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Insight Into Reduction of Wakefulness by Suvorexant in Patients With Insomnia: Analysis of Wake Bouts FREE

Vladimir Svetnik, PhD, Ellen S Snyder, PhD, Peining Tao, PhD, Thomas E Scammell, MD, Thomas Roth, PhD, Christopher Lines, PhD, W Joseph Herring, MD, PhD

Sleep, Volume 41, Issue 1, January 2018, zsx178, https://doi.org/10.1093/sleep/zsx178
Published: 03 November 2017

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Abstract

Study Objectives

To examine the duration and frequency of wake bouts underlying the wakefulness-after-sleep-onset (WASO) reduction with suvorexant.

Methods

We analyzed polysomnogram recordings from clinical trials involving 1518 insomnia patients receiving suvorexant (40/30, 20/15 mg) or placebo to determine the following: (1) the number of, and time spent in, long or short wake bouts and (2) the association between sleep quality and bout characteristics. We also compared wake and sleep bout characteristics of suvorexant in insomnia patients versus zolpidem in healthy subjects undergoing experimentally induced transient insomnia.

Results

Relative to placebo, suvorexant decreased the number and time spent in long wake bouts (>2 minutes) and increased the number and time spent in short wake bouts (≤2 minutes). The time spent in long wake bouts during Night-1 decreased by 32–54 minutes, whereas the time spent in short wake bouts increased by 2–6 minutes. On average, a patient returned to sleep from his or her longest awakening more than twice as fast on suvorexant than placebo. The reduced time spent in long wake bouts resulted in odds ratios of self-reported good or excellent sleep quality ranging from 1.59 to 2.19 versus placebo. The small increase in time spent in short wake bouts had no effect on odds ratios. Findings were more pronounced for the higher (40/30 mg) doses of suvorexant. The wake and sleep bout characteristics of suvorexant differed from zolpidem which equally decreased the number of wake and sleep bouts of all durations during the early part of the night.

Conclusion

Suvorexant reduces WASO by reducing long wake bouts. This reduction has a positive effect on sleep quality.

Clinical Trials

Trial registration at www.clinicaltrials.gov NCT01097616; NCT01097629.

orexin, suvorexant, zolpidem, wake bouts, insomnia

Statement of Significance

The orexin receptor antagonist suvorexant reduces wakefulness-after-sleep-onset (WASO) in insomnia patients. However, the detailed dynamics of the WASO reduction have yet to be defined. We found that suvorexant reduced WASO by reducing long awakenings while slightly increasing short awakenings. On average, a patient returned to sleep from his or her longest awakening more than twice as fast on suvorexant than on placebo. The reduction in long awakenings increased the odds of self-reported good or excellent sleep quality, whereas the increase in short awakenings had no effect on sleep quality. This supports the expectation that long awakenings are more impactful for insomnia patients than short awakenings. Zolpidem showed a different pattern of effects on awakenings and sleep episodes consistent with a broad CNS depressant effect.

INTRODUCTION

Suvorexant is an orexin receptor antagonist recently approved for treating insomnia.[1–6] Orexin receptor antagonists establish a sleep-permissive state in insomniac patients by specifically blocking the wake-promoting effects of orexin peptides.[7–9] In two pivotal phase–3 trials, suvorexant improved sleep onset and maintenance in elderly (15 or 30 mg) or nonelderly (20 or 40 mg) insomnia patients.[3]

Using pooled data from these two trials of suvorexant, Herring et al.[10] showed that the significant reduction in wakefulness-after-sleep-onset (WASO) as assessed by polysomnogram (PSG) was maintained throughout 8 hours of nighttime recording, thereby increasing total sleep time (TST). Conventional measures of sleep architecture (e.g., percentage of time spent in rapid eye movement sleep [REM] and Non-REM sleep stages 1, 2, and 3 [N1, N2, and N3]) and EEG spectra were largely unaffected.[11]

The orexin system stabilizes sleep–wake behavior, predominantly by sustaining long periods of wakefulness.[12] Loss of orexin neurons results in narcolepsy with cataplexy, a disorder characterized by difficulty maintaining long periods of wakefulness and rapid, unwanted, transitions into sleep during the day.[13] Insomnia, by contrast, is considered to be a disorder of hyperarousal in which wake-promoting systems, possibly including the orexin system, are hypothesized to be inappropriately active during the night.[9,14] In contrast to most commonly used sleep medications that promote sleep by broadly enhancing GABA-A signaling (e.g., zolpidem), suvorexant is thought to promote sleep by inhibiting orexin-mediated wakefulness. However, the precise effects of suvorexant on sleep or wake dynamics are currently unknown. In a genetically modified mouse model of orexin neuron loss, in which discontinuation of doxycycline induces a toxin that kills orexin neurons over a period of weeks, Branch et al.[15] effectively found, using a survival analysis approach, that the proportion of brief wake bouts (<1 minute) increased while the proportion of long wake bouts decreased with loss of orexin neurons. This raises the question as to whether similar effects are seen with an orexin receptor antagonist, i.e., whether suvorexant might decrease the number and time spent in long wake bouts while increasing the number and time spent in short wake bouts.

