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ORIGINAL RESEARCH ARTICLE

Treatment of Sleep, Motor and Sensory Symptoms with the Orexin Antagonist Suvorexant in Adults with Idiopathic Restless Legs Syndrome: A Randomized Double-Blind Crossover Proof-of-Concept Study

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Abstract

Background and Objectives Current treatment guidelines for restless legs syndrome (RLS) recommend treatment be initiated with non-dopaminergic drugs. Given the potential role of orexins in the pathophysiology of RLS, we performed a pilot, proof-of-concept study to investigate the therapeutic effects of suvorexant, a dual orexin receptor antagonist (DORA), on sleep and sensory/motor symptoms in individuals with idiopathic RLS.

Methods This was a randomized, double-blind, crossover and placebo-controlled study. Inclusion criteria were diagnosis with idiopathic RLS, an International RLS Study Group Severity Rating Scale (IRLS) score > 15, and the absence of significant RLS symptoms before 9 pm. Following washout from any previous central nervous system (CNS)-active drugs, patients were randomized to receive either suvorexant or placebo for two consecutive 2-week treatment periods. Treatment was administered at 9 pm at a fixed dose of 10 mg/day during the first week, and 20 mg during the second week. Primary and coprimary endpoints were wake after sleep onset (WASO) and total sleep time (TST), respectively, while IRLS rating scale score, multiple suggested immobilization tests (m-SIT), and periodic limb movements (PLMs) were secondary endpoints. RLS severity was measured weekly using the IRLS and Clinical Global Improvement (CGI) scales. m-SIT were also performed between 8 pm and midnight at the end of each treatment phase and were followed by a sleep study.

Results A total of 41 participants were randomized, 40 of whom completed the study. Compared with placebo, treatment with suvorexant significantly improved RLS symptoms (according to IRLS total score, CGI, and the m-SIT), PLM during sleep, and PLM with arousal. Improvement of RLS symptoms was greater in those who had not been exposed to dopaminergic agents in the past. Sleep architecture also improved with significant changes in TST, WASO, sleep onset latency, sleep efficiency, non rapid-eye movement stage 1 (N1) %, non rapid-eye movement stage 2 (N2) %, and rapid eye movement (REM) %. Suvorexant was well tolerated in RLS, with few and mild adverse events.

Conclusions Our results provide the first proof of evidence of the therapeutic efficacy of DORAs in improving sleep and sensory and motor symptoms in RLS. Given orexin's role in pain and sensory processing, potential mechanisms of action are discussed.

Classification of Evidence The study provides class II evidence supporting the therapeutic efficacy of suvorexant in patients with RLS with sleep disturbance. Trial Registration: EudraCT#: 2017-004580-12.

1 Introduction

Restless legs syndrome (RLS; also called Willis–Ekbom disease) is a common neurological disorder characterized by an urge to move the legs, usually accompanied by dysesthesias [1]. Approximately 60–75% of patients with RLS only have symptoms at bedtime, resulting in sleep disturbance [2].

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Key Points

We sought to investigate the therapeutic effects of suvorexant, a dual orexin receptor antagonist (DORA), on motor and sensory symptoms and sleep in patients with restless legs syndrome (RLS).

Treatment with suvorexant improved sleep, as well as sensory symptoms and motor dysfunction in patients with RLS.

SVX did not cause more adverse effects (AEs) than placebo. AEs were not severe and were similar to those reported for other patient populations.

Our results provide the first proof of evidence of the therapeutic efficacy of DORAs in improving RLS sensory and motor symptoms and sleep.

Although dopamine agonists (DAs) are widely used to treat RLS, there is growing concern about their long-term complications, especially dopaminergic augmentation of symptoms [3], which frequently leads to treatment discontinuation. After approximately 10 years of treatment, the prevalence of augmentation approaches 50% [4–7]. However, because RLS is often chronic, longer treatment will likely result in a higher prevalence of augmentation. The main international RLS expert organizations recognize that patients need treatment alternatives to dopaminergic agents and, therefore, recommend that patients begin treatment with drugs other than dopaminergic agonists [3].

Several drugs with non-dopaminergic mechanisms of action have shown therapeutic efficacy for RLS with varying degrees of evidence: alpha-2 delta ligands (pregabalin, gabapentin), opiates, and benzodiazepines. The only common mechanism through which these very different agents might improve RLS symptoms is by reducing arousal: even moderate RLS symptoms profoundly disturb sleep [8]. However, despite reduced sleep times, untreated patients with RLS complain less about daytime sleepiness than is expected. An alerting mechanism partially compensates for sleep loss, similar to hyperarousal in insomnia disorder [9]. Reduced adenosinergic activity is a potential mechanism that leads to increased arousal in RLS as it increases the disinhibition of glutamatergic corticostriatal pathways [10].

