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

adverse events judged by the investigator to be suggestive of either cataplexy or sleep onset paralysis were also considered for adjudication.

Efficacy was assessed with an electronic morning sleep diary completed daily throughout the study by the patient that included several subjective measures: subjective total sleep time (sTST, min), subjective time to sleep onset (sTSO, min), subjective wake after sleep onset (sWASO, min; total duration of night awakenings), subjective number of awakenings (sNAW, n), subjective quality of sleep (sQUAL), and subjective refreshed feeling on waking (sFRESH). The electronic diary was based on previously used and validated paper diaries,[20] a standard means for measurement of subjective effects and widely accepted by regulators and the academic community. At months 1, 3, 6, 12, 13, and 14 efficacy was also assessed by clinician and patient global impression of severity (CGI-S and PGI-S, respectively) and clinician and patient global impression of improvement (CGI-I and PGI-I, respectively) ratings.[21] The patient-reported Insomnia Severity Index (ISI)[22] was completed at months 1, 3, 6, and 12, and weekly during the discontinuation phase.

Outcomes

The protocol-specified primary objective for the 1-year phase was to assess the safety and tolerability of suvorexant. Prespecified secondary objectives were assessments of sTST and sTSO during the first month of treatment. Efficacy at later timepoints (months 2–12) were prespecified exploratory endpoints. Other diary endpoints (sWASO, sNAW, sQUAL, sFRESH) and rating scale endpoints (ISI, CGI-S, PGI-S, CGI-I, PGI-I, QIDS-SR) were also exploratory. The discontinuation phase was an exploratory study with relapse prevention as the primary endpoint. Rebound insomnia and assessment of withdrawal effects, as well as efficacy and safety in the discontinuation phase, were exploratory endpoints.

Statistical analysis

The planned number of enrolled patients was 500 patients on suvorexant and 250 patients on placebo with no more than 60% in either non-elderly or elderly age groups. The sample size was driven by regulatory guidelines to study at least 100 suvorexant-treated patients in each age group for at least 1 year rather than formal statistical considerations. The higher initial enrolment target was to allow for dropouts during the trial. For secondary efficacy hypotheses, the sample size provided greater than 99% power to detect a difference between treatments of 20 min for change from baseline in sTST and greater than 97% to detect a difference between treatments of 10 min for change from baseline in sTSO.

For analysis of safety and tolerability in the 1-year phase, differences between treatments were evaluated by 95% CIs for broad adverse event categories, specific adverse events which occurred in 1% or more patients in either treatment group, and prespecified events of clinical interest: cataplexy (adjudicated), sleep onset paralysis (adjudicated), sleep paralysis, complex sleep-related behaviours (eg, sleepwalking), suicidal ideation or behaviours, falls (adjudicated to establish whether the event was due to cataplexy), hypnogogic or hypnopompic hallucinations, excessive daytime sleepiness (to distinguish a more persistent daytime sleepiness from typical next-day residual somnolence), and selected events associated with potential for drug abuse. Summary statistics were calculated for predefined limits of change in laboratory, vital signs, and electrocardiogram measures. Analysis of safety and tolerability in the discontinuation phase was similar to that of the 1-year phase except that 95% CIs were not calculated.

Efficacy endpoints (sTST and sTSO) over the first month were assessed with a mixed model with terms for baseline value of the response variable, age (<65 years, ≥65 years), sex, region (Canada and USA, other), treatment, time (categorical variable), and treatment by time interaction. Hochberg's multiplicity procedure was prespecified to control type 1 error at 5% for secondary efficacy endpoints at month 1. The same analytical approach was used for assessing exploratory efficacy endpoints over 1 year. To assess the effect of dropouts on the treatment difference, the ETRANK procedure was prespecified as a sensitivity analysis.[23] For the discontinuation phase, several populations of responders were prespecified: a month-12 ISI score suggesting no or subthreshold insomnia, defined as an ISI score of 14 or less; and degree of improvement in sTST from study entry to month 12 using thresholds ≥20%, ≥10%, and ≥5%. For ISI responders at month 12, relapse was defined as a return to moderate or severe insomnia (ISI >14), and for sTST responders at month 12, relapse was defined as a worsening that crossed back over the specified threshold value relative to baseline. The primary comparison of interest was the suvorexant-suvorexant group versus the suvorexant-placebo group. Relapse prevention was assessed by a hazard ratio based on time to relapse. Efficacy during the discontinuation phase was assessed on the basis of all patients who entered the discontinuation phase, using the same methods as for the 1-year phase.

The analysis of rebound insomnia was based on all patients who entered the discontinuation phase. To assess rebound during the initial three days after discontinuation, the proportion of patients in each treatment group with worsening beyond the month 0 baseline in sTST and sTSO was calculated for each of the first three nights of the discontinuation phase and for any of the first three nights. The primary comparison of interest was between the suvorexant-placebo group and the placebo-placebo group.

Analysis of withdrawal was based on all patients who entered the discontinuation phase. The proportion of

patients with newly emergent or worsening of three or more symptoms on the 20-item Tyrer Withdrawal Symptom Questionnaire for each of the first three nights of the discontinuation phase and across the first three nights was calculated. The primary comparison of interest was between the suvorexant-suvorexant group and the suvorexant-placebo group.

Two interim safety analyses were done by a data monitoring committee of non-Merck clinical and statistical experts who were otherwise not involved with the trial and who were paid by Merck. At both analyses, the committee recommended that the study continue as planned without changes to the protocol. This trial is registered with ClinicalTrials.gov, number NCT01021813.

Role of the funding source

The sponsor of the study was involved in the design and conduct of the study, the collection, management, analysis, and interpretation of the data, and the preparation, review, and approval of the report. All authors had the opportunity to access all data. The decision to submit this paper, in accordance with Merck policy that all Merck sponsored phase 3 trials be submitted for publication, was taken by DM and WJH. All authors take overall responsibility for the report.

