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A double-blind, randomized, placebo-controlled plus open trial of adjunctive suvorexant for treatment-resistant insomnia in patients with bipolar disorder

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Abstract

Background. Sleep pattern alteration is a core feature of bipolar disorder (BD), often challenging to treat and affecting clinical outcomes. Suvorexant, a hypnotic agent that decreases wakefulness, has shown promising results in treating primary insomnia. To date, data on its use in BD are lacking. This study evaluated the efficacy and tolerability of adjunctive suvorexant for treatment-resistant insomnia in BD patients.

Methods. Thirty-six BD outpatients (19 BDI, 69.4% female, 48.9 [±15.2] years) were randomized for 1 week to double-blind suvorexant (10–20 mg/day) versus placebo. Then, all subjects who completed the randomized phase were offered open suvorexant for 3 months. Subjective total sleep time (sTST) and objective total sleep time (oTST) were assessed.

Results. During the randomized control trial (RCT) phase, an overall increase in the oTST emerged, which was statistically significant for the Cole–Kripke algorithm (p = 0.035). The comparison between the suvorexant and placebo groups was limited by significant differences between measurements at baseline. During the open phase, no significant improvement was detected relative to either sTST and oTST. No adverse events nor major intolerances were reported.

Discussion. Efficacy results are inconsistent. During the RCT phase, only a small increase in the objective oTST emerged, while during the open phase, no significant improvement was detected. While this is the first ever study of suvorexant in BD-related insomnia, the limitation of the small sample and the high rate of dropouts limits the generalizability of these findings. Larger studies are needed to assess suvorexant in treating BD-related insomnia.

Introduction

Sleep disruption represents a common feature of all phases of bipolar disorder (BD). Insomnia and hypersomnia are core symptoms of depressive episodes, while insomnia and decreased need for sleep are commonly observed during manic and hypomanic episodes. However, subjective sleep disturbances persist even during euthymia in most patients, despite treatment.[1–3] Abnormal sleep patterns have been also found in actigraphy studies, during both acute and remission periods.[4,5]

It is worth noting that sleep disturbances not only affect those with psychiatric illness but are also a common complaint in up to one third of the general population, affecting global health and quality of life.[6] The correlation between sleep disorders and the activation of the inflammatory response may in fact lead to the development and perpetuation of certain conditions, such as cognitive disorders, diabetes, cardiovascular diseases, and many psychiatric disorders.[7–10]

More specifically, growing evidence suggests that sleep pattern instability and alterations lead to worse clinical outcomes and relapse in BD. Sleep disturbance in remitted BD patients may represent a prodrome of an impending mood episode,[1] since it is often the earliest symptom of mania and the sixth most common in the presentation of depression,[11] whereas improvement in sleep quality during an acute mood phase may be an early marker of recovery from the episode.[1] Prospective studies show that poor sleep during euthymia is associated with worse subsyndromal symptoms and leads to earlier relapses.[12,13] Among 89 BD patients who achieved recovery from a

mood episode and were subsequently followed longitudinally in the Stanford Bipolar Disorders Clinic for at least 1 year, worse daytime dysfunction, subjective sleep quality, sleep latency, and global sleep disturbance on the Pittsburgh Sleep Quality Index (PSQI)[14] were associated with the presence of subsyndromal mood symptoms.[13] In addition, worse PSQI daytime dysfunction significantly predicted a shorter time to mood episode recurrence.[13] Furthermore, data from 2024 BD patients enrolled in the National Institute of Mental Health Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) showed that 32% of the patients had shorter sleep duration, associated with more severe symptomatology, and 23% longer sleep duration. Both altered sleep patterns were associated with poorer function and quality of life compared to normal sleep duration.[2]

Insomnia associated with BD can be challenging to treat, and the role of currently available medications in the long-term treatment of sleep pattern alteration is still unclear.[15] Suvorexant (Belsomra) is a novel hypnotic agent that promotes sleep via orexin receptor antagonism: it selectively binds to orexin 1 and 2 receptors, thereby decreasing wakefulness.[16,17]

Clinical trials have shown suvorexant to be effective and well-tolerated in the treatment of primary insomnia, in doses of 10–20 mg at bedtime.[18] Furthermore, a recent meta-analysis, conducted on 3,076 subjects from 4 randomized controlled trials (RCTs) comparing suvorexant with placebo, found that suvorexant was associated with a significant reduction in the subjective time to sleep onset at 1 month (95% confidence interval [CI], 5.38–13.00 minutes) and at 3 months (95% CI, 5.65–13.26 minutes), with an increased subjective total sleep time (sTST) at 1 month (95% CI, 14.19–26.00 minutes) and at 3 months (95% CI, 12.53–24.58 minutes).[19]

Despite the evidence of suvorexant efficacy in primary insomnia, there is a lack of data on its benefits and risks in mood disorders, where sleep issues may be among the primary complaints and concerns of patients. A recent review evaluating the role of orexins in the pathophysiology and treatment of depression suggested that orexin antagonists, like suvorexant, are promising as an augmenting treatment for major depressive disorder with residual insomnia, with notable benefits compared with currently available hypnotics.[20]

To the best of our knowledge, there is a single case report of an adolescent with BD type I with improved sleep using suvorexant after failure of multiple other agents.[21] This report is in line with a recent systematic review and meta-analysis on hypnotic and melatonin/melatonin-receptor agonist treatment in BD, in which authors could not identify consistent studies on the use of suvorexant in bipolar patients.[15] Insomnia, as a core symptom and a worse prognostic feature, still represents a challenge in BD. Even though suvorexant has shown encouraging results in treating primary insomnia in the general population and in patients with MDD, evidence on its efficacy in BD is limited. Thus, there is an unmet need for further investigating the use of suvorexant as a potentially effective option in sleep cycle regulation in BD.