Although bout analysis has been used previously in animal studies, the clinical literature on bout analyses in sleep research is relatively limited, in spite of many advantages of using bout statistics in the evaluation of sleep continuity and fragmentation. Several works describe statistical methods for estimation of sleep or wake bout characteristics[16,17] and the modeling of bout statistical distribution.[18,19] Klerman et al.[20,21] used bout survival analysis to study the effect of aging on sleep in healthy subjects. Most recently, Roth et al.[22,23] used bout analysis to evaluate sleep continuity in patients with fibromyalgia compared with insomnia patients and healthy sleepers.

Using PSG recordings from three previously reported clinical studies, we addressed three main objectives. First, we sought to evaluate the effects of suvorexant on wake bout characteristics using the data from two clinical trials in insomnia patients.[3] Second, we examined the clinical relevance of wake bout characteristics, by evaluating the association with self-reported sleep quality (sQUAL) the morning after PSG nights. Finally, we compared suvorexant wake and sleep bout characteristics with those of zolpidem using data from a transient insomnia study.[24]

METHODS

Suvorexant Studies

We analyzed PSG recordings from two similarly designed, randomized, double-blind, placebo-controlled 3-month trials with age-adjusted suvorexant dose regimes.[3] Nonelderly (<65 years old) insomnia patients received 20 or 40 mg suvorexant, whereas elderly (≥ 65 years old) patients received 15

or 30 mg. By design, fewer patients were assigned to the lower dose (20/15 mg) than the higher dose (40/30 mg) or placebo. We note that the recommended doses for treating insomnia are 10–20 mg, so 20/15-mg data are more clinically relevant while 40/30mg data may be more informative regarding the orexin mechanism. Overnight PSG recordings were performed at baseline and after dosing on Night 1, Month 1, and Month 3 of the treatment period in a subset of patients. Subjective (self-reported) sleep quality was assessed by the patients on a morning questionnaire after PSG nights. Table 1 shows the distribution of patients who received PSG by the treatment arm, age group, and gender. Inclusion or exclusion criteria and other details of the trial designs and results can be found in the work of Herring et al.[3]

Table 1

Distribution of Patients by Age Group, Treatment Arm, and Gender (Pooled Data from Two Studies).

Treatment arm	Age, years	Gender	Number of patients		
PBO	<65	F	208	333	585
		M	125		
	≥65	F	173	252	
		M	79		
SUV 20/15 mg	<65 (20 mg)	F	127	197	343
		M	70		
	≥65 (15 mg)	F	94	146	
		M	52		
SUV 40/30 mg	<65 (40 mg)	F	227	340	590
		M	113		
	≥65 (30 mg)	F	158	250	
		M	92		

SUV = Suvorexant; PBO = Placebo; F = Female; M = Male.

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Zolpidem Study

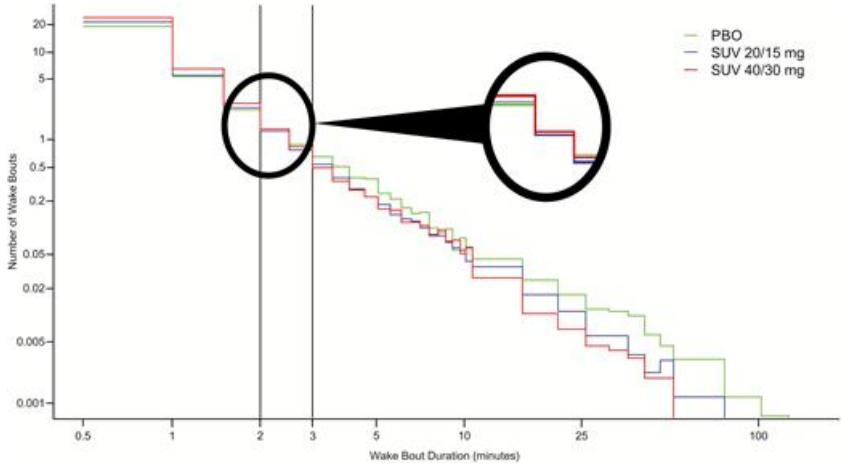
We analyzed PSG data from a study investigating the efficacy of zolpidem and gaboxadol for treating transient insomnia.[24] In this study, transient insomnia was simulated by advancing bedtime 4 hours ahead of habitual bedtime of good sleepers. The design of the study was a 5-period crossover (three doses of gaboxadol, zolpidem 10 mg, and placebo) with 82 healthy subjects (45 females) aged between 18 and 60 years old. For the analysis in this paper, we used each subject's PSG recordings from two nights when subjects were administered zolpidem and placebo. Details of the study can be found in the work of Walsh et al.[24]