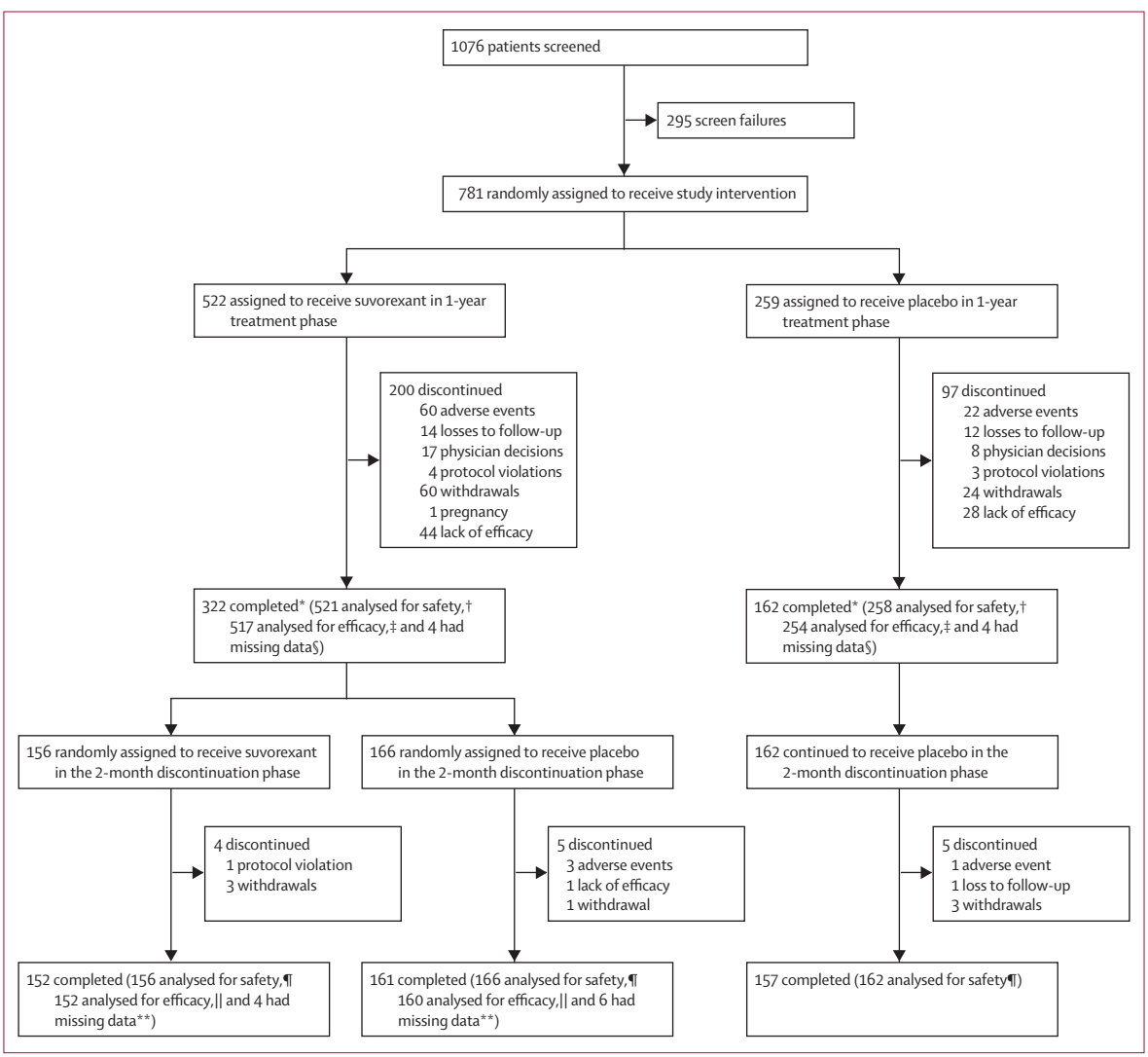

Figure 1: **Trial profile**

sTST=total sleep time. *Includes one patient in each group who did not receive study treatment; these two patients were excluded from the analyses. †Number of patients included in the analysis of adverse events. ‡Number of patients included in the analysis of sTST over month 1. §Patients who did not have baseline data, or at least one sTST measure subsequent to at least one dose of randomly allocated study treatment. ¶Number of patients included in the analysis of adverse events. ||Number of patients included in the analysis of sTST at month 1 of the randomised discontinuation phase. **Patients who did not have month 12 data for the preceding initial 12-month treatment trial, or at least one sTST measure subsequent to at least one dose of randomised discontinuation phase treatment, were excluded. The counts for discontinuations due to adverse events are based on the period in which the patient discontinued the study.

Results

Of 1076 patients who were screened, 781 were randomly assigned to study groups, and 484 completed the 1-year phase (figure 1). The proportions of patients discontinuing during the 1-year phase, overall and by reason, were similar between treatments. Analyses of time to discontinuation, overall and by reason, did not suggest treatment differences (appendix). Of 484 patients who entered the discontinuation phase, 470 completed.

Table 2 summarises the patient characteristics and baseline symptom severity. Most patients reported mild-to-moderate insomnia at baseline, taking roughly 1 h to fall asleep (sTSO) and sleeping about 5·5 h (sTST). Characteristics of patients who entered the discontinuation phase are given in the appendix.

