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Original Article

A 12-week open-label, multicenter study evaluating the safety and patient-reported efficacy of sodium oxybate in patients with narcolepsy and cataplexy

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ABSTRACT

Objective: This study aimed to evaluate safety and efficacy of sodium oxybate (SXB) titrated to effect.
Methods: SXB-naive patients who had participated in a randomized SXB clinical trial and had not been titrated to adequate clinical effect were initiated on open-label SXB at 4.5 g/night and titrated in 1.5-g increments to 6, 7.5, or 9 g/night or down to 3 g/night, based on individual clinical response. Treatment was 12 weeks; safety was the primary outcome. Efficacy was evaluated using the Narcolepsy Symptom Assessment Questionnaire (NSAQ), a five-point scale ("much improved" to "much worse") that assessed changes from baseline in specific symptoms. Response was defined as "much improved" or "somewhat improved" overall at weeks 6 and 12.
Results: Of 202 patients, 171 (85%) completed treatment; final doses were 3 g ($n = 5$), 4.5 g ($n = 29$), 6 g ($n = 80$), 7.5 g ($n = 66$), and 9 g ($n = 22$). Adverse events (AEs) were reported in 114 patients (56%), serious AEs in five (2%). The most common AEs were nausea (10%), headache (7%), and dizziness (5%). Response rate was 92% at week 6 and 90% at week 12; most patients reported improvements in all individual symptoms. Overall, 60% of patients rated their symptoms at 12 weeks as "much improved," and this improvement was dose dependent.
Conclusions: The SXB safety profile was consistent with parent trials. Ninety percent of patients reported improvements as measured by the NSAQ.

1. Introduction

Narcolepsy, a chronic neurologic disease, is under-recognized in the clinical setting [1,2] despite advances in the understanding of its etiology and pathophysiology [3,4]. Narcolepsy is associated with high medical and psychiatric comorbidity burdens [5,6] as well as a substantial socioeconomic burden resulting from increased health-care resource utilization, reduced daily function, poorer quality of life, and lower productivity relative to those without narcolepsy [7–11].

Narcolepsy is characterized by a pentad of symptoms that includes cataplexy, excessive daytime sleepiness (EDS), disturbed nighttime sleep (DNS), hypnagogic/hypnopompic hallucinations, and sleep paralysis [12]. Although cataplexy is pathognomic for narcolepsy, it is not uniformly present, occurring in approximately 70% of narcolepsy patients, and its absence increases the challenge of diagnosis [13]. In contrast, EDS, which is most often the first presenting symptom, is present in all patients with narcolepsy. DNS is a frequent complaint and has been reported to be present in most narcolepsy patients [14]; the symptoms of hallucinations and sleep paralysis are of variable prevalence and can contribute to disturbed sleep.

Because narcolepsy has an early onset, generally during childhood or early adulthood [15,16], and the disease is lifelong with no cure, patient management relies on a variety of pharmacologic therapies that target specific symptoms [17]. Sodium oxybate (SXB), the

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sodium salt of gamma hydroxybutyrate, which is an endogenous metabolite of gamma-aminobutyric acid, is a central nervous system depressant that is indicated in the US for the treatment of both cataplexy and EDS associated with narcolepsy [18]. SXB has also been reported to impact other narcolepsy symptoms and features [19–21].

The efficacy of SXB for reducing cataplexy attacks and improving EDS was demonstrated in pivotal clinical trials [22–24]. However, placebo-controlled treatment duration in these trials was only up to 8 weeks, and patients were not necessarily titrated to clinical effect. The purpose of this study was to provide an open-label treatment extension to evaluate SXB over a longer period of time (12 weeks) among patients who were either naive to SXB or were not titrated to adequate response in clinical trials.

2. Methods

2.1. Design and patients

This 12-week, multicenter, open-label treatment study enrolled patients with a history of narcolepsy with cataplexy who were SXB-naive or had participated in one of three randomized clinical trials of SXB and had not been titrated to adequate clinical effect [19,22,24]. The study was performed in accordance with the Declaration of Helsinki, and the protocol received approval from the appropriate Institutional Review Board or Ethics Committee of the participating centers; all patients provided written informed consent prior to participation.