We conducted a randomized, double-blind, placebo-controlled study assessing the efficacy of adjunctive (added to existing treatments) suvorexant in depressed or euthymic (but not hypo/manic) patients with BD (type I, type II, or type not otherwise specified [NOS]) with persistent complaints of insomnia despite treatment with traditional hypnotic agents, anxiolytics, atypical antipsychotics, mood stabilizers, and/or antidepressants.

We hypothesized that adjunctive suvorexant 20 mg at bedtime compared to adjunctive placebo for 1 week would yield significantly greater increases in sTST, as assessed by self-report, as well as in objective total sleep time (oTST), as assessed by sleep actigraphy. Second, we hypothesized that adjunctive open suvorexant 20 mg at bedtime for 3 months, would increase both sTST and oTST. Therefore, we first aimed to assess the acute (1 week) efficacy of adjunctive suvorexant, and second assess its possible chronic (3 months) effectiveness on treatment-resistant insomnia in BD patients.

Methods

Subjects

This study was approved by the Stanford University Administrative Panel on Human Subjects. All subjects provided verbal and written informed consent prior to participation. Adult outpatients aged 18 years and older who met Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (DSM-IV-TR)[22] criteria for BDI, BDII, or BDNOS, with concurrent insomnia associated with BD (with sTST <6 hours on at least 1 night during the prior week) were recruited at the Stanford Bipolar Disorders Clinic and at Veterans Affairs (VA) Palo Alto Health Care System Bipolar and Depression Research Program. At enrollment, they were taking 1 or more prescription psychotropic medications (hypnotic agents, anxiolytics, atypical antipsychotics, mood stabilizers, and/or antidepressants) for management of BD. Subjects were also required to be evaluated during the study by the STEP-BD clinical monitoring form (CMF).[23] Subjects were excluded if they: (1) had hypo/manic symptoms, at baseline visit, as evidenced by Young Mania Rating Scale (YMRS)[24] total score ≥12; (2) had alcohol or substance use disorder, at baseline visit or in the past 6 months, as determined by assessment with the Mini-International Neuropsychiatric Interview (MINI)[25]; (3) had psychosis at baseline visits, as determined by assessment with the MINI; (4) had clinically significant abnormalities on baseline laboratory tests (comprehensive metabolic panel, fasting lipid panel, blood cells count with differential, and thyroid stimulating hormone); (5) had any unstable and/or potentially confounding neurological and/or medical disorder; or (6) were pregnant or breastfeeding women (Table 1).

Study design

Participants who met study entry criteria were randomized to receive either adjunctive double-blind placebo or adjunctive double-blind suvorexant 10 mg at bedtime for 3 nights, which was then

Table 1. Inclusion and Exclusion Criteria for the Recruitment in the Study

Inclusion criteria	Exclusion criteria
• Age > 18 years • DSM–IV–TR diagnosis of BDI, BDII, and BDNOS • Insomnia: sTST <6 h at least 1 night in the prior week • Ongoing therapy with psychotropic medications for the management of BD	• Baseline YMRS ≥ 12 • Alcohol or substance use disorder at baseline or in the prior 6 mo[a] • Psychotic symptoms at baseline[a] • Clinically significant anomalies at baseline laboratory tests • Unstable or potentially confounding neurological or medical disorder • Pregnant and breastfeeding women

Abbreviation: BDNOS, bipolar disorder, not otherwise specified; BDI, bipolar disorder, type I; BDII, bipolar disorder, type II; DSM-IV-TR, Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision (APA, 2000).

[a]As determined by assessment with MINI: Mini-International Neuropsychiatric Interview (Sheehan et al., 1998).

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increased to 20 mg at bedtime for 4 nights. Following the 1-week RCT phase, all subjects received open suvorexant 10 mg at bedtime for 3 nights, which was then increased to 20 mg at bedtime for 3 months. All subjects who completed the randomized phase of the trial (ie, those in both the active drug and placebo groups) were started on a 10-mg dose at the start of the open treatment phase to protect the blind.