Statistical Methods

Each 30-second epoch of PSG recording during the 8-hour time between lights off and lights on was scored using Rechtschaffen and Kales criteria[25] and the American Academy of Sleep Medicine Manual for the Scoring of Sleep and Associated Events[26] as sleep (N1, N2, N3, or REM) or wake. Based on these scores, each wake bout, i.e., a continuous sequence of wake epochs occurring *after* the beginning of persistent sleep, was identified and uniquely described by their starting time and duration in minutes. Sleep was defined as persistent if it followed the first occurrence of 10 consecutive minutes of any sleep stage, i.e., N1, N2, N3, or REM. A wake bout could be as short as 0.5 minutes (one epoch) and could occur at any time after persistent sleep and before lights on. Thus, a bout of wake could theoretically be as long as 470 minutes = 8 hours × 60 minutes − 10 minutes (the shortest time to persistent sleep).

From a statistical point of view, bouts within each recording are recurrent events whose number and durations are random variables with an unknown probability distribution. We calculated the histogram of the bout durations for each recording. If plotted, the *y*-value of the histogram was the number of bouts whose duration (*x*-value) was equal to one of the possible bout durations (0.5, 1,…, 470 minutes). For many of the *x*-values, the number of bouts was zero, since a recording does not include bouts of all possible durations. Averaging histograms of the recordings collected from a specified cohort of patients resulted in the estimate of the mean histogram for this cohort. Figure 1 shows examples of the mean histogram, corresponding to three treatment cohorts. No formal testing was done to test differences between mean histograms. Instead, we visually inspected them and generated hypotheses for further analysis and testing.

Figure 1



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Mean number of wake bouts on Night 1 of treatment by wake bout duration for suvorexant (SUV 20/15 mg, 40/30 mg) and placebo (PBO). *X*- and *Y*-axes use logarithmic scales. The larger circle magnifies the 1.5–3 minutes bout duration segment identified in the smaller circle and shows that compared with placebo suvorexant increased the number of wake bouts ≤2 minutes and decreased the number of wake bouts ≥2.5 minutes. On the basis of this finding, bout duration was defined as “short” if ≤2 minutes and “long” if >2 minutes.

In addition to the bout histograms for each recording, we calculated within-recording bout statistics (parameters or characteristics). These were the *total* number and *total* time spent in two groups of bouts—those with duration ≤2 minutes (referred to as “short bouts”) and those with duration >2 minutes (“long bouts”) (see details below), as well as the maximum duration and percentiles of the durations of a single long bout. Our focus on long and short bouts is explained in more detail in Results section.

We used linear mixed effect models for comparison of the short and long bout statistics between cohorts of interest. In this model, a (within-recording) statistic, e.g., total time in or total number of long or short bouts, was the response variable. The predictor variables included the baseline value of the response variable, age group (<65, ≥65 years), treatment (15/20, 30/40 mg, placebo), night (Night 1, Month 1, Month 3), and treatment by night and by age group interaction. Reponses on different nights were modeled as repeated measures within a subject. Unstructured correlation matrix was used to account for within-subject correlation, while the subject effect was considered as random. Analyses of the short and long bouts were done separately and independently of each other.

To analyze drug effects at different sleep periods in addition to the analyses of the whole night, we also analyzed data by three parts of the night, part 1, 2, and 3. Each part was equal to one-third of the whole night (8 hours × 60 minutes/3 = 160 minutes).

Analysis of association between sQUAL and bout duration was done using mixed effect logistic regression. sQUAL was assessed using a 4-point scale (poor, fair, good, excellent). To simplify interpretation of the analysis results, the 4-point scale was converted to a binary response variable equal to 0 when quality was reported as poor or fair and 1 when it was reported as good or excellent. The number of, and time spent in, long wake bouts and time spent in short wake bouts were three predictor variables representing the fixed effect. We did not include the number of short bouts in the model due to its high (>0.96 Pearson and Spearman) correlation with the time in short wake bouts. Regressions were calculated with all the data, i.e., data from all four nights and all treatments. The response variable sQUAL was modeled as a repeated (over the PSG nights) measure within a subject, with the subject modeled as the random effect. We chose to use a compound symmetry type of within-subject correlation matrix instead of the more typical unstructured correlation matrix to achieve convergence of the SAS PROC GLIMMIX numerical procedure.