Other inclusion criteria were age ≥16 years; a history of daytime sleepiness; had not taken any investigational therapy, with the exception of SXB within 30 days prior to screening; and if female, was surgically sterile, two years post-menopausal, or if of childbearing potential, used a medically accepted method of birth control and agreed to continue use of this method for the duration of the study. Exclusion criteria were the presence of any condition that would place the patient at risk during the study or compromise study completion or accurate collection of subjective responses; history of substance use disorder within the past year; history of seizure disorder, head trauma, or intracranial surgery; and taking hypnotics, tranquilizers, antihistamines (except for non-sedating antihistamines), anticonvulsants, or clonidine at the start of treatment. All patients provided written informed consent prior to participation in the study.

All patients in the current study were initially treated with oral SXB at 4.5 g/night, given in two equally divided doses 2.5–4 h apart, and titrated in 1.5-g increments to 6, 7.5, or 9 g/night or down to 3 g/night, with dose adjustments every two weeks. Patients were allowed to continue stable doses of stimulants for EDS and of tricyclic or selective serotonin reuptake inhibitor antidepressants for cataplexy.

2.2. Outcomes

Safety and tolerability were evaluated based on the incidence of adverse events (AEs) throughout the study, and on clinical laboratory assessments and vital sign measurements that were measured at every 6-week visit.

Efficacy was evaluated subjectively using the Narcolepsy Symptom Assessment Questionnaire (NSAQ; see supplementary material). The NSAQ is an unvalidated patient-reported outcome that assesses changes in the patient's overall narcolepsy status as well as in individual symptoms. A similar questionnaire was used previously in a small pilot study of SXB [19]. The recall period of the questionnaire is the past week, and the questionnaire consists of one question on the overall condition and 6 items reflecting individual symptoms of cataplexy ("Number of cataplexy attacks"); EDS ("Number of daily inadvertent naps or sleep attacks" and "Severity of daytime sleepiness"); DNS ("Number of awakenings at night"); hypnagogic hallucinations ("Number of hypnagogic hallucinations"); and sleep paralysis ("Number of sleep paralysis episodes"). There are also two additional items, one that assesses sleep quality ("Quality of sleep at night") and one that evaluates concentration ("Ability to concentrate").

The overall condition is rated on a five-point Likert-type scale that ranges from "Much improved" to "Much worse." The six individual items on the core narcolepsy symptom pentad are rated as "Increased," "Decreased," or "Remains the same." The other two items are rated using the same scale as for the overall condition. The NSAQ was administered at 6 and 12 weeks, with responses relative to the patient's symptoms during the week before initiating treatment (baseline).

2.3. Statistical analysis

The safety population represents all patients who received at least one dose of study drug, and the efficacy analysis was based on the intent-to-treat population, defined as patients who received at least one dose of study drug and completed baseline and at least one post-baseline NSAQ. Unless otherwise specified, all analyses were based on the final dose that the patient was taking. Baseline demographic and clinical variables were analyzed using one-way analysis of variance for continuous variables and chi-square test for categorical variables. The primary outcomes of safety and tolerability are reported as incidence of AEs and no statistical inferences were made.

For efficacy evaluation, the proportion of patients who responded to treatment was determined at week 6 and week 12, with responders defined as those who reported overall symptoms on the NSAQ as "much improved" or "somewhat improved" relative to baseline. Fisher's exact test was used to compare the responder rates among treatments by last dosage, and also in a post hoc analysis to evaluate the proportion of patients across doses who reported "much improved." The proportions of patients who reported improvements on individual items of the NSAQ were determined.

3. Results

3.1. Disposition and demographics

A total of 202 patients enrolled in the study and 171 (85%) completed treatment; all patients were included in the safety analysis and 171 patients comprised the intent-to-treat population. The primary reasons for discontinuation were AEs (4%), patient noncompliance (3%), lost to follow-up (1%), protocol departure (1%), and other (4%). Sixty-five percent of patients were female and the mean age at baseline was similar across groups based on final dose (41.9 ± 14.9 years overall; Table 1). While baseline height and weight were significantly different across final doses (both $p < 0.05$), body mass index (BMI) was not significantly different ($p = 0.090$), although larger patients were generally titrated to higher doses. Sympathomimetic stimulants were the most common concomitant medication received during the study, and were taken by 87% of patients.