Efficacy and safety assessments

Screening evaluation (V screen), 1 week before the randomization, included diagnostic and clinical symptom assessments, and laboratory tests. Diagnostic assessments were made with the STEP-BD Affective Disorders Evaluation,[26] MINI, and DSM-IV-TR insomnia related to BD checklist. Clinical symptoms assessments included the STEP-BD CMF, sTST, YMRS, and Montgomery–Åsberg Depression Rating Scale (MADRS).[27] Laboratory tests consisted of a comprehensive metabolic panel, fasting lipid panel, complete blood count with differential, thyroid stimulating hormone, and urine pregnancy test (only for women of reproductive potential). Evaluations performed at Controlled Week-0 (V1: randomization; beginning of 1 week of double-blind, placebo-controlled adjunctive suvorexant), Controlled Week-1 (V2: end of 1 week of double-blind, placebo-controlled adjunctive suvorexant), Open Month-1 (V3: after 1 month of open suvorexant), Open Month-2 (V4: after 2 months of open suvorexant), Open Month-3 (V5: after 3 months of open suvorexant) included the following assessments: STEP-BD CMF, YMRS, MADRS, electronic self-report sleep diary including sTST, sleep actigraphy including oTST assessed with actigraphy watch (ActiGraph GT9X Link, https://actigraphcorp.com/actigraph-link/) using Sadeh and Cole–Kripke (CK) algorithms, Frequency and Intensity of Side Effects Ratings/Global Rating of Side Effects Burden (FISER/GRSEB).[28] Study procedures and subject flow are shown in Figure 1.

Statistical analysis

Statistical analyses assessed sTST, according to self-report, at Controlled Week-0, Controlled Week-1, Open Month-1, Open Month-2, and Open Month-3; and oTST, according to the actigraphy watch, at Controlled Week-0, Controlled Week-1, Open Month-1, Open Month-2, and Open Month-3. Descriptive statistics were performed using the independent samples *T*-test for continuous variables and the chi-square test for categorical variables, comparing demographic and clinical characteristics of the 2 subgroups (drug vs. placebo). For the RCT phase, outcomes for adjunctive suvorexant versus adjunctive placebo were assessed using paired- and unpaired-samples *T*-tests comparing subjects for which measurements for both phases of the evaluation were available (ie, excluding subjects with missing data at V1 and V2). For the open extension study, the outcomes were assessed in the