Table 3 summarises the adverse events. There were no deaths. Similar proportions of patients treated with suvorexant or placebo discontinued because of adverse events. The proportion of patients with serious adverse events was similar among the treatment groups and there was no clinically important difference between treatment groups in the specific types of serious adverse event that were reported (data not shown). The most common adverse events that were increased for suvorexant versus placebo were somnolence, fatigue, and dry mouth. Somnolence was the adverse event with the highest incidence for discontinuations, (suvorexant 20/521 [4%] *vs* placebo 2/258 [1%]). Somnolence was most common in the first 3 months (57/527 [11%] for suvorexant *vs* 6/258 [2%] for placebo) and was less commonly reported by the second 3 months (11/425 [3%] for suvorexant *vs* 1/254 [<1%] for placebo). Somnolence was mostly mild or moderate in severity (64 of 69 reports in the suvorexant group).

Table 3 includes a summary of predefined events of clinical interest. Four events of suicidal ideation were reported, all by patients on suvorexant. Two of the patients had a previous history of suicidal ideation, and the other two reported multiple stressors associated with the onset of the ideation. Two of these patients discontinued treatment whereas the other two continued treatment without incident. Events suggesting drug abuse were similar across suvorexant and placebo, with most seeming to be drug administration errors rather than intentional misuse. One complex sleep-related behaviour of somnambulism, three events of hypnagogic hallucination, and one event of hypnopompic hallucination were reported for the suvorexant group, with none in the placebo group (table 3). Events of excessive daytime sleepiness were more common in the suvorexant group than the placebo group. Two events of sleep paralysis for patients on suvorexant were reported, of which one, at sleep onset, was confirmed by adjudication. The incidence of falls was similar across treatment groups (table 3). No falls suggested cataplexy or were adjudicated as such. One non-fall-related event of muscle weakness in the legs was reported as an event suggestive of potential cataplexy, but was judged to not be cataplexy by the adjudication committee.

Two motor vehicle accidents with injury were reported, both in patients on suvorexant. In one case the patient was hit by another car from behind while stopped at a traffic light; in the other case the patient reported driving on a rainy day when the car in front abruptly changed lanes and the patient collided into the back of the car.

	Suvorexant, N=521	Placebo, N=258
Age, years	61·3 (14·5)	62·0 (14·6)
<65 years	213 (41%)	107 (42%)
≥65 years	308 (59%)	151 (59%)
Body-mass index, kg/m²	27·2 (4·3)	27·1 (4·4)
Underweight <18·5	3 (1%)	1 (<1%)
Healthy 18·5–24·0	165 (32%)	81 (31%)
Overweight 25·0–30·0	231 (44%)	116 (45%)
Obese >30·0	121 (23%)	60 (23%)
Sex		
Female	287 (55%)	149 (58%)
Male	234 (45%)	109 (42%)
Race		
White	476 (91%)	231 (90%)
Black	33 (6%)	24 (9%)
Other	12 (2%)	3 (1%)
Ethnic origin		
Not Hispanic or Latino	452 (87%)	227 (88%)
Hispanic or Latino	68 (13%)	31 (12%)
Geographical location		
North America	319 (61%)	159 (62%)
Europe	169 (32%)	84 (33%)
Other	33 (6%)	15 (6%)
Diary measure scores		
sTST, min	320·4 (76·1)	330·1 (79·4)
sTSO, min	65·9 (63·8)	64·9 (60·6)
sWASO, min	80·1 (57·2)	71·4 (56·1)
sNAW, n	2·1 (1·2)	2·0 (1·1)
sQUAL, 1–4 scale	2·0 (0·5)	2·1 (0·5)
sFRESH, 0–4 scale	1·4 (0·7)	1·4 (0·7)
Rating scale scores		
ISI, 0–28 scale	14·5 (4·4)	13·7 (4·6)
CGI-S, 1–7 scale	4·4 (0·9)	4·3 (0·8)
PGI-S, 0–5 scale	3·2 (0·9)	3·1 (0·9)
QIDS-SR, 0–27 scale	4·5 (2·5)	4·3 (2·4)

Data are mean (SD) or n (%). Total numbers of patients were smaller for some baseline scores because of missing data: for suvorexant, numbers ranged from 488 to 517 depending on the measure; for placebo, numbers ranged from 240 to 254 depending on the measure. sTST=total sleep time. sTSO=time to sleep onset. sWASO=wake after sleep onset. sNAW=number of awakenings. sQUAL=quality of sleep. sFRESH=refreshed feeling on waking. ISI=Insomnia Severity Index. CGI-S=clinician global impression of severity. PGI-S=patient global impression of severity. QIDS-SR=Quick Inventory of Depressive Symptomatology—Self Report.

Table 2: **Baseline demographic and clinical characteristics**

	Suvorexant, N=521	Placebo, N=258	Difference
General categories of events			
≥1 adverse event	362 (69·5%)	164 (63·6%)	5·9 (–1·1 to 13·1)
≥1 drug-related adverse event*	182 (34·9%)	53 (20·5%)	14·4 (7·8 to 20·6)
≥1 serious adverse event	27 (5·2%)	17 (6·6%)	–1·4 (–5·5 to 1·9)
≥1 serious drug-related adverse event*	1 (0·2%)	3 (1·2%)	–1·0 (–3·2 to 0·1)
Discontinued owing to adverse event	61 (11·7%)	22 (8·5%)	3·2 (–1·5 to 7·4)
Events showing an increase versus placebo			
Somnolence	69 (13·2%)	7 (2·7%)	10·5 (6·8 to 14·1)
Fatigue	34 (6·5%)	5 (1·9%)	4·6 (1·6 to 7·4)
Dry mouth	26 (5·0%)	4 (1·6%)	3·4 (0·7 to 5·9)
Dyspepsia	10 (1·9%)	0	1·9 (0·4 to 3·5)
Peripheral oedema	9 (1·7%)	0	1·7 (0·3 to 3·3)
Prespecified events of clinical interest			
Suicidal ideation	4 (0·8%)	0	0·8 (–0·7 to 2·0)
Events suggesting drug-abuse potential†	18 (3·5%)	10 (3·9%)	–0·4 (–3·8 to 2·2)
Complex sleep-related behaviours	1 (0·2%)	0	0·2 (–1·3 to 1·1)
Hypnagogic hallucination	3 (0·6%)	0	0·6 (–0·9 to 1·7)
Hypnopompic hallucination	1 (0·2%)	0	0·2 (–1·3 to 1·1)
Excessive daytime sleepiness‡	13 (2·5%)	2 (0·8%)	1·7 (–0·5 to 3·6)
Sleep paralysis	2 (0·4%)	0	0·4 (–1·1 to 1·4)
Sleep onset paralysis (adjudicated)	1 (0·2%)	0	0·2 (–1·3 to 1·1)
Cataplexy (adjudicated)	0	0	0
Falls§	12 (2·3%)	8 (3·1%)	–0·8 (–3·9 to 1·5)