However, the orexin system may also play a role in causing RLS-related hyperarousal as orexins are important in the central regulation of both motor control and arousal [11–16]. Two studies have examined orexin cerebrospinal fluid (CSF) levels in patients with RLS. Compared with controls and treated patients, one small study found increased evening orexin-1 in previously untreated patients with early onset RLS [17]. These findings were not replicated in a later study [18]. The differences in findings may be explained by the treatment status and the use of different CSF extraction methods.

Suvorexant is a dual orexin receptor agonist approved in the USA and Japan for the treatment of insomnia [19]. We hypothesized that treatment of RLS with suvorexant might improve sleep patterns as well as RLS-specific sensory symptoms and motor dysfunction. Specifically, the objectives of this study were to investigate the effects of a 2-week treatment with 20 mg suvorexant upon objective sleep patterns (total sleep time and wake time after sleep onset), as well as upon RLS dysesthesias and periodic leg movements during sleep.

2 Methods

2.1 Standard Protocol Approvals, Registrations, and Patient Consent

The study was performed at the Sleep Research Institute, in Madrid, Spain, and approved was obtained by the local institutional review board (CEIC Hospital La Princesa, Madrid) on 23 December 2017 (approval number: 21/2017). Written informed consent was obtained from all participants. This study was registered at the EUDRA-Clinical Trials registry (EudraCT#: 2017-004580-12).

2.2 Study Design and Procedures

The study followed a double-blind, randomized, crossover, placebo-controlled design. Following a washout of 2 weeks for any previous RLS and psychotropic medications, patients were evaluated for RLS severity at baseline and then randomized to receive suvorexant or placebo for 2 weeks (allocation ratio: 1:1). All patients received 10 mg of suvorexant (or placebo) during the first week, and 20 mg during the second. Following a washout period of 14 days, patients underwent another 2-week treatment with the alternate treatment. The study was performed on outpatients. Adherence to treatment was evaluated by means of diaries and drug counting.

Medication was administered each day in a single dose between 9 and 10 pm. Symptom severity was assessed every week using the International Restless Legs Study Group Severity Rating Scale (IRLS) [20], Clinical Global Impression Severity (CGI–S) [21], Medical Outcome Survey sleep scale (MOS-sleep) [22, 23], and a visual analog scale (VAS) for pain. Furthermore, patients were required to keep consistent bed and wake times and to keep a sleep diary for the

duration of the study, including during both washout periods and when on treatment.

The m-SIT is a validated test [24] that evaluates the severity of motor and subjective RLS symptoms in the evening while the patient is awake and immobile, and has been used in previous RLS treatment trials. Three 1-h SITs were performed, at the end of each treatment period, at 8 pm, 10 pm, and 12 am, during which the patients were asked to remain immobile. During each 1 h period, a m-SIT disturbance index scale (m-SIT-ds) was administered every 10 min and the periodic leg movements during wakefulness index (PLMW) score were calculated, according to standard procedures [24]. Subjects were immediately followed by a sleep study that took place between 1 am and 8 am. On these two days, the medication was administered punctually at 9 pm. The baseline value of the m-SIT-disturbance scale was the one obtained at 8 pm , since it was obtained before the administration of the study medication. We calculated the baseline-corrected mean values for the 1-h immobilization tests taking place at 10 pm and 12 am on each study visit.

Periodic leg movements were measured with bilateral anterior tibialis muscle surface electromyography (EMG). Every 10 min during the test, patients completed a numerical symptom severity scale [m-SIT disturbance scale (m-SIT-ds), range of 0–10, with a possible maximum total sum of 60). No sleep episodes were allowed between the three tests or after the last one and the initiation of the polysomnography (PSG). PSG was performed according to the American Academy of Sleep Medicine (AASM) criteria and included bilateral EMG recording of the anterior tibialis to measure the periodic limb movement during sleep index (PLMSI) as well as the periodic limb movement arousal index (PLMAI). PSG-recorded sleep parameters were evaluated according to AASM criteria [25]. Digital acquisition of both mSIT and sleep studies was performed using a BWIII SleepVirtual (Neurovirtual USA, Fort Lauderdale, FL). All adverse events were registered by means of a checklist we devised on the basis of the existing suvorexant literature.

2.3 Primary and Secondary Endpoints

The primary and coprimary endpoints were wake-after-sleep onset (WASO) and total sleep time (TST), respectively. Secondary endpoints were change from baseline across treatment conditions in IRLS score, m-SIT (m-SIT discomfort scale), and PLMs.