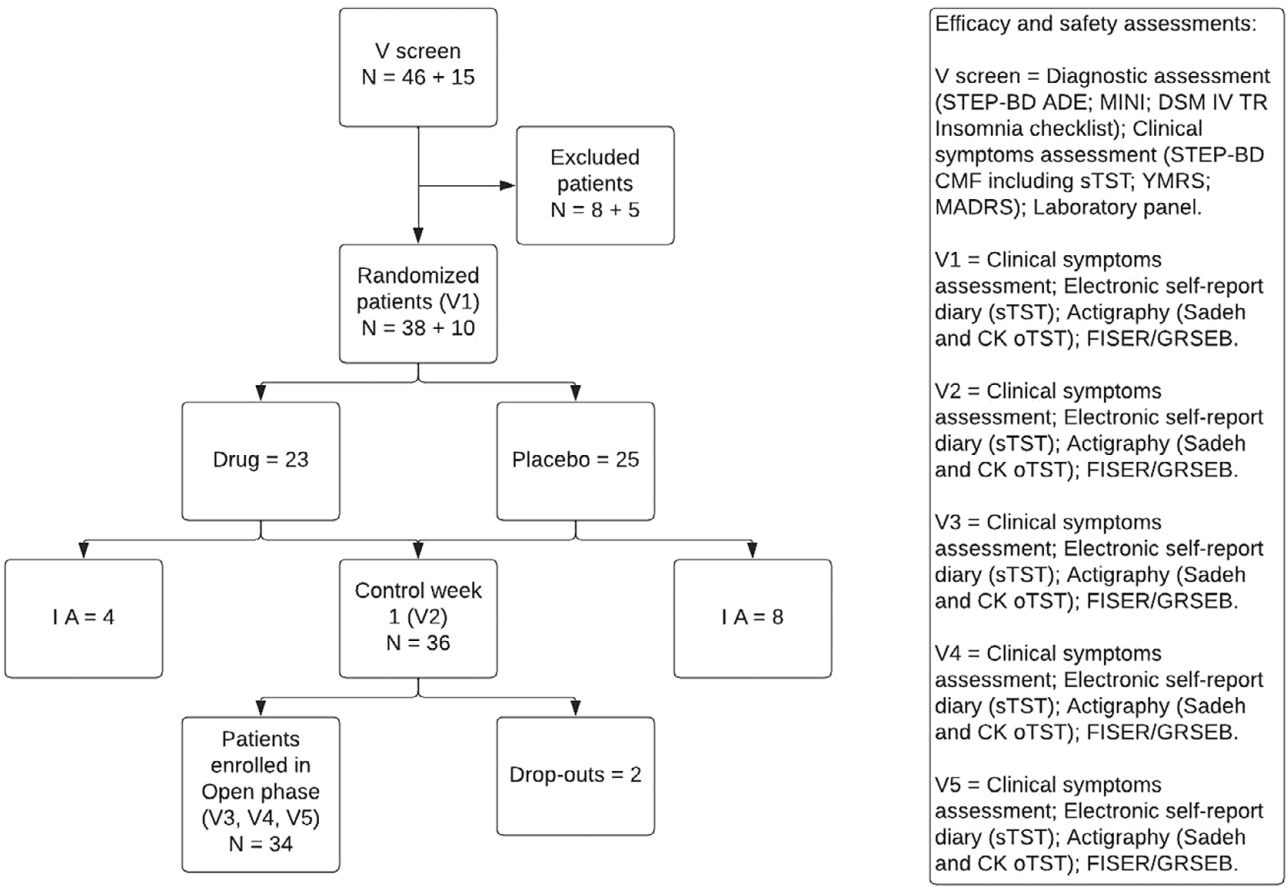

Figure 1. Study design and efficacy and safety assessments. The number of subjects showed at V screen, excluded patients and randomized patients, refers to the ones evaluated at Stanford + VA sites. IA: inappropriate allocation; V screen: screening visit, 1 week before randomization; V1: Control Week-0, the begin of the RCT phase; V2: Control Week-1, the end of the RCT phase; V3: Open Month-1, the end of the first month of the open phase; V4: Open Month-2, the end of the second month of the open phase; V5: Open Month-3, the end of the third month of the open phase.

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entire group and controlled by acute treatment arm (ie, blind adjunctive suvorexant followed by open adjunctive suvorexant and blind adjunctive placebo followed by open adjunctive suvorexant), using paired- and unpaired-samples *T*-tests. Two subjects dropped-out before terminating the RCT phase and were therefore excluded from the open phase. Of the 34 subjects who enrolled in the subsequent phase, analyses were carried out including subjects who completed at least 1 evaluation during the 3 months of trial (ie, subjects with at least 1 measurement at either V3, V4, or V5), collectively designated as VO (any visit during the open phase months). In order to account for the great number of missing data and dropouts, generalized linear mixed models for repeated measures (GLMM–RM) were then used to analyze the sample both for the RCT phase and the open phase, controlling for time and dropouts in both study phases and randomization (drug vs. placebo) in the open phase only. Statistical significance was set at $p < 0.05$. Analyses were performed using Statistical Package for the Social Sciences (SPSS) Version 27, Release 27.0.0 (IBM Corporation, Somers, NY, USA) software.

Results

Patient characteristics and dispositions

At baseline, 46 patients were screened at the Stanford site, of whom 8 were excluded (2 because of substance use, others withdrew consent after learning study requirements, including wearing actigraphy watch and monitoring sleep daily) and 15 at VA site, of whom 5 were excluded (1 for separate medical issues, 1 for substance use, 1 for new medication added prior to study, and 2 for sleep disorder on screen). Hence, 38 subjects were randomized at Stanford and 10 at VA. Among 38 patients recruited at Stanford, 17 were allocated on drug and 21 on placebo. However, 4 in the drug group and 8 in the placebo were inappropriately allocated during the study week, because of a mistake in coding of bottles leading to a mixed suvorexant and placebo being received mid-week during the blinded 1-week treatment phase. This error was reported to the Institutional Review Board, and these subjects excluded from the subsequent analyses. Among 10 patients enrolled at VA, 6 were allocated on drug and 4 on placebo. Hence, 36 subjects (19 BDI, 15 BDII, 2 BDNOS, 69.4% female, mean [±SD] age 48.9 [±15.2] years) were randomized to suvorexant ($N = 19$) versus placebo ($N = 17$). Baseline demographics and clinical characteristics of the 36 subjects enrolled in the study are shown in Table 2. There were no substantial differences between the 2 groups in terms of sociodemographic and clinical characteristics, except for the higher rate of concurrent prescription of mood stabilizers in the control group compared to the drug group (14 vs. 9, $p = 0.029$). At baseline, 44.4% (16/36) of subjects were taking antipsychotics, more than half of subjects (61.11%, 22/36) were taking hypnotics/benzodiazepines, and 58.3% (21/36) were on antidepressants, while 47.2% (17/36) were on other psychotropic drugs. Of note, during follow-up, 18 withdrawals (2 in the RCT [1 placebo, 1 drug]; 16 in Open) were registered at Stanford: 1 for perceptual disturbances, 1 for sleep paralysis, 1 for sleep walking, 3 for nonadherence (new job, school), 2 for not wearing the actigraphy watch appropriately, 2 for distance from the study site, 5 for inefficacy, 1 for loss of follow-up, and another one for sudden mania (not assessed to be related to study procedures). Another 4 withdrawals (all in the open phase) were registered at VA site: one for loss to follow-up, one for intolerance, one for depression, and another one for nonadherence.