Data are n (%) or difference (95% CI). The counts for discontinuations due to adverse events are based on the period in which the adverse event started. *Established by the investigator to be related to the drug (determination made while allocations were masked). †Terms included depersonalisation, derealisation, dissociation, euphoric mood, mania, hallucination, and potential misuse of study drug. ‡Excessive daytime sleepiness was defined as a more persistent daytime sleepiness than typical next-day residual somnolence; patients were not assessed with ICSD criteria for the excessive daytime sleepiness symptom diagnosis. §Falls were adjudicated to establish whether they suggested cataplexy.

Table 3: **Summary of adverse events over the 1-year treatment phase (primary endpoint)**

	Suvorexant, N=517*	Placebo, N=254*	Difference	p value
sTST				
Week 1	41·1 (36·9 to 45·3)	14·1 (8·2 to 20·1)	27·0 (19·7 to 34·3)	<0·0001
Week 2	32·4 (28·1 to 36·7)	14·7 (8·6 to 20·8)	17·7 (10·2 to 25·2)	<0·0001
Week 3	39·6 (35·3 to 44·0)	16·4 (10·3 to 22·6)	23·2 (15·6 to 30·7)	<0·0001
Week 4	41·6 (37·1 to 46·1)	18·7 (12·3 to 25·1)	22·9 (15·0 to 30·7)	<0·0001
Month 1, average weeks 1–4	38·7 (35·0 to 42·3)	16·0 (10·8 to 21·2)	22·7 (16·4 to 29·0)	<0·0001
sTSO				
Week 1	–17·7 (–20·9 to –14·5)	–6·8 (–11·4 to –2·3)	–10·9 (–16·4 to –5·3)	0·0001
Week 2	–15·7 (–19·2 to –12·2)	–7·5 (–12·4 to –2·6)	–8·2 (–14·2 to –2·2)	0·0077
Week 3	–18·7 (–22·2 to –15·2)	–10·0 (–14·9 to –5·0)	–8·7 (–14·8 to –2·7)	0·0047
Week 4	–19·9 (–23·1 to –16·6)	–9·4 (–14·1 to –4·8)	–10·4 (–16·1 to –4·7)	0·0004
Month 1, average weeks 1–4	–18·0 (–20·9 to –15·1)	–8·4 (–12·5 to –4·3)	–9·5 (–14·6 to –4·5)	0·0002

Least squares mean change from baseline (95% CI) by treatment and difference (95% CI) between suvorexant and placebo. Based on a mixed-effects model with terms for baseline value, age category (<65, ≥65), region, sex, treatment, timepoint, and treatment-by-timepoint interaction as covariates. Weekly means are the average of the daily electronic diary values for the week, measured in min; month 1 is the mean of weekly means for weeks 1–4. sTST=total sleep time. sTSO=time to sleep onset. *Sample size for average of weeks 1–4; sample sizes were smaller at individual weeks.

Table 4: **Efficacy secondary endpoints over month 1**

Data on the MVAV questionnaire were available for 397 patients on suvorexant and 196 patients on placebo. The number of patients with MVAV events was 22 (6%) for suvorexant and eight (4%) for placebo. This number excludes one of the accidents described above because the accident occurred before the MVAV questionnaire procedure was implemented.

There were no clinically meaningful differences between groups in vital signs or laboratory values, whether analysed as mean changes or categorical predefined limits of change (data not shown). Mean change from baseline in weight at 1 year was 0·6 kg (SD 2·7) for suvorexant and 0·0 kg (3·2) for placebo. The proportion of patients who gained or lost weight during the 1-year phase did not differ between groups (patients with ≥7% increase: suvorexant 26/518 [5%], placebo 14/255 [5%]; patients with ≥7% decrease: suvorexant 19/518 [4%], placebo 16/255 [6%]).

Over the first month, the suvorexant group showed significant improvements in sTST and sTSO compared with the placebo group (table 4). The improvements were maintained throughout the 1-year phase (appendix). Results for other efficacy endpoints at month 1 and month 12 are summarised in table 5. Suvorexant was better than placebo on all subjective sleep measures at month 1 and month 12, except for sNAW at month 1. Suvorexant was also better than placebo at both timepoints on the ISI, CGI-S, PGI-S, CGI-I, and PGI-I. The prespecified ETRANK sensitivity analysis to assess the effect of dropouts on the treatment difference provided similar conclusions to those in the primary analysis (appendix).

Suvorexant had no effect on mood as assessed by the QIDS-SR (table 5). There was no evidence that the effect of suvorexant on QIDS-SR score differed in the subgroup of patients with depressive symptomatology at baseline (QIDS-SR score ≥10; n=26 for suvorexant, n=12 for placebo) and those without depressive symptoms at baseline (QIDS-SR score <10; n=464 for suvorexant, n=228 for placebo) at month 1 (difference from placebo in least-square-means: QIDS-SR <10=–0·2 [95% CI –0·5 to 0·1], QIDS-SR ≥10=0·1 [–1·3 to 1·4]) or month 12 (QIDS-SR <10=–0·1 [–0·6 to 0·3], QIDS-SR ≥10=–0·1 [–1·9 to 1·7]).