2.4 Participants

Patients attending our clinic and diagnosed with idiopathic RLS were enrolled. Inclusion criteria were current age between 18 and 80 years old, meeting International Restless Legs Syndrome Study Group (IRLSSG) criteria for idiopathic RLS [1], a history of RLS symptoms on 3 or more days per week for at least 12 months, and an IRLS score of ≥ 15 at baseline, with an absence of significant RLS symptoms before 9 pm (measured by diary) but with significant sleep disturbance (≥ 3 days per week). In addition, patients had a WASO ≥ 60 min, a TST < 6.6 h, and a periodic limb movement arousal index (PLMAI) of ≥ 15 during baseline polysomnography. Furthermore, those with any secondary forms of RLS, current (but not past) presence of augmentation, a serum ferritin level < 18 µg/ml, currently being employed in shift work, or currently suffering from other clinically relevant diseases or undergoing treatment that could confound assessments or RLS symptoms were excluded from participating in this study.

If treated with drugs likely to influence sleep architecture or motor manifestations during sleep, a washout period of at least five half-lives was performed. If pretreated with levodopa or dopamine agonists, the washout period lasted 2 weeks.

2.5 Randomization, Allocation, and Blinding

A randomization list was obtained by an external pharmacy using a computerized allocation system with half the patients starting with placebo and the other half with suvorexant. Treatment assignment was implemented through an interactive voice response system. No access to the double-blind list was granted to the study investigators, site staff, patients, m-SIT scorers, or the monitoring staff during the entire study. Blinding was completed prior to receiving the drug at the study site; manufactured placebo capsules were equal in aspect, size, color, and taste to the active compound.

2.6 Data Analysis

We based our analysis on the hypothesis that treatment with suvorexant, when compared with placebo, might improve (or not, but never worsen) the primary and secondary endpoints.

The calculation of the sample size used the results of two previous studies [26, 27], which provided the estimation of the effect size for the primary endpoint.

Based on these data, we assumed a clinically meaningful mean difference of 25 min [standard deviation (SD) 40] on the WASO for suvorexant compared with placebo. Thus, with 29 participants (divided into two similar-sized groups) the study had at least 90% power to detect a difference between treatments on both primary endpoints if the true difference was at least 25 minutes.

Corresponding values for TST, the coprimary endpoint, were 6 and 5.5 h (range 0.1–0.9). The coprimary endpoint

required 31 individuals to obtain at least 90% power to detect a difference between treatments of 0.5 h.

However, to meet a sufficient effect size for the secondary endpoints, we increased the recruitment sample to 41 patients. For both primary and secondary endpoints, the test assumed a Type I error of 0.025 with one-sided testing.

All efficacy analyses were carried out using the intent-to-treat population (ITT), which was defined as all patients who were randomized.

The Kolmogorov–Smirnoff test was used to evaluate the normality of distributions. Paired sample tests were used to analyze dependent variables (primary and secondary endpoints), with the paired *t*-test used if data was normally distributed, and Wilcoxon test if not. We used a significance level of 0.01. All data used for statistical comparison were obtained from the end of each treatment condition. Statistical analyses were performed by means of SPSS V14 (SPSS Inc, Chicago, IL, USA).

3 Results

3.1 Patient Disposition and Demographics

The recruitment period started in July 2019 and finished in March 2021. As shown in Fig. 1, 43 individuals were screened, 41 were randomized, and 40 completed the study. Recruitment ceased when we met our predefined sample size of 41. Three patients had to discontinue prematurely: two left due to the severity of symptoms during the first wash-out period, and another person discontinued during the treatment period with placebo without ever receiving suvorexant.

Table 1 shows the mean (SD, %) clinical characteristics and demographics of the patient sample.

3.2 Efficacy Variables

There were no differences in any of the efficacy endpoints between patients first treated with placebo and those first treated with suvorexant. Furthermore, there were no