Table 2. Sociodemographic and Clinical Variables of the Whole Sample

	Suvorexant group Mean ± SD or *N* (%)	Placebo group Mean ± SD or *N* (%)	All subjects Mean ± SD or *N* (%)
N	19 (52.8%)	17 (47.2%)	36 (100%)
Age (years)	52.84 ± 14.792	44.53 ± 14.841	48.92 ± 15.197
Gender (female)	14 (56%)	11 (44%)	25 (69.4%)
Race/ethnicity			
Asian	1 (5.3%)	0	1 (2.8%)
Black	1 (5.3%)	2 (11.8%)	3 (8.3%)
Hispanic	0	2 (11.8%)	2 (5.5%)
White	12 (63.2%)	9 (52.9%)	21 (58.3%)
Multi/other	5 (26.3%)	3 (17.6%)	8 (22.2%)
Marital status			
Single	6 (31.6%)	8 (47.1%)	14 (38.9%)
Married	9 (47.4%)	5 (29.4%)	14 (38.9%)
Divorced/separated	3 (15.8%)	4 (23.5%)	7 (19.4%)
Education			
High school	1 (5.3%)	1 (5.9%)	2 (5.5%)
Some college	3 (15.8%)	3 (17.6%)	6 (16.7%)
College degree	3 (15.8%)	5 (29.4%)	8 (22.2%)
Some grad school	4 (21.1%)	0	4 (11.1%)
Graduate degree	2 (10.5%)	4 (23.5%)	6 (16.7%)
Employment			
Full time	8 (42.1%)	9 (52.9%)	17 (47.2%)
Disabled	1 (5.3%)	3 (17.6%)	4 (11.1%)
Student	2 (10.5%)	1 (5.9%)	3 (8.3%)
Unemployed	4 (21.1%)	2 (11.8%)	6 (16.7%)
Retired	2 (10.5%)	0	2 (5.5%)
Diagnosis			
Bipolar I	11 (57.9%)	8 (47.1%)	19 (52.8%)
Bipolar II	7 (36.8%)	8 (47.1%)	15 (41.7%)
Bipolar NOS	1 (5.3%)	1 (5.9%)	2 (5.5%)
Illness characteristic			
Onset age (years)	23.56 ± 3.48	21.5 ± 2.57	22.59 ± 2.178
Illness duration (years)	29 ± 4.04	24.3 ± 3.39	26.79 ± 2.66
Rapid cycling prior year	4 (21.1%)	4 (23.5%)	8 (22.2%)
Baseline clinical characteristic			
No. of concurrent psych meds	3.32 ± 0.54	3.94 ± 0.46	3.61 ± 0.35
No. of concurrent non–psych meds	4.11 ± 1.30	2.71 ± 1.07	3.44 ± 0.85
Concurrent meds			
Mood stabilizer*	9 (47.4%)	14 (82.4%)	23 (63.9%)
Antipsychotic	8 (42.1%)	8 (47.1%)	16 (44.4%)
Sedative/hypno	11 (57.9%)	11 (64.7%)	22 (61.1%)

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Table 2. *Continued*

	Suvorexant group Mean ± SD or *N* (%)	Placebo group Mean ± SD or *N* (%)	All subjects Mean ± SD or *N* (%)
Antidepressant	11(57.9%)	10 (58.2%)	21 (58.3%)
Other psychotropics	7 (36.8%)	10 (58.2%)	17 (47.2%)
Baseline clinical status			
Recovered	9 (47.4%)	5 (29.4%)	14 (38.9%)
Continued symptomatic	5 (26.3%)	4 (23.5%)	9 (25%)
Depression	5 (26.3%)	7 (41.2%)	12 (33.3%)
Mania	0	0	0

Note: No other significant difference ($p < 0.05$) was found between the groups, that is, blind adjunctive suvorexant followed by open adjunctive suvorexant and blind adjunctive placebo followed by open adjunctive suvorexant.
*$p < 0.05$ (between groups).

Efficacy measures

Randomized controlled phase

Results from the RCT phase are shown in Table 3. Of the 36 recruited subjects, 6 subjects (16%) (2 from the drug group vs. 4 from the placebo group) did not report at least 1 efficacy measure at week 1 (V2). Therefore, they were excluded from the analysis. sTST was provided from 14 subjects from the drug group and 10 subjects from the placebo group. oTST, analyzed with both Sadeh and CK algorithms, was collected from 14 subjects from the blinded medication group (82% of these subjects). From the placebo group, data for the Sadeh algorithm were available for 11 subjects (84% of the placebo group), while for the CK algorithm data were available for 10 subjects (77% of the placebo group).

Table 3. Randomized Blinded Controlled Phase: Week 0 (V1), Week 1 (V2), and Change in Mean (±SD) Subjective and Objective Total Sleep Time, and YMRS and MADRS Scores

	Suvorexant group (n = 14)	Placebo group (n = 10)
sTST V1	7.04 ± 1.16	7.03 ± 0.55
sTST V2	7.53 ± 1.43	7.20 ± 0.68
sTST V2–V1	0.49 ± 1.03	0.17 ± 0.90
	Suvorexant group (n = 14)	Placebo group (n = 11)
Sadeh oTST V1	6.30 ± 1.90	8.56 ± 4.54
Sadeh oTST V2	6.83 ± 2.33**	9.63 ± 3.90**
Sadeh oTST V2–V1	0.54 ± 1.71	1.07 ± 3.10
	Suvorexant group (n = 14)	Placebo group (n = 10)
CK oTST V1	6.46 ± 2.06**	9.50 ± 4.64**
CK oTST V2	7.20 ± 2.60**	10.10 ± 4.10**
CK oTST V2–V1	0.74 ± 1.17*	0.61 ± 3.15
	Suvorexant group (n = 17)	Placebo group (n = 13)
YMRS V1	5.24 ± 3.77	5.46 ± 3.99
YMRS V2	4.76 ± 3.55	5.77 ± 4.87
YMRS V2–V1	−0.47 ± 4.50	0.31 ± 1.70
	Suvorexant group (n = 17)	Placebo group (n = 13)
MADRS V1	13.24 ± 8.58	18.46 ± 9.58
MADRS V2	13.18 ± 7.47	15.46 ± 12.73
MADRS V2–V1	−0.06 ± 6.35	−3.00 ± 8.82