The comparison of suvorexant and zolpidem took into account the fact that the rationale for classifying wake bouts as short and long was based on

suvorexant data only. Therefore, instead of evaluating short and long wake bouts, we used mean cumulative sums of the number and duration of bouts. In addition to wake bouts, we also analyzed sleep bouts for both the suvorexant and zolpidem datasets. To obtain mean cumulative sums, we first calculated the cumulative sums for each recording and then averaged them over the cohorts of interests similarly to how we calculated the other mean statistics described above. To estimate the effects of suvorexant and placebo on cumulative sums, we used the mixed model described above with either the cumulative sum of the number of bouts or the cumulative time in the bouts as response variables. In the rest of the paper, we drop the word "sum" and simply use cumulative number of, or time spent in, bouts. We used suvorexant and placebo data from Night 1 and the dataset was restricted to nonelderly insomnia patients (<65 years old) to more closely match the age of subjects in the zolpidem dataset (<60 years old). For zolpidem, we used the nights when a subject was administered zolpidem 10 mg or placebo. Due to the crossover study design, different subjects had treatments on different nights. Also, for zolpidem, we used a different mixed effect model where two fixed effect variables were the period and treatment, whereas the subject effect was modeled as the random variable.

All analyses and graphics were done using SAS 9.4 (SAS Institute Inc., Cary, NC) and R 3.2.4 (R core team).[27]

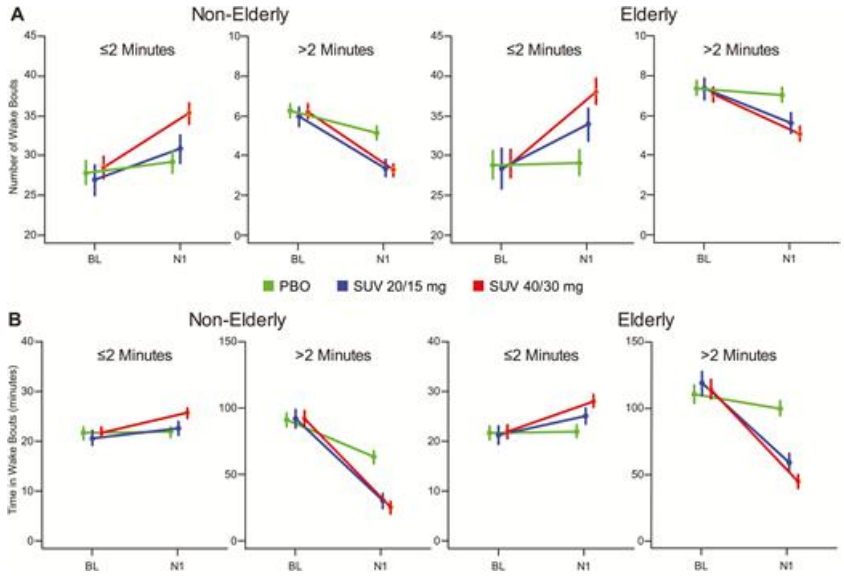
RESULTS

Suvorexant Effects on Wake Bout Characteristics

Suvorexant reduced the number of long wake bouts compared with placebo (Figure 1). The mean number of all (long) wake bouts with duration ≥2.5 minutes was *less* with suvorexant than with placebo. On the other hand, the mean number of all (short) wake bouts with duration ≤2 minutes was larger with suvorexant than with placebo.

This observation is reinforced by considering the number of (Figure 2a), and time spent in (Figure 2b), short and long wake bouts at baseline and on Night 1 of treatment. Suvorexant increased the mean number of, and time spent in, short bouts versus placebo and baseline and decreased the mean number of, and time spent in, long bouts. This pattern was also present at Months 1 and 3 of treatment, and it was also present in the first, second, and third parts of the night (see Supplementary Figures S1–S7). The findings tended to be more apparent for 40/30 mg versus 20/15 mg dose of suvorexant and for elderly versus nonelderly patients (Figure 2, Supplementary Figures S1–S7). This was also the case for the other analyses subsequently reported here, so we do not highlight it further unless particularly relevant.

Figure 2



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(a) Mean number (+/− 2 SEM) of short (≤2 minutes) and long (>2 minutes) wake bouts at baseline (BL) and Night 1 (N1) by treatment. (b) Mean time (+/− 2 SEM) spent in short (≤2 minutes) and long (>2 minutes) wake bouts at baseline (BL) and Night 1 (N1) by treatment.

Table 2 shows the mean values for the number of, and time spent in, short and long wake bouts as well as effects of suvorexant, calculated as baseline-adjusted mean differences from placebo. Note that almost all effects were highly significant ($p < .001$), and the drug effect on decreasing

the time spent in long bouts was far larger than its effects on increasing the time spent in short bouts. For example, for suvorexant 40/30 mg versus placebo in elderly patients, the maximum mean reduction in the time spent in long wake bouts adjusted for baseline was approximately 54 minutes, whereas the increase in the time spent in short wake bouts was only about 6 minutes (Table 2).

Table 2

Baseline-Adjusted Effects of Suvorexant (SUV 20/15 mg, 40/30 mg) on Mean Number of, and Time Spent in, Short (≤2 minutes) and Long (>2 minutes) Wake Bouts During Night 1 of Treatment.