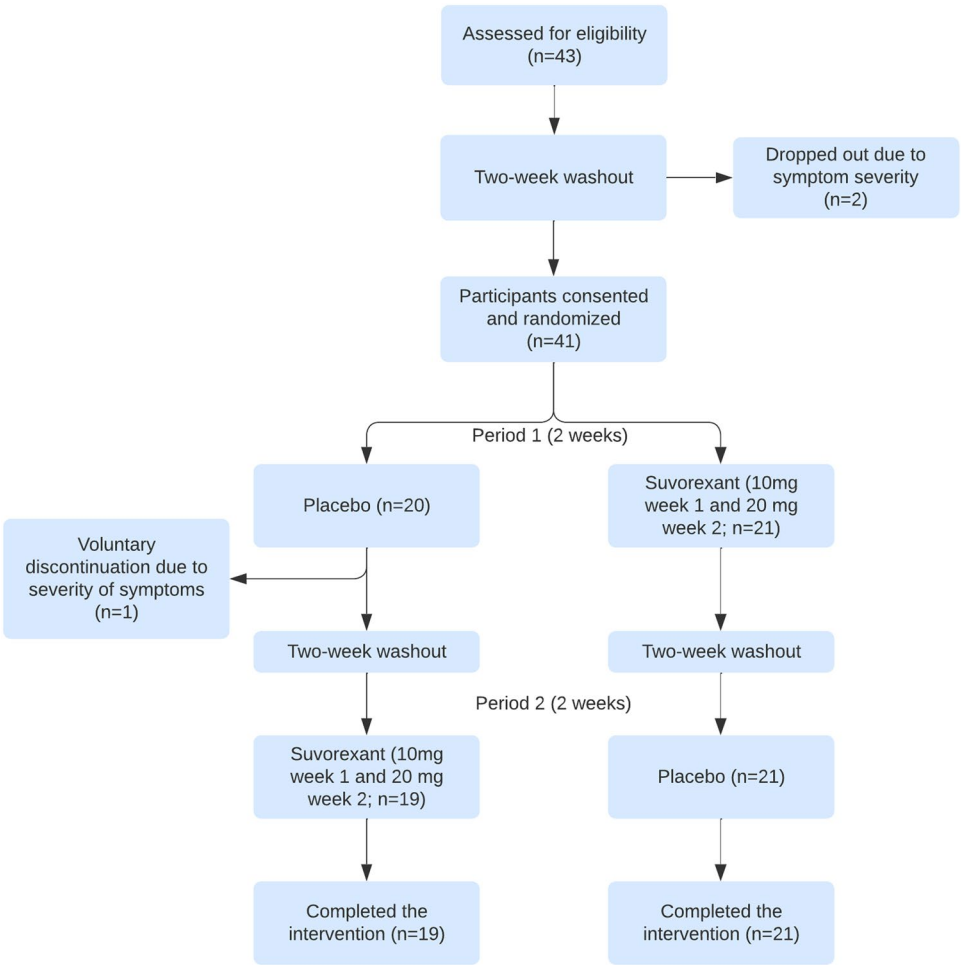

Fig. 1 Consort flowchart

Table 1 Summary of demographics (mean ± SD)

	Mean (SD)
Age (years)	52.7 (13.4)
Men/women (%)	36/64
Duration of disease (years)	17.9 (14.5)
Duration of disease since diagnosis (years)	13.4 (11.8)
Positive family history, *n* (%)	22 (55%)
Serum ferritin (ng/ml)	160.1 (135.5)
Duration of previous treatment (years)	11.2 (7.3)
Treatment with dopaminergics, *n* (%)	9 (22.5%)
Duration of previous treatment with dopaminergics (*n* = 9) (years)	8.1 (5.9)
Previous history of augmentation, *n* (%)	9 (22.5%)
Augmentation at screening, *n* (%)	0 (0%)

differences in bed and waketimes between the washout periods or treatment conditions.

3.2.1 Primary Endpoints: Effects on Sleep

Figure 2 shows the effects of suvorexant and placebo on WASO and TST (primary and coprimary endpoints). Following the 2-week treatment period with suvorexant, and compared with placebo, WASO decreased by a mean of 39.7 min (SD 24.3 min), while TST increased by a mean of 64.3 min (SD 32.2 min; both $p > 0.001$) (Table 2).

Table 3 shows additional sleep parameters as recorded on polysomnography under both treatment conditions. In addition to improving TST and WASO, suvorexant significantly improved sleep latency and sleep efficiency, decreased arousal index, N1%, N2%, and increased REM sleep (%).