Note: The number of subjects reported for each measurement corresponds to the number of subjects for which that measure was available at both time points. No other significant differences ($p < 0.05$) were found within or between groups.
Abbreviation: CK, Cole–Kripke's algorithm; oTST, objective total sleep (actigraphy); Sadeh, Sadeh's algorithm; sTST, subjective total sleep.
*$p < 0.05$ (within group difference).
**$p < 0.05$ (between group difference).

Mean sTST (hours) (±SD) change from week 0 (V1) to week 1 (V2) was 0.49 ± 1.03 hours in the suvorexant group versus 0.17 ± 0.90 hours in the placebo group, with no statistically significant difference within groups and between them. When considering the oTST collected through the Sadeh algorithm, the mean change from V1 to V2 was an increase of 0.54 ± 1.71 hours in the suvorexant group and increase of 1.07 ± 3.10 hours in the placebo group, with no statistically significant difference between the changes in the two means. However, considering the mean oTST Sadeh at V2, there was a statistically significant difference ($p = 0.036$) between the 2 groups (6.83 ± 2.33 in the drug group vs. 9.63 ± 3.90 hours in the placebo one). Analyzing oTST data collected through the CK algorithm, the mean change between V1 and V2 of the suvorexant-treatment group was 0.74 ± 1.17 hours, with a statistically significant within-group difference ($p = 0.035$). Even though no statistically significant difference was found comparing the mean change between the 2 groups, there was a significant difference in the absolute values of oTST CK at V1 (6.46 ± 2.06 hours in the drug group vs. 9.50 ± 4.64 hours in the placebo one, $p = 0.04$) and at V2 (7.20 ± 2.60 hours for the suvorexant group vs. 10.10 ± 4.10 hours in the placebo one, $p = 0.045$).

When using GLMM–RM to evaluate the influence of randomization, time, and dropouts on sTST values, the model failed to predict significant differences between suvorexant and placebo groups, as well as between subjects that completed the first week of the trial and those who did not. Evaluating both Sadeh and CK oTST values, the GLMM–RM detected a significant negative correlation of randomization on oTST values ($p = 0.011$ for Sadeh and $p = 0.015$ for CK oTST), with no significant influence by time and dropouts. This result reflects the great difference between the 2 groups both at V1 and V2, with higher mean values reported by the placebo group at each time point.

No significant difference between the scores of the YMRS and the MADRS were detected at V1 or V2, nor did these symptom scores change significantly during the trial.

Open phase

Results from the open phase of the study are shown in Table 4. Given the high rate of dropouts and the small size of the sample, we included in the analyses subjects who completed at least one of the evaluations for the open phase (i.e., either V3, V4, or V5, collectively designated as VO). For sTST, data were collected from 24 subjects (67%), while oTST with Sadeh and CK algorithms were collected from 24 (67%) and 23 (64%) subjects, respectively.

No significant improvement was reported either by subjective or objective measurements during the open phase trial. Of note, controlling for randomization, no differences were found between subjects allocated to the drug group versus the placebo group during the first week of the trial for subjective or objective sleep measurements.

The YMRS and MADRS scores did not change significantly during the trial; however, subjects who were randomized in the placebo group reported higher mean scores at the MADRS at every time point.

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Table 4. Open Phase: Week 1 (V2), Open Months (VO – Either V3, V4, or V5), and Change in Mean (±SD) Subjective and Objective Total Sleep Time, and YMRS and MADRS Scores

	Entire group (n = 24)
sTST V2	7.24 ± 1.32
sTST VO	7.25 ± 1.56
sTST VO–V2	0.01 ± 1.29
	Entire group (n = 24)
Sadeh oTST V2	8.29 ± 3.21
Sadeh oTST VO	8.50 ± 3.54
Sadeh oTST VO–V2	0.22 ± 3.25
	Entire group (n = 23)
CK oTST V2	8.69 ± 3.44
CK oTST VO	9.58 ± 4.56
CK oTST VO–V2	0.88 ± 3.82
	Entire group (n = 29)
YMRS V2	5.41 ± 4.09
YMRS VO	4.48 ± 3.65
YMRS VO–V2	−0.93 ± 3.01
	Entire group (n = 29)
MADRS V2	13.45 ± 9.41
MADRS VO	11.17 ± 9.16
MADRS VO–V2	−2.28 ± 10.53

Note: The number of subjects reported for each measurement corresponds to the number of subjects for which that measure was available at both time points. No significant differences ($p < 0.05$) were found within the groups, that is, blind adjunctive suvorexant followed by open adjunctive suvorexant and blind adjunctive placebo followed by open adjunctive suvorexant. Abbreviation: CK, Cole–Kripke's algorithm; oTST, objective total sleep (actigraphy); Sadeh, Sadeh algorithm; sTST, subjective total sleep.