3.2. Study SXB doses

Dose assessments were recorded every 2 weeks for each patient, with doses adjusted as necessary to optimize efficacy and tolerability. The greatest number of patients received 6 g/night of SXB as their optimized dose ($n = 80$; 40%), followed by 7.5 g/night ($n = 66$; 33%), 4.5 g ($n = 29$; 14%), and 9 g ($n = 22$; 11%), with the 3-g dose taken by the fewest patients ($n = 5$; 2%). A total of 966 dose assessments were conducted, and of these, 30% resulted in a dose increase, 4% in a dose decrease, and the majority (66%) remained unchanged.

Table 1
Demographic characteristics of the population by last dose of SXB.

Variable	SXB 3 g (*n* = 5)	SXB 4.5 g (*n* = 29)	SXB 6 g (*n* = 80)	SXB 7.5 g (*n* = 66)	SXB 9 g (*n* = 22)	*p*
Age, years, mean (SD)	35.6 (12.3)	43.7 (14.2)	41.4 (16.4)	43.4 (13.7)	38.3 (14.4)	0.510
Female, *n* (%)	5 (100.0)	22 (75.9)	54 (67.5)	41 (62.1)	10 (45.5)	0.079
Weight, kg, mean (SD)	59.4 (11.0)	78.1 (22.5)	84.6 (22.8)	89.0 (19.1)	92.8 (15.0)	0.003
Height, cm, mean (SD)	159.0 (6.9)	164.3 (8.9)	167.5 (8.9)	169.2 (8.4)	171.0 (7.1)	0.006
BMI, kg/m^2, mean (SD)	23.4 (3.6)	29.3 (8.7)	29.9 (7.4)	31.4 (7.1)	32.0 (6.5)	0.090

BMI, body mass index; SXB, sodium oxybate.

Most (95%) of the dose increases were due to insufficient response (the reasons for the remaining 5% of increased doses were not recorded), and while decreases in dose were mainly due to AEs (45%), in 43% of decreases, the reason for the decreased dose was not captured.

3.3. Safety and tolerability

As shown in Table 2, 56% of patients reported AEs. Nine patients discontinued due to a variety of AEs that included psychosis, migraine headache, dizziness, nausea, anxiety, fatigue, insomnia, abdominal pain, shortness of breath, and depression. Five patients had serious AEs, and two of these were serious AEs that were considered treatment related: headache in a patient taking 7.5 g/night who continued with study participation, and psychosis in a patient taking 9 g/night who discontinued treatment. Most AEs were considered by the investigators to be of mild or moderate severity. The most common AEs were nausea (10%), headache (7%), and dizziness (5%), and did not appear to be dose related (Table 2).

Overall changes in laboratory results were minimal and appeared to be unrelated to dose. No trends were observed for the few changes in vital signs or physical examination variables that were reported.

3.4. Efficacy

Based on the response criterion of "much improved" or "somewhat improved" relative to baseline for overall symptoms on the NSAQ, 92% of all patients were rated as treatment responders at week 6, and 90% were responders at week 12. The response rate among patients across treatment doses was similar at the two time points (Fig. 1). At week 6, 54% of all patients reported being "much improved," and 60% at week 12 (Fig. 1). The post hoc analysis showed that the proportion of patients who rated their symptoms as "much

Table 2
AEs by SXB dose at AE onset.

