor agonist (eg, temazepam) and benzodiazepine-like insomnia treatments (eg, zolpidem, zopiclone) are thought to promote sleep by increasing the function of GABA, the major inhibitory neurotransmitter in the brain.[9] By contrast, orexin receptor antagonists dampen the orexin-mediated wakefulness system of the brain[10,11] that controls the transition between arousal and sleep. Suvorexant (MK-4305) is a potent and selective orexin receptor antagonist previously shown to increase sleep in animals and healthy people.[12–14] A phase 2 proof-of-concept trial showed that suvorexant was effective and well tolerated for treating insomnia for periods up to 4 weeks in adult patients younger than 65 years.[15] Our aim was to extend these findings in a phase 3 trial assessing the safety and tolerability of suvorexant during long-term treatment of insomnia in patients older and younger than 65 years, and to assess the efficacy of suvorexant at 1 month. Important exploratory objectives were to assess the longer-term efficacy of suvorexant and the effects of abruptly stopping treatment after 1 year.

	Treatment	Duration of primary randomised, double-blind treatment period	Sample size	Discontinuation phase after or during primary treatment period
Roehrs et al, 2012[3]	Zolpidem	12 months (intermittent)	33	1-week double-blind placebo substitution at months 1, 4, and 12
Randall et al, 2012[4]	Zolpidem	8 months (intermittent)	91	1-week double-blind placebo substitution at months 1 and 4
Mayer et al, 2009[5]	Ramelteon	6 months	451	2-week single-blind placebo run-out after 6 months
Krystal et al, 2008[6]	Zolpidem extended-release	6 months	1018	1-week open-label no-treatment run-out after 6 months
Walsh et al, 2007[7]	Eszopiclone	6 months	830	2-week single-blind placebo run-out after 6 months
Krystal et al, 2003[8]	Eszopiclone	6 months	734	6-month open-label extension after 6 months

Table 1: **Previously published randomised, double-blind, placebo-controlled insomnia treatment trials of longer than 3 months' duration**

Methods

Participants

The trial was done at 106 academic and private investigational centres in the Americas, Australia, Europe, and South Africa from December, 2009, to August, 2011 (sites are listed at the end of the report). Study participants were identified by individual site investigators. Patients were aged 18 years or older and met the DSM-IV-TR criteria for primary insomnia[16] assessed by a clinical interview and a structured sleep diagnostic interview. We aimed to enrol equal proportions of non-elderly (ie, younger than 65 years) and elderly (ie, 65 years or older) patients and therefore the number enrolled in either age group could not exceed 60% of the planned total. Major exclusion criteria included potentially confounding neurological disorders, major affective or psychotic illness, substance abuse, or an unstable medical disorder. The appendix lists the full inclusion and exclusion criteria.

See Online for appendix

Written informed consent was obtained from all patients before entering the trial. The trial was done in accordance with principles of Good Clinical Practice and was approved by the appropriate institutional review boards and regulatory agencies for each site.

Randomisation and masking

Patients were assigned to treatment groups using an allocation-schedule system that provided a computer-generated randomisation schedule based on input from a Merck statistician from whom treatment allocation was masked. The schedule was implemented through an interactive voice response system. Randomisation was stratified by age (non-elderly *vs* elderly) and geographical region. Treatment allocation was masked from study investigators, site staff, patients, and Merck monitoring staff throughout the study. The groups for the two trial phases were allocated at the initial randomisation. Suvorexant or placebo were provided as matching tablets to be taken orally at bedtime.

Procedures

After a 1-week single-blind placebo run-in screening phase, patients were randomly assigned to receive double-blind treatment for 1 year with suvorexant or placebo at a 2:1 ratio. The dose of suvorexant was 30 mg nightly for elderly patients and 40 mg nightly for non-elderly patients, to adjust for plasma exposure differences between non-elderly and elderly individuals noted in phase 1 trials (Merck & Co Inc, Whitehouse Station, NJ, USA, unpublished). After 1 year, patients assigned to receive suvorexant were randomly assigned to receive a continuation of their previous dose (suvorexant-suvorexant group) or to switch to placebo (suvorexant-placebo group) in a 1:1 ratio for two additional months. Those originally assigned to receive placebo remained on placebo (placebo-placebo group). Treatment remained double-blind during the randomised discontinuation phase.

Patients were scheduled to attend the investigation centre or clinic at week 2 and months 1, 3, 6, 9, 12, 13, and 14, with phone calls at each of the intervening months. Safety assessments included open-ended questioning for adverse events at clinic visits or phone calls, and the Columbia Suicide Severity Rating Scale[17] and laboratory and electrocardiogram assessments at clinic visits. A Motor Vehicle Accidents and Violations (MVAV) questionnaire was implemented after the trial was started; it was administered at scheduled clinic visits or phone calls and assessed the occurrence of motor vehicle accidents or citations (ie, notice to attend court) when the patient was the driver. The Quick Inventory of Depressive Symptomatology—Self Report (QIDS-SR)[18] was administered at clinic visits starting at month 1 to assess mood. The Tyrer Withdrawal Symptom Questionnaire[19] was administered before dosing for three consecutive evenings at the start of the randomised discontinuation phase.

A committee of three non-Merck academic or clinical experts in neurology, psychiatry, and sleep, who were paid by Merck, was established to adjudicate prespecified events of clinical interest including events potentially suggestive of intrusion of rapid eye movement (REM) sleep into wakefulness (cataplexy) or initiation of sleep (sleep onset paralysis). Falls were adjudicated to ascertain whether they were potentially due to cataplexy. Any other