When using GLMM–RM to evaluate the possible influence of time and dropouts on both sTST and oTST values during the open phase, the model failed to predict significant improvements in sleep during the 3 months, nor detect any difference between subjects that completed the trial or dropouts. A GLMM–RM was also used to look for any possible influence of randomization on total sleep time (TST) during the open phase, with no significant difference detected between the drug versus the placebo groups.

Safety and tolerability measures

There were no serious adverse events (AEs) related to the study drug. Overall, considering total AE, 11 (57.9%) were registered in subjects taking suvorexant (1 during the RCT, N = 19, and 10 during the open phase, N = 34), and 5 (29.4%) were reported by subjects in the placebo group (N = 17) during the RCT. Perceptual disturbance was experienced by 2 subjects taking suvorexant (10.5%), both reported during the open phase. Hypersomnolence was reported from 4 subjects taking suvorexant (21.1%), 1 from RCT phase and 3 from the open phase, as well as from 1 patient from the RCT placebo group. Insomnia was reported in 1 case (5.3%) during the open phase. Headache was experienced by 1 patient during the open phase (5.3%), and by 1 patient from the RCT placebo group. There was just 1 case of sleepwalking (present prior to this study but recurred during the study) during the open phase. Of note, in the placebo RCT group, there was 1 case of sleep paralysis (had been present prior to this study but recurred during the study), 1 case of mania (not thought related to study procedures), and 1 case of depression (not thought related to study procedures). Regarding wearing the actigraphy watch, adherence was an issue for 2 subjects in the open phase (10.5%). Finally, 1 serious AE was registered in the placebo RCT group, consisting of a breast drainage followed by hospitalization, and unrelated to the trial.

Discussion

In the present study, double-blind, randomized, placebo-controlled plus open trial of adjunctive suvorexant for treatment-resistant insomnia in patients with BD, the efficacy and tolerability of adjunctive suvorexant for treatment-resistant insomnia in BD patients were evaluated. Suvorexant was well tolerated, but efficacy results are inconsistent. In fact, during the RCT phase, only a small increase in the oTST emerged, while during the open phase, no significant improvement was detected.

Insomnia in BD is highly prevalent, affecting up to 70% of patients[29] and associated with poorer longitudinal outcomes,[2,30] leading to an impelling need to find more effective treatments. Given the lack of evidence regarding suvorexant use in treating insomnia in BD, we assessed the efficacy of adjunctive suvorexant versus placebo in a 1-week RCT phase plus 3-month open phase study.

During the RCT phase, we found an overall improvement in both sTST and oTST in the drug group, which was, however, only statistically significant for the CK algorithm. On the other hand, interpretation of this result through the comparison with the placebo group was not possible because of the significant difference in both V1 and V2 oTST between the 2 groups.

When analyzing data from the GT9X actigraph watch, the TST was measured with 2 algorithms: one developed by Cole et al.[31] and the other by Sadeh et al.[32] The CK algorithm was validated in an adult sample (35–65 years), while the Sadeh one was originally validated on a healthy sample of adolescents and young adults (10–25 years). Each algorithm has already shown comparable accuracy in the estimation of sleep and wakefulness compared to polysomnography.[33,34] However, the CK algorithm was more sensitive in detecting sleep but less specific for wakefulness than the Sadeh algorithm.[35] This difference could, at least in part, explain the slightly higher mean values in the TST detected with the CK algorithm while potentially decreasing the significance of our results.

In some of our measurements, subjective sleep time tended to be lower than objective assessment. The subjective perception of poor sleep is a central criterion for insomnia. It has been extensively studied how insomnia patients tend to report greater sleep onset latency and less TST than estimates from objective measures.[36] Several terms have been used to capture these phenomena including sleep misperception, paradoxical insomnia, and subjective insomnia. Another term that has been used is subjective–objective sleep discrepancy[37] and is defined as the time differences between subjective and objective measures of sleep features. Instead of assuming that these discrepancies are primarily an error on the part of the sleeper, many studies suggest that objective and subjective measures give valid information on different aspects of sleep and should both be taken into consideration to fully capture sleep disturbances.[38] Our result is consistent with several studies that have described discrepancies between subjective and objective

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measures of sleep in BD, with patients often underestimating their sleep duration,[29,39] especially when depressed.[40,41] In relation to the population under study, though not statistically significant, high mean MADRS scores were detected, especially in the placebo group, thus potentially explaining the difference between the objective and subjective measurements of this portion of the sample. Furthermore, it seems that patients with insomnia exhibit hyperarousal that correlates with enhanced attention and reduced inhibition during the initial phase of sleep, which might modulate the subjective perception of sleep.[42]