Using the sTST 20%, sTST 10%, and sTST 5% responder definitions, risk for relapse in the suvorexant-placebo group was greater than in the suvorexant-suvorexant group (table 6). Using the ISI definition, the difference in risk for relapse between the suvorexant-placebo and suvorexant-suvorexant groups was not statistically significant.

Figure 2 shows the effects of abruptly stopping treatment for all patients who entered the discontinuation phase, irrespective of responder status. During the discontinuation phase the suvorexant-suvorexant group maintained its improvement compared with the placebo-placebo group, whereas the suvorexant-placebo group experienced return of symptoms similar in severity to those in the placebo-placebo group (appendix).

	Month 1				Month 12			
	Suvorexant, N=492*	Placebo, N=245*	Difference	p value	Suvorexant, N=298*	Placebo, N=147*	Difference	p value
Diary measures†								
sTST, min	40·9 (36·7 to 45·0)	17·5 (11·7 to 23·4)	23·3 (16·2 to 30·5)	<0·0001	60·5 (54·0 to 66·9)	33·0 (23·7 to 42·2)	27·5 (16·2 to 38·8)	<0·0001
sTSO, min	−19·2 (−22·5 to −16·0)	−9·0 (−13·6 to −4·3)	−10·3 (−15·9 to −4·6)	0·0004	−26·6 (−30·5 to −22·7)	−17·0 (−22·6 to −11·4)	−9·7 (−16·5 to −2·9)	0·0055
sWASO, min	−23·5 (−26·3 to −20·7)	−14·5 (−18·5 to −10·6)	−9·0 (−13·8 to −4·1)	0·0003	−33·5 (−37·4 to −29·7)	−23·8 (−29·3 to −18·3)	−9·7 (−16·5 to −3·0)	0·0048
sNAW, n	−0·2 (−0·3 to −0·1)	−0·3 (−0·4 to −0·2)	0·1 (−0·0 to 0·2)	0·1898	−0·2 (−0·4 to −0·1)	−0·5 (−0·7 to −0·3)	0·2 (0·0 to 0·4)	0·0216
sQUAL, 1–4 scale	0·3 (0·3 to 0·3)	0·1 (0·1 to 0·2)	0·2 (0·1 to 0·2)	<0·0001	0·4 (0·3 to 0·4)	0·3 (0·2 to 0·4)	0·1 (0·0 to 0·2)	0·0338
sFRESH, 0–4 scale	0·4 (0·3 to 0·4)	0·2 (0·1 to 0·3)	0·2 (0·1 to 0·3)	0·0001	0·5 (0·5 to 0·6)	0·4 (0·3 to 0·5)	0·2 (0·0 to 0·3)	0·0162
Rating scales‡								
ISI, 0–28 scale	−3·6 (−4·0 to −3·2)	−2·2 (−2·8 to −1·6)	−1·4 (−2·1 to −0·7)	<0·0001	−5·3 (−5·8 to −4·8)	−4·4 (−5·1 to −3·7)	−0·9 (−1·8 to −0·0)	0·0390
CGI-S, 1–7 scale	−0·9 (−0·9 to −0·8)	−0·5 (−0·6 to −0·4)	−0·3 (−0·5 to −0·2)	<0·0001	−1·3 (−1·5 to −1·2)	−0·9 (−1·1 to −0·8)	−0·4 (−0·6 to −0·2)	0·0003
PGI-S, 0–5 scale	−0·8 (−0·9 to −0·7)	−0·5 (−0·6 to −0·4)	−0·3 (−0·4 to −0·1)	0·0026	−1·1 (−1·3 to −1·0)	−0·9 (−1·0 to −0·7)	−0·3 (−0·5 to −0·1)	0·0110
CGI-I, 1–7 scale	2·9 (2·8 to 3·0)	3·3 (3·2 to 3·4)	−0·4 (−0·6 to −0·3)	<0·0001	2·5 (2·4 to 2·6)	3·0 (2·8 to 3·2)	−0·5 (−0·7 to −0·3)	<0·0001
PGI-I, 1–7 scale	2·8 (2·7 to 3·0)	3·4 (3·2 to 3·5)	−0·5 (−0·7 to −0·3)	<0·0001	2·5 (2·4 to 2·6)	3·0 (2·8 to 3·2)	−0·5 (−0·7 to −0·3)	<0·0001
QIDS-SR,0–27 scale	−0·4 (−0·6 to −0·2)	−0·2 (−0·4 to 0·1)	−0·2 (−0·5 to 0·1)	0·1655	−0·5 (−0·7 to −0·2)	−0·3 (−0·7 to 0·0)	−0·1 (−0·6 to 0·3)	0·5188

Least squares mean change from baseline (95% CI) by treatment and difference (95% CI) between suvorexant and placebo. sTST=total sleep time. sTSO=time to sleep onset. sWASO=wake after sleep onset. sNAW=number of awakenings. sQUAL=quality of sleep. sFRESH=refreshed feeling on waking. ISI=Insomnia Severity Index. CGI-S=clinician global impression of severity. PGI-S=patient global impression of severity. CGI-I=clinician global impression of improvement. PGI-I=patient global impression of improvement. QIDS-SR=Quick Inventory of Depressive Symptomatology—Self Report. *Sample sizes shown are for sTST; sample sizes differed for some of the other endpoints. †For electronic diary measures, month 1 is the average of the daily diary values for the last 14 days of month 1 measured in minutes. Months 2–11 are the average of the daily electronic diary values centred on the monthly visit. Month 12 is the average of the last 14 daily electronic diary values up to and including the month 12 visit day. This approach differs from that used for the analysis of secondary endpoints shown in table 4, and hence the month-1 values for sTST and sTSO shown in this table differ slightly from those shown in table 4. Results based on a mixed-effects model with terms for baseline value, age category (<65, ≥65), region, sex, treatment, timepoint, and treatment-by-timepoint interaction as covariates. ‡For rating scale measures, results based on a mixed-effects model with terms for baseline value, sex, region, treatment, time, and treatment-by-time interaction.