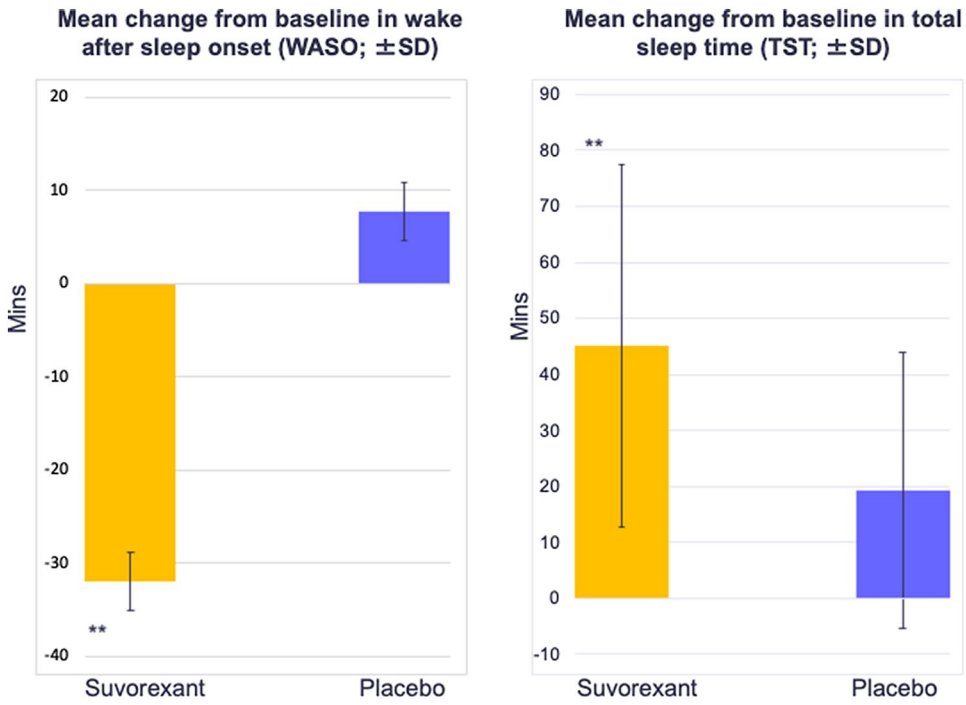

Fig. 2 The effects of suvorexant and placebo on WASO and TST (primary and coprimary endpoints) at the end of each study phase. Whiskers indicate one standard deviation above and below the mean of the dataset. $^{**}p < 0.001$

Table 2 Sleep parameters in both treatment groups

	Baseline (BL)		Suvorexant		Placebo		Mean difference		
	Mean	SD	Mean	SD	Mean	SD	δ (BL-SVX) versus δ (BL-placebo)	Wilcoxon (or *t*-test, when applicable)	*p*
Primary endpoints									
Total sleep time (min)[a]	314.6	57.3	359.7	25.0	295.4	32.7	− 64.3	− 12.6	< **0.001**
Wake after sleep onset (min)	44.1	17.9	12.2	14.7	51.9	21.0	46.5	802.0	< **0.001**

Table 3 Polysomnographic endpoints in both treatment groups

	Baseline (BL)		Suvorexant		Placebo		Mean difference		
	Mean	SD	Mean	SD	Mean	SD	δ (BL-SVX) versus δ (BL-placebo)	Wilcoxon (or *t*-test, when applicable)	*p*
PSG parameters									
PLM index (no./h)	39.0	10.4	18.2	12.1	37.1	9.9	18.9	6.6	< **0.001**
PLM arousal index (no./h)[a]	26.3	10.7	5.0	3.8	25.0	10.1	20.0	10.4	< **0.001**
Arousal index (no./h)	34.8	15.1	11.8	5.6	32.1	7.5	11.01	338.5	< **0.001**
Sleep latency (min)	29.5	10.1	13.4	11.4	31.6	13.4	19.8	737.0	< **0.001**
Sleep efficiency (%)	81.2	6.7	93.3	4.5	78.1	6.9	− 16.5	5.0	< **0.001**
N1 time (min)	28.5	11.7	25.2	12.9	24.8	10.2	0.4	459.0	n.s.
N2 time (min)[a]	194.1	50.9	221.6	41.9	213.0	46.6	− 8.7	− 1.1	n.s.
N3 time (min)	34.5	21.6	45.5	30.5	30.6	22.8	− 15.7	120.0	< **0.001**
REM time (min)	57.4	33.3	66.6	29.2	63.8	37.0	− 6.5	330.0	n.s.
N1%	9.6	4.4	7.1	3.8	8.5	3.6	1.4	695.0	< **0.001**
N2%	61.4	9.8	61.5	10.4	67.5	9.2	5.7	685.0	< **0.001**
N3%	11.4	6.9	12.7	8.5	10.5	7.9	− 1.7	247.0	n.s.
REM%	17.6	8.0	18.7	8.0	13.5	7.9	− 5.7	164.0	< **0.001**
REM latency (min)	121.4	108.9	91.6	42.0	105.6	94.7	3.0	441.0	n.s.
Cardiorespiratory parameters									
Mean HR[a]	64.1	8.4	63.9	8.5	63.9	8.5	− 0.04	0.0	n.s.
SaO_2 baseline (%)	93.9	1.4	94.2	1.7	93.9	1.5	− 0.5	151.0	n.s.
SaO_2 mean (%)	92.2	2.6	92.7	2.2	92.8	2.0	0.0	283.0	n.s.
CT-90 (%)	1.6	1.7	1.3	1.7	1.3	1.4	0.1	210.0	n.s.
Respiratory disturbance index (no./h)	7.7	5.7	8.6	5.1	7.4	5.4	1.7	923.0	n.s.

[a]*t*-test. If not specified, the comparative analysis was a Wilcoxon test

3.2.2 Secondary Endpoints

3.2.2.1 RLS Severity Rating Scales The IRLS scale and the CGI-I were used to assess subjective symptoms. Both instruments showed that the severity of RLS subjective symptoms was similar at the beginning of both treatment periods (see Table 4).

As shown in Fig. 3, treatment with suvorexant led to a greater improvement in the IRLS total score and CGI when compared with placebo. However, such improvement was particularly visible in the 31 patients who had not previously received dopaminergic treatment [IRLS mean (SD) change of − 15.1 (5.1) versus − 2.4 (5.8) for suvorexant and placebo, respectively]. In contrast, the nine patients who had been previously treated with dopaminergics improved under suvorexant by just − 4.6 (3.6) versus a worsening of 5.7 (4.2) under placebo.