It is worth mentioning that the majority of subjects did not complete the entire trial. Beside the availability on the market of suvorexant that could have decreased the drive for trial adherence and completion, for most of the subjects, this could be due to perceived lack of efficacy. In order to account for the high number of dropouts, we also conducted GLMM–RM for both the RCT phase and the open phase, looking for the possible influence of both randomization and dropouts on the subjective and objective outcomes. These analyses failed to provide significant correlation between our efficacy measures and predictor variables, even though the difference between drug versus placebo groups in both V1 and V2 at the Sadeh and CK oTST was underlined. This difference could be at least partially explained by the relatively higher mean MADRS score detected in the placebo group, who could reflect a higher proportion of depressed subjects in this group and, therefore, a higher discrepancy between subjective and objective sleep measurements, as well as higher rates of inactivity, which could have biased the actigraphy measures.[43]

Of note, the FDA approved the use of suvorexant at 10, 15, and 20 mg as the maximal daily dose. However, in the first randomized, double-blind, placebo-controlled, crossover clinical trial assessing suvorexant efficacy in treating primary insomnia, participants received two 4-week sessions of orally administered suvorexant at different doses (10 mg, $n = 62$; 20 mg, $n = 61$; 40 mg, $n = 59$; or 80 mg, $n = 61$) in one (4-week) session and placebo ($n = 249$) in the other 4-week session. Polysomnography was performed on night 1 and at the end of week 4 of each period. Suvorexant showed significant dose-related improvement compared with placebo in sleep efficiency ($p < 0.01$) on night 1 as well as at the end of week 4.[44]

In the current study, subjects were first randomized, and then all treated up to a maximum daily dose of 20 mg. This could explain, at least in part, the relatively high rate of subjective lack of efficacy, that lead to most of the dropouts: 5 subjects discontinued due to inefficacy and 8 for reasons that could be related to suboptimal effectiveness (distance, lost to follow-up, new job or school, and inconvenience of wearing the actigraphy watch). On the other hand, the maximum dose used in this trial turned out to be well tolerated, since only few subjects experienced sedation or parasomnias. Moreover, for some subjects, we were not able to collect every efficacy measure at every given time point. Therefore, the analyses for the RCT phase were carried out only comparing subjects who provided the requested measurements at both considered time points (ie, V1 and V2), while for the open phase data, we included subjects who concluded at least one of the given evaluations (ie, V3, V4, and V5), limiting the possibility to analyze the effect of the drug over time.

The strength of the present study lays in the concurrent evaluation of objective and subjective sleep measures in BD subjects. However, several limitations should be acknowledged. First, as previously stated, the small sample size could have limited the statistical power of our analyses. The different diagnostic subtypes, mood phases, and concurrent pharmacotherapy, even though enhancing the generalizability of the results, may have decreased the ability to detect significant differences between suvorexant and placebo. In addition, the generalizability may have been decreased by the exclusion of patients with substantial medical comorbidities or substance use disorder, as well as increased by the selection of a real-life sample, broadly complex and ill, as already acknowledged (eg, a patient had a sudden onset episode of mania unrelated to the study drug just after the study, another patient had to undergo a breast cyst drainage, and another was hospitalized for severe depression). Furthermore, we should acknowledge some confounds linked to insomnia assessment during follow-up: we asked subjects to keep the actigraphy watch on for the entire 3 months, and we only looked at the final week of each month, without checking in with the subjects during the month to encourage actigraphy watch use adherence. Moreover, it has to be acknowledged that more than half of the sample (57.9%) was taking antidepressants, which are known to induce or exacerbate insomnia, especially in bipolar patients, thus potentially limiting suvorexant efficacy. In this perspective, many other pharmacological and non-pharmacological strategies can be implemented in order to manage sleep disturbances in BD, avoiding the potential risk of manic-induced symptoms, such as insomnia. Although their efficacy is limited, it might be useful for clinicians to propose such strategies, including cognitive behavioral therapy, social rhythm therapy, increased physical activity, lamotrigine, and low-dose lithium, before augmenting the chosen pharmacological treatment, especially when antidepressant medications are used. Finally, although concurrent pharmacological treatments may have affected clinical outcomes, they were overlapping across groups, thus attenuating the risk of confounding results. On the other hand, the high proportion of subjects concurrently already taking other hypnotic agents (11/19 in the suvorexant group and 11/17 in the placebo one) could have limited the perceived efficacy of suvorexant, possibly also leading to an early trial dropout.

From this perspective, due to the limited number of subjects and data collected, few and speculative results can be drawn from our study, results that mainly suggest the need to better assess oTST and sTST in BD subjects with sleep disturbances in order to identify the correct treatment strategy.

Conclusions

In conclusion, the present study, assessing adjunctive suvorexant in treating insomnia in BD, has shown mixed and inconsistent results. Even though well tolerated, during the RCT phase, only a slight increase in the oTST emerged, while during the open phase, no significant improvement was detected relative to both sTST and oTST. Larger studies with more robust actigraphy measurements are warranted to further assess the effectiveness of suvorexant therapy in BD patients. Studies enrolling BD subjects with untreated insomnia (ie, not concurrently taking other hypnotic agents) could lead to a better understanding of suvorexant efficacy. Given the discrepancy between subjective and objective sleep measures, our study underlines a known but important limitation, when trying to assess sleep measures, especially in such a complex population of BD patients.

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