Table 5: **Exploratory endpoints at month 1 and month 12**

Discontinuation of study drug during the 2-month discontinuation phase was well tolerated, with no marked between-group differences in adverse events (appendix).

Analyses of rebound insomnia during the first three nights of the discontinuation phase are summarised in the appendix. There were no statistically significant differences with regard to worsening of sTST or sTSO for each night or for any of the three nights for the prespecified comparison of the suvorexant-placebo to the placebo-placebo group. However, the proportions of patients with rebound insomnia on all comparisons were numerically greater in the suvorexant-placebo group compared with the placebo-placebo group.

Withdrawal assessed by the Tyrer Withdrawal Symptom Questionnaire is summarised in the appendix. There were no significant differences in the numbers of patients meeting the prespecified withdrawal criteria for the comparison of the suvorexant-suvorexant versus suvorexant-placebo groups.

	Responders at 1 year*	Responders with relapse†	Hazard ratio (95% CI), suvorexant-suvorexant *vs* suvorexant-placebo‡	p value‡
ISI				
Suvorexant-suvorexant	127	28 (22%)	0·617 (0·378 to 1·007)	0·0532
Suvorexant-placebo	140	38 (27%)	..	
sTST 20%				
Suvorexant-suvorexant	71	24 (34%)	0·471 (0·286 to 0·776)	0·0031
Suvorexant-placebo	77	44 (57%)	..	
sTST 10%				
Suvorexant-suvorexant	95	38 (40%)	0·640 (0·424 to 0·968)	0·0344
Suvorexant-placebo	111	56 (51%)	..	
sTST 5%				
Suvorexant-suvorexant	116	38 (33%)	0·551 (0·365 to 0·832)	0·0046
Suvorexant-placebo	123	57 (46%)	..	

ISI=Insomnia Severity Index. Suvorexant-suvorexant=suvorexant for 1 year with subsequent suvorexant for 2 months. Suvorexant-placebo=suvorexant for 1 year with subsequent placebo for 2 months. sTST=total sleep time. *For the ISI definition, number of patients randomly allocated to study groups who had an ISI total score of 0–14 at 1 year; for sTST definitions, number of patients randomly allocated to study groups who had greater than 20%, 10%, or 5% increases in sTST at the end of 1 year compared with baseline. †For the ISI definition, number (%) of ISI responders at 1 year who had relapse (ISI total score of 15–28) at any assessment during the randomised discontinuation phase; for sTST definitions, number (%) of sTST responders at 1 year who had relapse (sTST return to within 20%, 10%, or 5% of their baseline) at any week during the randomised discontinuation phase. ‡p value and 95% CI based on Cox proportional hazards model including terms for treatment and baseline value (ie, the 1-year value); a hazard ratio <1 suggests a lower risk of relapse with suvorexant-suvorexant than suvorexant-placebo.

Table 6: **Number and proportion of patients in the suvorexant-suvorexant and suvorexant-placebo groups meeting relapse definitions in the randomised discontinuation phase**

Discussion

Over 1 year, suvorexant was generally safe and well tolerated by a group of patients with insomnia that included both elderly and non-elderly individuals, and most completed a full year of treatment. Somnolence was the most common adverse event associated with suvorexant compared with placebo, but rarely resulted in study discontinuation (panel). Severe, impairing daytime somnolence, captured in adverse events as "excessive daytime sleepiness", also occurred in more patients on suvorexant than placebo, but was rare in all groups. Abrupt discontinuation of suvorexant under double-blind conditions was not associated with an

increase in adverse events, nor was there significant withdrawal or rebound insomnia.

A small number of sleep-related hallucinations, sleep paralysis, and complex sleep-related behaviours were reported by patients taking suvorexant. However, such adverse events have also been reported in previous trials of other sedative hypnotics and seem unlikely to be specific to orexin antagonism.[24–26] Orexin neuron loss has been reported in patients who have narcolepsy with cataplexy[27,28] and although it is hypothetically possible that antagonism of the orexinergic system could produce narcolepsy-like or cataplexy-like symptoms,[29] no events of narcolepsy or cataplexy were noted. Because patients with narcolepsy were excluded, the effects of suvorexant in those patients, many of whom are thought to have an underlying reduction in orexin tone, could differ. Suvorexant did not have meaningful effects on bodyweight compared with placebo.