3.2.2.2 Multiple Suggested Immobilization Test (m-SIT) As shown in Fig. 4a, compared with placebo, treatment with suvorexant led to a significant improvement in sensory disturbance as measured on the m-SIT-ds. As further shown in Fig. 4b, motor disturbance significantly improved as measured on the m-SIT under suvorexant, compared with placebo.

Table 4 Secondary endpoints in both treatment groups

Secondary endpoints	Suvorexant				Placebo				Mean differences		
	BL	SD	Week 2	SD	BL	SD	Week 2	SD	δ (BL-SVX) versus δ (BL-placebo)	Wilcoxon (or *t*-test, when applicable)	*p*
IRLS scale	26.3	5.1	11.5	7.8	25.8	4.8	24.2	7.0	− 11.6	− 14.0	< **0.001**
CGI–S	4.7	1.5	3.0	1.6	4.4	1.6	4.6	1.5	− 1.3	− 6.4	< **0.001**
m-SIT discomfort scale	–	–	*18.6*	*8.3*	–	–	29.5	11.9	− 10.9	− 5.5	< **0.001**
MOS scale	*3.0*	*1.7*	*5.2*	*1.9*	2.6	1.3	2.7	1.2	− 2.16	+ 8.283	< **0.001**

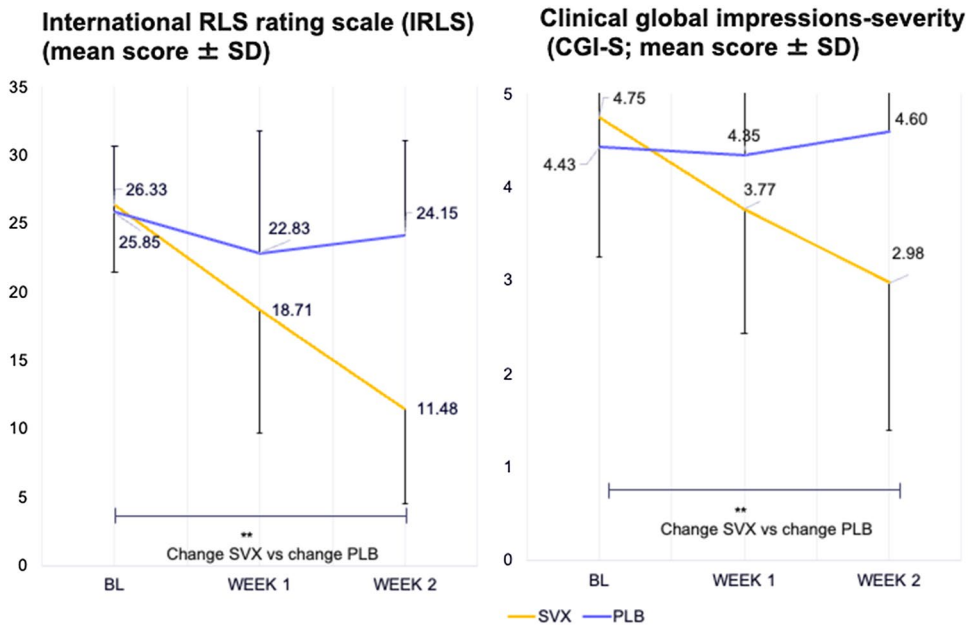

Fig. 3 The effects of suvorexant (SVX) and placebo (PLB) on the IRLS scale and the CGI across treatment conditions. On either side, the *p* value represents a paired *t*-test for repeated samples performed on change [baseline (BL) versus week 2] on SVX versus PLB. $^{**}p < 0.001$