Age group	Bout parameter	Parameter mean			Mean difference from PBO	
		PBO	SUV 20/15 mg	SUV 40/30 mg	SUV 20/15 mg vs PBO	SUV 40/30 mg vs PBO
Nonelderly <65	No. of short bouts	29.2	30.9	35.3	2.3*	5.8***
	No. of long bouts	5.1	3.4	3.3	−1.7***	−1.9***
	Time in short bouts (min)	21.6	22.3	25.4	1.2	3.7***
	Time in long bouts (min)	60.4	28.6	23.6	−32.0***	−37.0***
Elderly ≥65	No. of short bouts	29.1	34.0	38.1	5.2***	8.9***
	No. of long bouts	7.1	5.6	5.1	−1.4***	−1.9***
	Time in short bouts (min)	21.7	24.7	27.8	3.2***	6.0***
	Time in long bouts (min)	95.1	56.0	41.7	−41.5***	−54.4***

*$p < .05$, **$p < .01$, ***$p < .001$.

SUV = Suvorexant; PBO = Placebo.

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To further examine this shortening of wake bouts, we analyzed the mean baseline-adjusted within-subject maximum long bout duration, and also the 90th, 75th, 50th (median) percentiles and the mean wake bout duration (Table 3). The reduction in the maximum bout duration was on average between 18.4 and 32.0 minutes (54.8% and 63.4% of placebo) depending on the treatment dose and age group. This means that, on average, suvorexant reduced the longest time to fall back to sleep after an awakening by about 54.8% to 63.4% compared with placebo.

Table 3

Mean of Statistical Distribution Parameters for the Duration of a Single Long (>2 minutes) Wake Bout and Baseline-adjusted Effects of Suvorexant (SUV 20/15 mg, 40/30 mg) for Night 1 of Treatment.

Age group	Parameter of statistical distribution	Parameter mean (min)			Mean difference from PBO (min)	
		PBO	SUV 20/15 mg	SUV 40/30 mg	SUV 20/15 mg vs PBO	SUV 40/30mg vs PBO
Nonelderly <65	Max	33.5	15.6	12.0	−18.4***	−21.6***
	90th	32.4	15.1	11.6	−17.7***	−20.8***
	75th	20.2	10.4	8.6	−10.0***	−11.6***
	Median	9.0	5.9	5.0	−3.2***	−4.1***
	Mean	13.6	7.6	6.2	−6.1***	−7.6***
Elderly ≥65	Max	49.2	27.1	18.6	−24.1***	−31.3***
	90th	44.7	26.0	17.8	−20.9***	−27.8***
	75th	21.8	15.8	11.4	−6.7***	−10.8***
	Median	8.5	7.4	6.5	−1.1	−2.2**
	Mean	15.6	10.9	8.4	−4.9***	−7.4***

*p < .05, **p< .01, ***p< .001.

SUV = Suvorexant; PBO = Placebo.

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The maximum duration of a long bout (i.e., the longest wake bout) contributed the most to the reduction of time in all long bouts. For example, the mean time in long wake bouts for the elderly patients decreased by about 41.5 and 54.4 minutes for suvorexant 20/15 and 40/30 mg, respectively, as shown in Table 2. Per Table 3, more than half of this reduction came from the decrease by 24.1 and 31.3 minutes, respectively, in the duration of the longest bout.

Similar findings to those described above for Night 1 were also apparent at Months 1 and 3 (see Supplementary Tables S1–S4).

Association of Wake Bout Duration with sQUAL

Table 4 shows treatment effects, i.e., means of baseline-adjusted differences from placebo (as in Table 2) and the corresponding odds ratios of good or excellent sQUAL for suvorexant versus placebo for Night 1 of treatment. Patients treated with suvorexant spent less time in long wake bouts, with reductions from placebo ranging from 32.0 to 54.4 minutes, depending on the dose and age group. This decrease was associated with a 59%–119% increase in the odds of good or excellent sQUAL compared with placebo. In contrast, the mean increase in time spent in short bouts was at most 6.0 minutes (suvorexant 40/30 mg, elderly group). The odds ratio corresponding to this increase did not differ from placebo (0.99; 95% CI: 0.95, 1.03). Note also from Table 4 that the decrease in time spent in long wake bouts had a much higher positive effect on odds ratios than the positive effect of the decrease in the number of long wake bouts. Thus, this analysis shows that with respect to sQUAL, the positive effects of suvorexant on reducing time in long wake bouts greatly outweigh any effect of more time in short wake bouts. A similar pattern of findings was apparent at Months 1 and 3 (Supplementary Tables S5 and S6).