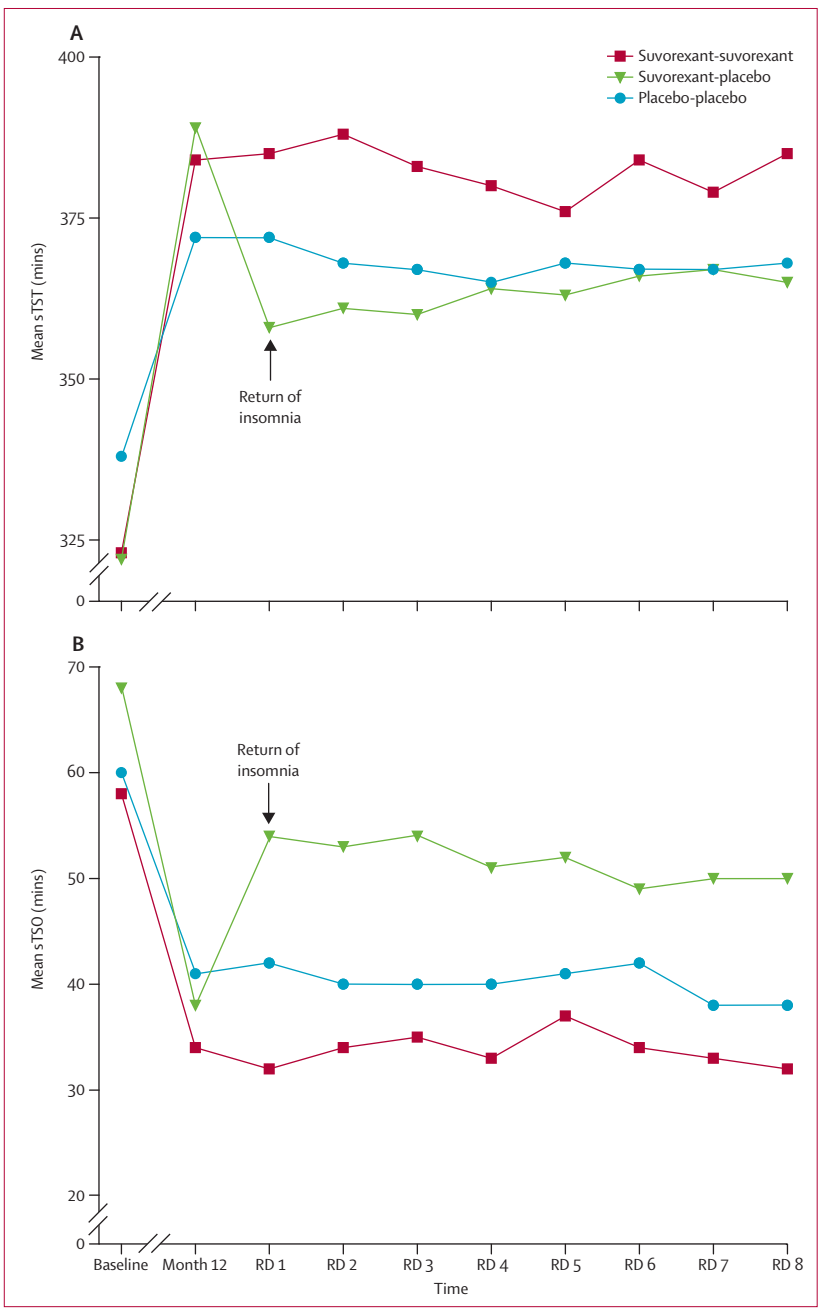

Figure 2: **Observed mean sTST and sTSO**
Observed mean sTST (A) and sTSO (B) at month 0, month 12, and during each week of the 2-month randomised discontinuation phase for patients who entered this phase. sTST=total sleep time. sTSO=time to sleep onset. Suvorexant-suvorexant=patients initially assigned to receive suvorexant for months 1–12 who remained on suvorexant for the randomised discontinuation phase. Suvorexant-placebo=patients initially assigned to receive suvorexant for months 1–12 who were switched to placebo for the randomised discontinuation phase. Placebo-placebo=patients initially assigned to placebo for months 1–12 who remained on placebo for the randomised discontinuation phase. RD=week of randomised discontinuation phase.

There was no evidence for an effect on mood symptoms as assessed by the mean QIDS-SR score, irrespective of the presence or absence of depressive symptoms at baseline. Four patients reported suicidal ideation and all of these were assigned to suvorexant. However, two occurred in the context of new onset external stressors, whereas the other two occurred in patients with histories of depression and suicidal ideation. All episodes were transient, and in the two patients who continued on drug did not recur. These results do not suggest a marked likelihood for worsening mood or suicidality but in view of the rarity of such events and the apparent imbalance between groups we cannot exclude the possibility of a small increase in risk.

The patients with insomnia treated with suvorexant in this study, which included elderly and non-elderly patients, reported greater improvements in sleep onset and sleep maintenance compared with those assigned to receive placebo. Improvements were evident early (week 1) and were sustained throughout 1 year. Suvorexant improved patients' perceptions of sleep quality and feeling refreshed in the morning as well as patient and clinician global assessments of disease severity and improvement.

After 1 year, continuing treatment was associated with better retention of treatment gains than treatment discontinuation. However, although the return of symptoms was worse by all measures in 1-year responders who discontinued treatment compared with responders who continued treatment, most patients retained some degree of treatment gain for the 2 months after suvorexant was discontinued. These findings suggest that for those patients who wish to discontinue treatment after longer-term use, a trial period in which suvorexant is stopped under medical supervision might be appropriate. Because we cannot predict which patients are most likely to worsen, the decision to modify treatment should be tailored to the individual patient and balance the disruptiveness and discomfort of possible symptom return with the tolerability and burden of treatment.

We cannot definitively establish whether the return of symptoms after suvorexant discontinuation represents a recrudescence of the underlying insomnia disorder, is

related to rebound or withdrawal effects, or represents a combination of these mechanisms. Results of the Tyrer Withdrawal Symptom Questionnaire suggested that patients who stopped suvorexant did not experience a withdrawal syndrome, at least with respect to the symptoms queried; neither was there a pattern of adverse events reported by patients in the suvorexant-placebo group suggestive of withdrawal characteristics. With regard to rebound insomnia, in all groups a proportion of patients experienced symptom return above baseline during the discontinuation phase, perhaps related to an expectancy effect based on the knowledge that a change in treatment allocation was possible. The number of patients in the at-risk group switched from suvorexant to placebo who experienced rebound insomnia during the initial three nights of the discontinuation phase seemed to be slightly greater than in the group on placebo throughout the trial. This difference was not statistically significant in the prespecified analysis, but the study was not designed with power to detect a very small effect. That symptom return did not exhibit a spike with subsequent resolution, and the persistence of effects over the discontinuation phase, suggests that symptom return probably represents an unmasking of the underlying disorder rather than a drug-related rebound. Irrespective of cause, these differences were small and are unlikely to be clinically important for most individuals.