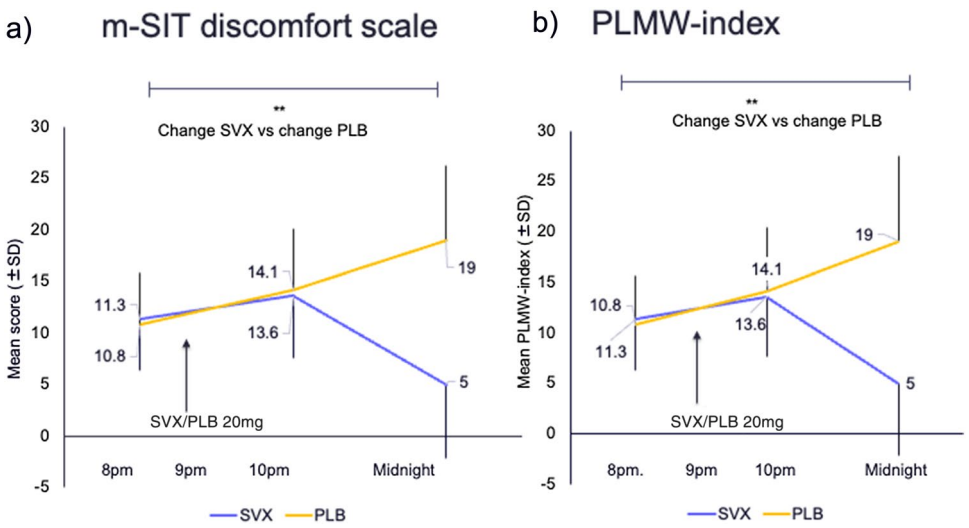

Fig. 4 Multiple suggested immobilization tests with suvorexant (SVX) and placebo (PLB). Comparisons were performed by means of a paired *t*-test for repeated samples performed on change (baseline versus week 2) on SVX versus PLB. **A**) shows the result of an m-SIT-discomfort scale (showed as the sum score, see methods) in all three SITs (8pm, 10pm, and midnight). On the right, graph **B**) shows the PLMW-index (PLM during wakefulness per hour). ** $P < 0.001$. *m-SIT* multiple suggested immobilization test, *PLB* placebo, *PLMW* periodic limb movements while awake, *SVX* suvorexant

3.2.2.3 Periodic Leg Movements During Sleep and Arousal PLMSI and PLMAI were significantly lower during treatment with suvorexant (see Table 3).

3.2.2.4 Subjective Sleep (MOS Scale) Subjective sleep reports were evaluated using the Sleep Adequacy Subscore of the MOS-sleep. As shown in Fig. 5, treatment with suvorexant led to a significant improvement in sleep adequacy.

3.2.2.5 VAS Scale Due to the small number of subjects reporting pain (six), no analyses was performed on the VAS scale.

3.3 Adverse Events

Table 5 shows the list of reported adverse events under both treatment conditions. Overall, 12.5% of patients reported adverse events under suvorexant, compared with 17.5%

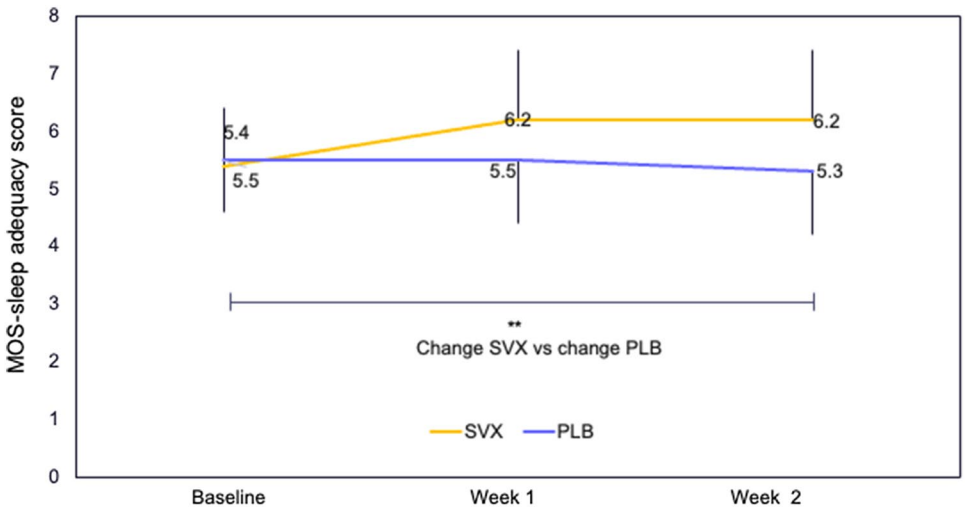

Fig. 5 MOS sleep adequacy score across both treatment condictions. Comparisons were performed by means of a paired T-test for repeated samples performed on change (baseline vs week 2) on suvorexant vs placebo

Table 5 Adverse effects on both treatment groups

	Suvorexant ($n = 40$)	Placebo ($n = 40$)
Any	5 (12.5%)	7 (17.5%)
Headache	5 (12.5%)	8 (20%)
Low back pain	2 (5%)	0 (0%)
Daytime somnolence	2 (5%)	0 (0%)
Abnormal dreams	2 (5%)	1 (2.5%)
Dizziness	1 (3%)	1 (2%)
Depression	1. (2.5%)	0 (0%)
Gastric pain/reflux	0 (0%)	2 (5%)
Diarrhea	0 (0%)	2 (5%)

under placebo. Low back pain, daytime somnolence, abnormal dreams, dizziness, and depression occurred more frequently under suvorexant than under placebo.

4 Discussion

Our study shows that suvorexant improves sleep patterns such as TST and sleep maintenance (as reflected by WASO) in patients with RLS. Notably, it also markedly improved our predefined secondary endpoints, namely RLS subjective symptoms (focal akathisia, etc.), as shown on the IRLS scale, CGI, and the m-SIT. Furthermore, there were significant improvements in PLMs both during wakefulness (as shown on the m-SIT) and during sleep. Polysomnographic recordings also showed an improvement in other sleep architecture measures with improvements in sleep latency, N1%, N2%, and the arousal index, as well as an increase in sleep efficiency and REM%. Overall, these improvements in sleep architecture are consistent with previous findings on suvorexant in other conditions such as chronic insomnia disorder [28].