Table 4

Odds Ratios (Odds of Good/Excellent sQUAL for Suvorexant vs Placebo) Corresponding to the Mean Baseline-adjusted Effects of Suvorexant (SUV 20/15 mg, 40/30 mg) on the Time Spent in Short (≤2 minutes) Wake Bouts, the Number of Wake Bouts, and Time Spent in Long (>2 minutes) Wake Bouts for Night 1 of Treatment.

Age group	Bout parameter	Mean difference from PBO (min)		Odds ratios (odds of good/excellent sQUAL SUV vs. PBO) and 95% CI	
		SUV 20/15 mg vs PBO	SUV 40/30 mg vs PBO	Odds ratio SUV 20/15 mg vs PBO	Odds ratio SUV 40/30 mg vs PBO
Nonelderly < 65	Time in short bouts	1.2	3.7***	1.00 (0.99, 1.01)	1.00 (0.97, 1.02)
	Time in long bouts	−32.0***	−37.1***	1.59 (1.48, 1.70)	1.70 (1.57, 1.85)
	No. of long bouts	−1.7***	−1.9***	1.07 (1.02, 1.12)	1.08 (1.02, 1.14)
Elderly ≥65	Time in short bouts	3.2***	6.0***	1.00 (0.97, 1.02)	0.99 (0.95, 1.03)
	Time in long bouts	−41.5***	−54.4***	1.82 (1.66, 2.00)	2.19 (1.95, 2.47)
	No. of long bouts	−1.4***	−1.9***	1.06 (1.02, 1.10)	1.08 (1.02, 1.14)

*p < .05, **p< .01, ***p< .001.

SUV = Suvorexant; PBO = Placebo; sQUAL = sleep quality.

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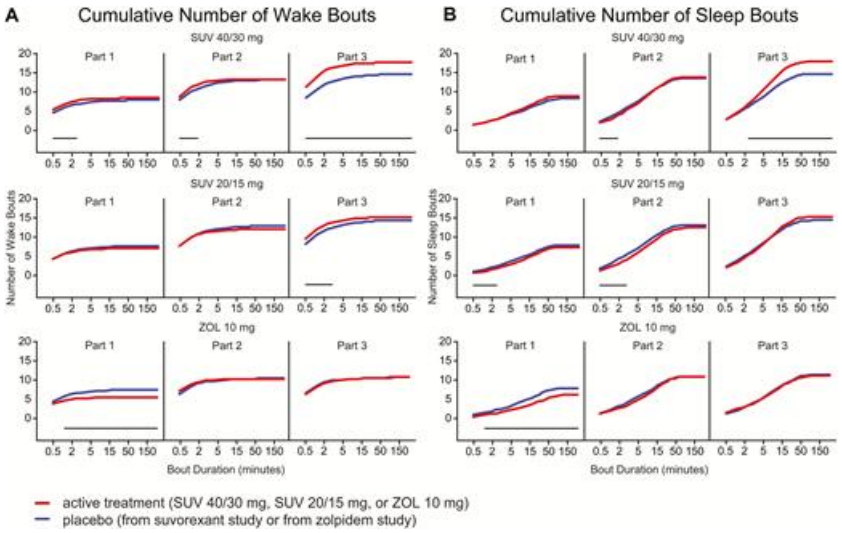
Comparison of Suvorexant and Zolpidem Wake and Sleep Bout Characteristics

Figures 3 and 4 show mean cumulative number of, and time spent in, wake and sleep bouts for suvorexant, zolpidem, and their respective placebo arms by part of the night.

Figure 3



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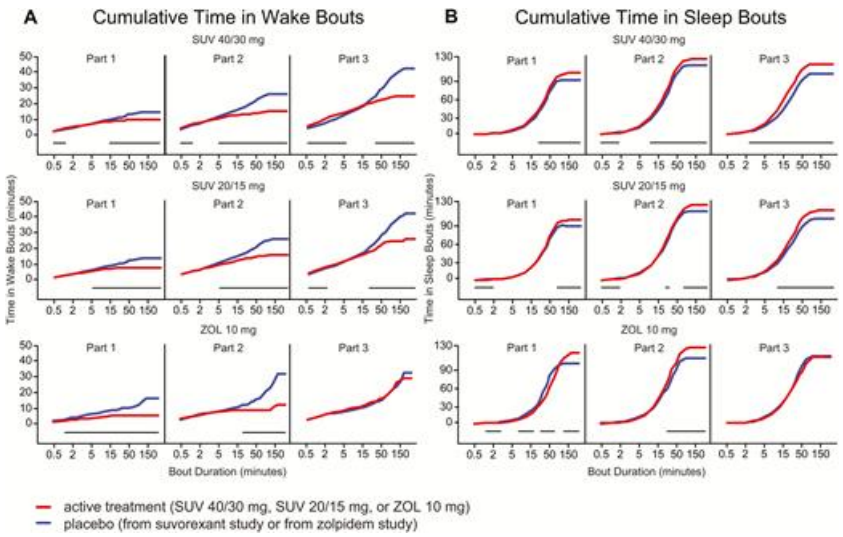
Cumulative number of bouts with bout duration ≤ *X*-axis value for suvorexant (SUV 40/30 mg, 20/15 mg) and zolpidem (ZOL 10 mg) vs placebo by part of the night. The *y*-values when, e.g., *x* = 5 equals the total number of bouts whose duration is ≤5 minutes. The rightmost points of each graph have *y*-coordinates equal to the mean (total) numbers of bouts of all durations for the corresponding part of the night. Bout durations where the differences between cumulative time under treatment and under placebo are statistically significant, p-values <0.05, are indicated by the black bars.