Several factors limit the interpretation of our findings. Our safety data are restricted to 1 year and could differ after longer-term use or in a larger sample. The trial did not include objective tests of daytime function or assessments of quality of life and work performance, which restricts conclusions about next-day residual effects. Although no effect on driving was recorded as assessed by motor vehicle violations and accidents, the rarity of these events could have masked a small but potentially important effect and, as with other hypnotics, patients should be cautioned about the potential risks of somnolence while driving the day after using suvorexant. The trial recruited patients with primary insomnia, and results could differ in patients with insomnia secondary to other factors. The trial did not include objective (polysomnographic) measurements of sleep parameters and our efficacy conclusions are based on patient self-reports, although suvorexant was effective when assessed objectively in other trials.[15,30,31] Dose response was not studied in this trial, although several other studies have investigated different doses over shorter periods.[15,30,31] No active comparator was included in the study, and we cannot make direct inferences about suvorexant relative to other drugs indicated for insomnia. Finally, we note that the US Food and Drug Administration (FDA) has stated that their general approach to insomnia drugs is to use the lowest effective dose.[32] Although we judged the 30 mg or 40 mg dose to be generally safe and well tolerated by most patients in this trial, after its review of suvorexant the FDA concluded that the safety and tolerability data across the development programme, including results from driving studies in healthy participants, did not support the use of the 30 mg or 40 mg dose for the treatment of insomnia. The FDA suggested that the totality of the clinical data supported the use of lower suvorexant doses of 10–20 mg.[32]

Panel: Research in context

Systematic review

We searched PubMed with the terms "orexin", "insomnia", and "randomized controlled trial" for reports in English as of Feb 4, 2014. We reviewed randomised double-blind controlled trials involving use of sleep drugs for 3 months or longer in patients with insomnia.

Interpretation

Few randomised controlled trials have assessed the clinical profile of hypnotics for more than 3 months, and none has investigated the clinical profile of an orexin receptor antagonist for longer than 3 months (table 1). Furthermore, no trial has assessed the effects of suddenly stopping an insomnia drug after a full year of treatment using a rigorous controlled and blinded design whereby patients previously on an active treatment were randomly assigned either to be switched to placebo or to remain on active treatment. To our knowledge, our trial of suvorexant is the longest clinical assessment so far of an orexin receptor antagonist and the first time that the effects of suddenly stopping an insomnia drug after 1 year of nightly use have been examined in a randomised, controlled, and blinded fashion. Suvorexant was generally safe, well tolerated, and efficacious for the treatment of insomnia over 1 year. Abruptly stopping suvorexant after 1 year was associated with a higher likelihood of symptom return compared with continued use of suvorexant, but not any serious safety concerns.

Contributors

WJH, ES, MC-L, DBS, JKW, ADK, RMB, TR, and DM conceived and designed the study. WJH, EP, JH, and DM were involved in study administration. MC was an investigator in the study. WJH, ES, MC-L, DBS, JKW, ADK, RMB, TR, and DM were involved in data analysis and interpretation. ES, MC-L, and DBS undertook or supervised the statistical analysis. WJH, CL, and DM wrote the first draft of the report. All authors reviewed and commented on the draft, and approved the final submission.

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Declaration of interests

WJH, ES, EP, MC-L, DBS, JH, CL, and DM are employees of Merck & Co Inc and own stock or stock options in Merck. JKW has received research support from several organisations in the past 2 years (Apnex, Merck, Novo Nordisk, Respironics, Vanda), and has provided consulting services to Merck, Somnus, Transcept, Vanda, Ventus, and Vivus. ADK has received grants or research support from NIH, Teva/Cephalon, Pfizer, Sunovion/Sepracor, Transcept, Phillips-Respironics, Astellas, Abbott, Neosynch, and Brainsway. He has served as a consultant to Abbott, Astellas, AstraZeneca, BMS, Teva/Cephalon, Eisai, Eli Lilly, GlaxoSmithKline, Jazz, Johnson and Johnson, Merck, Neurocrine, Novartis, Ortho-McNeil-Janssen, Respironics, Roche, Sanofi-Aventis, Somnus, Sunovion/Sepracor, Somaxon, Takeda, Transcept, and Kingsdown Inc. RMB has served as a consultant for Merck and Sanofi-Aventis. MC has received grants from Merck, Aventis, Cephalon, GlaxoSmithKline, Neurocrine, Pfizer, Sanofi, Sepracor, Somaxon, Takeda, Actelion, Arena, Aventis, Cephalon, Evotec, Forest, and Organon; has acted as a consultant for Actelion, Sanofi, Merck, and Neurocrine; and has participated in speaking engagements supported by Sanofi, Takeda, Sepracor, Purdue, Somaxon, and King. TR has received grants or research support from Aventis, Cephalon, GlaxoSmithKline, Neurocrine, Pfizer, Sanofi, Schering-Plough, Sepracor, Somaxon, Syrex, Takeda, TransOral, Wyeth, and Xenoport; has acted as a consultant for Abbott, Acadia, Acoglix, Actelion, Alchemers, Alza, Ancil, Arena, AstraZeneca, Aventis, AVER, BMS, BTG, Cephalon, Cypress, Dove, Elan, Eli Lilly, Evotec, Forest, GlaxoSmithKline, Hypnion, Impax, Intec, Intra-Cellular, Jazz, Johnson and Johnson, King, Lundbeck, McNeil, MediciNova, Merck, Neurim, Neurocrine, Neurogen, Novartis, Orexo, Organon, Pfizer, Prestwick, Procter and Gamble, Purdue, Resteva, Roche, Sanofi, Schering-Plough, Sepracor, Servier, Shire, Somaxon, Syrex, Takeda, TransOral, Vanda, Vivometrics, Wyeth, Yamanuchi, and Xenoport; and has participated in speaking engagements supported by Cephalon, Sanofi, and Takeda.

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