Interestingly, our data suggest a potential dose-dependent relationship between suvorexant dose and the magnitude of therapeutic effects. In other words, exposure to 10 mg suvorexant resulted in a minor effect, neither clinically nor statistically significant compared with placebo). Only when 20 mg were administered could a meaningful difference be observed.

An alternative explanation would be to attribute the improvement less to the dosage and more to the treatment duration. While this is unlikely, given that no other RLS treatments have ever shown "latency to treatment effects" as is the case with antidepressants, for example, it cannot be ruled out. To investigate the potential treatment effect of dose or time dependency, future controlled studies may consider using parallel designs with multiple treatment arms, maintaining constant doses, and extending the duration of treatment.

All these findings were observed following a short-term, 2-week, administration of 20 mg suvorexant (10 mg during the first week), and in our view, constitute the first proof of concept of the therapeutic efficacy of DORAs, not just on sleep, but more importantly on RLS symptoms. In this way, the clinical relevance of these findings is that they show, for the first time, that non-dopaminergic, non-glutamatergic drugs can be effective and clinically useful for the treatment of RLS. However, studies with longer treatment periods are needed to demonstrate the persistence of efficacy over the long term, as our study only exposed patients to 2 weeks of treatment.

None of the patients included in this study had dopaminergic augmentation at the time of the study, and few had been previously treated with dopaminergic agents. In an earlier study, we showed that previous dopaminergic treatment impairs the response of patients with RLS to non-dopaminergic treatments [29]. Indeed, patients who had received previous dopaminergic treatment showed a

smaller improvement on suvorexant compared with those who had never been exposed to dopaminergics. Suvorexant was well tolerated in RLS, with relatively few and mild adverse events.

This study was conceived as a proof-of-concept investigation designed to explore a positive signal of suvorexant on RLS symptoms and sleep. However, its main limitations are the relatively small sample size and its short duration, which might have limited any generalization regarding efficacy and safety. It is also possible that the crossover design reduced the habitual placebo response found in most parallel designs in RLS [30].

As suvorexant is the first dual orexin antagonist to have been investigated in RLS, the inevitable question is how a drug specifically acting on orexin receptors exerts such therapeutic effects. First, it is possible, although still controversial [17, 18], that patients with RLS have increased CSF orexin levels in the evening. Second, orexin plays a substantial role in pain regulation: orexin receptors are displayed in the nucleus accumbens [31, 32], locus coeruleus, thalamus [33], and periaqueductal gray, but also in the dorsal root ganglia and spinal cord, and are thought to play a role in sensory processing [34–36]. Orexin neurons co-release dynorphin, an agonist of opioid kappa-receptor [37]. Orexin antagonists would, thus, act as a kappa-receptor antagonist, thereby improving RLS symptoms. Orexin also stimulates dopaminergic neurons at the ventral tegmental area, increasing dopaminergic function [38]. Finally, melanin-concentrating hormone neurons co-release glutamate, thereby causing RLS [39]. Furthermore, it is unclear whether DORAs could have the same therapeutic effects on RLS symptoms in circumstances where orexin activity remains low, like in the case of RLS coexisting with narcolepsy type 1 [40].

5 Conclusions

Our study provides proof of evidence of the therapeutic effects of suvorexant on RLS symptoms. These included sleep disturbance as well as sensory–motor symptoms. Further research is needed to establish the long-term efficacy and safety of suvorexant in RLS, as well as the generalizability of these therapeutic effects with other orexin antagonists.

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Declarations

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Conflict of interest Dr. Garcia-Borreguero has received research grants from MSD and Roche and consultancy fees from Idorsia. Drs. Garcia Aragón, Moncada, Romero, Granizo, Quintas, and Castillo report no conflicts of interest.

Availability of data and materials The data generated during the course of this study are available upon reasonable request. The study protocol can be viewed by contacting the corresponding author. No changes were made to the methods, including outcomes, after trial commencement.

Ethics approval The study was performed at the Sleep Research Institute, in Madrid, Spain, and approved by the local institutional review board (CEIC Hospital La Princesa, Madrid) on Dec 23, 2017 (approval number: 21/2017).

Author contributions DGB conceived and designed the analysis; DGB, AG, BM, and SR collected and analyzed the data. Statistical analysis completed by JJG. All authors contributed to the analysis of data and the writing of the paper, approved the current manuscript, and accepted its submission to CNS Drugs.

Consent for publication Not applicable.

Consent to participate Written informed consent was obtained from all participants.

Code availability Not applicable.

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