Figure 4



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Mean cumulative time in bouts with bout duration ≤ *X*-axis value for suvorexant (SUV 40/30 mg, 20/15 mg) and zolpidem (ZOL 10 mg) vs placebo by part of the night. The *y*-values when, e.g., x=5 equals the total time spent in bouts whose duration is ≤5 minutes. The rightmost points of each graph have *y*-coordinates equal to the total time spent in bouts of all durations for the corresponding part of the night. Bout durations where the differences between cumulative time under treatment and under placebo are statistically significant, p-values <0.05, are indicated by the black bars.

Figure 3a shows that compared with placebo, suvorexant 20/15 mg in part 3 of the night, and suvorexant 40/30 mg in all parts of the night, had higher cumulative numbers of shorter wake bouts. In part 1 and 2 for suvorexant 40/30 mg and in part 3 for suvorexant 20/15 mg only, the excess of shorter bouts was "compensated" by the fewer number of longer bouts (the curves converged as fewer than placebo longer bouts were added under the treatments). For suvorexant 40/30 mg in part 3, however, the cumulative number of bouts remained higher since the excess in the number of shorter bouts was not offset by the reduction in the number of longer bouts. (As shown in the bottom left panel of Supplementary Figure S3, the increase in the number of short bouts was larger than the decrease in number of long bouts.)

With respect to sleep, suvorexant 40/30 mg significantly increased the cumulative number of longer sleep bouts in part 3 (Figure 3b). Suvorexant at both doses generally decreased the cumulative time in longer wake bouts (Figure 4a) and increased the cumulative time in longer sleep bouts (Figure 4b) in all parts of the night.

Zolpidem showed different effects on sleep dynamics. With zolpidem, the cumulative number of wake bouts of almost all durations was reduced in part 1 of the night (Figure 3a). Furthermore, zolpidem decreased the number of sleep bouts of almost all durations in part 1 (Figure 3b). Figure 4 shows that in spite of the differing effects on the number of wake and sleep bouts, both suvorexant and zolpidem, as expected, decreased the time spent in wake and increased the time spent in sleep overall (see the *y*-values of the rightmost points of graphs in Figure 4a and 4b). In addition, in part 1 of the night, zolpidem decreased time spent in sleep bouts with shorter durations up to about 50 minutes and increased time spent in bouts of longer duration (Figure 4b). Suvorexant also consistently reduced time spent in longer wake bouts throughout the night (Figure 4a), whereas zolpidem did so only in the earlier parts of the night, which reflects the latter's short, 1.5–2.4 hours, half-life and associated duration of efficacy (see, e.g., the work of Parino and Terzano[28]).

DISCUSSION

In this analysis of large PSG databases from two clinical trials of suvorexant, we found that suvorexant reduced WASO by reducing the number of, and amount of time spent in, long (>2 minutes) wake bouts. Furthermore, the longest duration of a wake bout (i.e., an awakening) was reduced by 54.8% and 63.4% compared with placebo, indicating that on average, a patient returned to sleep from his or her longest awakening more than twice as fast on suvorexant than on placebo. The effect of suvorexant on reducing long wake bouts was apparent at Night 1 and maintained over three months. In addition, suvorexant increased the mean number of short wake bouts (≤2 minutes), but as these bouts are so short, this resulted in only about 3–6 minutes more time spent in short wake bouts. The increased number of short wake bouts under suvorexant is presumably due to replacement of segments within long wake bouts by one or more sleep bouts. This replacement may leave some short wake "gaps" between the

sleep bouts, thus increasing the total number of short wake bouts. These findings for suvorexant tended to be dose-related and more apparent for elderly versus nonelderly patients.

From an insomnia perspective, the reduction in long wake bouts may be more clinically important than the increase in short wake bouts associated with suvorexant. Firstly, as noted above, suvorexant's effect on reducing long wake bouts was greater than its effects on increasing short wake bouts. Secondly, the potential impact of being awake for long periods (more rumination, more frustration and anxiety, and more opportunity to develop counterproductive behaviors that worsen psychophysiological elements) is likely to be greater than that of being awake for short periods. Our analysis of sleep quality supports this. The odds ratio that a patient reports good or excellent sleep quality due to the reduced time in long bouts by suvorexant ranged from 1.59 to 2.19 versus placebo, whereas the slightly increased number of short wake bouts (≤2 minutes), and time spent in them, had no effect on patient-reported sleep quality. Previous studies suggest that approximately 5 minutes of continuous wakefulness are required to form a memory for an awakening,[29] and consequently, patients may not remember or perceive short wake bouts subjectively as awakenings. Furthermore, the subjective number of awakenings generally correlates poorly with the number of actual awakenings as assessed by PSG. For example, using the datasets described in the present paper, we found that the correlations between the numbers of all, short, and long wake bouts with the subjective number of awakenings were 0.08, 0.03, and 0.21, respectively.

It could be further speculated that brief arousals from sleep are normal and desirable to monitor the environment and to enable responses to physiological challenges (e.g., apnea, chronic obstructive pulmonary disease, and gastroesophageal reflux disease) during the night. In an animal study, Tannenbaum et al.[30] found that sleeping monkeys given an orexin receptor antagonist retained the capacity to awaken to emotionally salient acoustic stimuli while still preserving uninterrupted sleep in response to irrelevant stimuli. In contrast, a GABA-A receptor modulator induced lighter sleep but impaired the monkeys' ability to wake to salient stimuli. Possibly, the ability to process the stimuli properly with an orexin antagonist could be due to an increased number of short wake bouts allowing the monkeys to be "sufficiently" alert to listen to the stimuli, whereas reduction in the number of long wake bouts increases their sleep time. However, a more likely explanation is that orexin receptor antagonists preserve a "normal" arousal threshold, whereas the threshold to arouse is higher with drugs that enhance GABA signaling. A comparable study looking at the effects of an orexin receptor antagonist on arousal to salient stimuli in humans has not yet been performed, although a study looking at auditory awakening threshold is underway and includes a GABA-A receptor modulator comparator (clinicaltrials.gov: NCT03008447).

An open question is whether the pattern of findings we observed with suvorexant differs from that with GABAergic hypnotics such as zolpidem. Our attempt to address this was limited or complicated by differences in the datasets available to us including the type of subject (insomnia patients for suvorexant versus healthy subjects undergoing a phase advance model of transient insomnia for zolpidem), study design (parallel group studies for suvorexant versus crossover study for zolpidem), number of subjects (relatively smaller dataset for zolpidem), and by differences in pharmacokinetic profiles between the two drugs (shorter half-life for zolpidem versus suvorexant). The observation that zolpidem does not differentially impact the number of wake and sleep bouts of differing durations during the early parts of the night can be interpreted as suggesting that zolpidem has an early broad CNS depressant effect without the interplay between short and long bouts observed with suvorexant. However, direct comparative studies are needed to confirm and more fully evaluate potential differences between suvorexant and zolpidem in this regard.

In addition to the limitations noted above for the zolpidem comparison, our analysis had other limitations. Foremost, this was a post hoc analysis and subject to the well-known limitations associated with such an approach. Secondly, the 2-minute cutpoint for our definition of "short" and "long" wake bouts was empirically determined based on the observed suvorexant data and may not be suitable in analyzing other treatments (hence our differing analytic approach for the zolpidem comparison). Thirdly, the strongest findings with suvorexant tended to be observed for the highest 40/30 mg dose. Although this is interesting regarding implications for the orexin mechanism, the recommended clinical doses of suvorexant are 10–20 mg, so 20/15 mg data are more clinically relevant.

Despite these limitations, the approach to analysis of wake bouts employed in our study provides novel insights into sleep or wake dynamics, and future studies could use these approaches to further explore differences between sleep-promoting medications and good sleepers versus insomnia patients.

SUPPLEMENTARY MATERIAL

Supplementary material is available at *SLEEP* online.

FUNDING

The study was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

AUTHOR CONTRIBUTIONS

VS and ESS designed the study. VS, ESS, and PT performed the analyses. VS, ESS, and CL drafted the paper. All authors contributed to the interpretation of the data, reviewed drafts of the paper, and approved the final version.

DISCLOSURE STATEMENT

VS, ESS, PT, CL and WJH are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ USA and own or owned stock/stock options in the company. 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 – Johnson, King, Lundbeck, McNeil, MediciNova, MSD, Neurim, Neurocrine, Neurogen, Novartis, Orexo, Organon, Prestwick, Procter – Gamble, Pfizer, 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.

TS has received consulting fees from Avadel Pharmaceuticals, Balance Therapeutics, Jazz Pharmaceuticals, J&J, Marathon Pharmaceuticals, Merck, Ono Pharmaceuticals, Purdue Pharma, Reset Therapeutics, SK Biopharmaceuticals, Takeda, Umecrine Cognition, and Voyager Therapeutics.

ACKNOWLEDGMENTS

The authors wish to thank Sheila Erespe, MS, of Merck & Co., for her assistance with the submission.

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