AE	Number of Patients (%)					
	SXB 3 g (*n* = 10)	SXB 4.5 g (*n* = 189)	SXB 6 g (*n* = 171)	SXB 7.5 g (*n* = 99)	SXB 9 g (*n* = 27)	Total (*N* = 202)
Any AE[a]	5 (50)	48 (25)	54 (32)	35 (35)	10 (37)	114 (56)
Severe AEs	1 (10)	5 (3)	7 (4)	4 (4)	0	15 (7)
Serious AEs	0	1 (<1)	2 (1)	1 (1)	1 (4)	5 (2)[b]
Discontinuations due to AE	0	2 (1)	5 (3)	1 (1)	0	7 (3)[c]
Treatment-related AEs	3 (30)	25 (13)	34 (20)	19 (19)	8 (30)	74 (37)
Treatment-related serious AEs	0	0	0	1 (1)	1 (4)	2 (1)
Most frequent AEs[d]						
Body as a whole						
Headache	1 (10)	3 (2)	6 (4)	3 (3)	2 (7)	14 (7)
Pain	1 (10)	1 (<1)	1 (<1)	1 (1)	0	4 (2)
Viral infection	0	4 (2)	3 (2)	3 (3)	0	10 (5)
Digestive system						
Appetite lost	1 (10)	0	0	0	1 (4)	2 (1)
Bloating	1 (10)	0	0	0	0	1 (<1)
Nausea	4 (40)	8 (4)	4 (2)	5 (5)	0	21 (10)
Vomiting	1 (10)	1 (<1)	0	1 (1)	0	3 (1)
Nervous system						
Anxiety	1 (10)	1 (<1)	3 (2)	0	0	5 (2)
Concentration impaired	1 (10)	1 (<1)	0	0	0	2 (1)
Dizziness	1 (10)	4 (2)	4 (2)	4 (4)	0	11 (5)
Sedation excessive	1 (10)	1 (<1)	0	1 (1)	0	3 (1)
Unresponsive	1 (10)	0	0	0	0	1 (<1)
Respiratory system						
Sinusitis	2 (20)	4 (2)	2 (1)	1 (1)	0	9 (4)
Special senses						
Otitis media	1 (10)	0	0	0	0	1 (<1)
Urogenital system						
Enuresis	0	0	3 (2)	0	2 (7)	5 (2)
Urinary tract infection	1 (10)		0	1 (1)	0	3 (1)

AEs, adverse events; SXB, sodium oxybate.
[a] Patients who reported ≥1 AE.
[b] Does not include one patient who experienced high blood pressure that was not recorded as an AE.
[c] Does not include two patients whose AEs occurred predose and one patient whose AEs were not captured in the summary tables because the patient's AEs were not associated with a dose.
[d] ≥ 5% at any dose level (Coding Symbols for a Thesaurus of Adverse Reaction Terms).

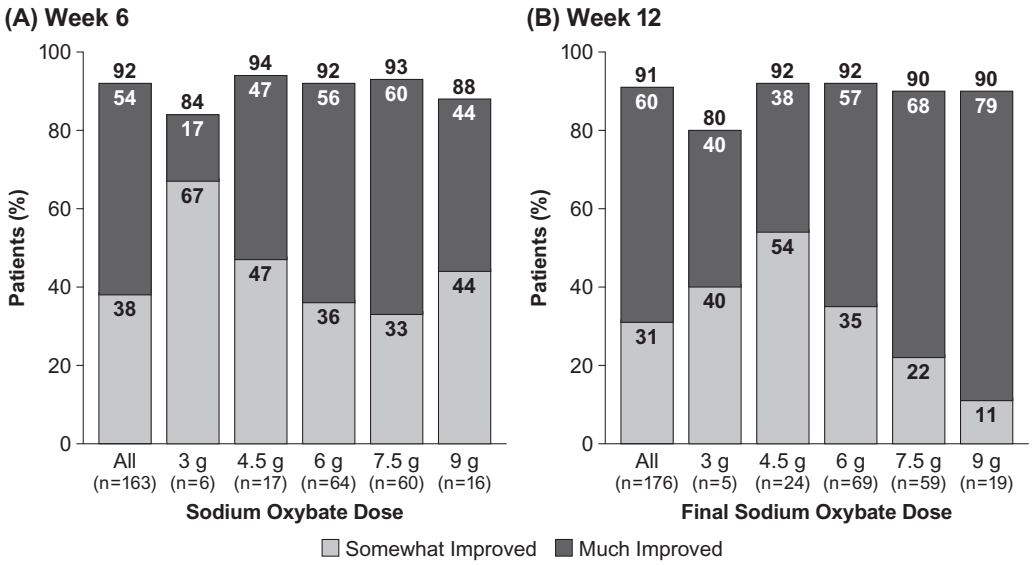

Fig. 1. Percent responders, defined as patients who reported overall symptoms "somewhat improved" or "much improved" on the Narcolepsy Symptom Assessment Questionnaire: (A) Week 6; (B) Week 12.

improved" at week 12 appeared dose dependent as indicated by overall significance across doses ($p = 0.029$); the proportions at week 6 showed no difference across doses ($p = 0.263$).

The majority of patients reported reductions from baseline in the core narcolepsy symptoms assessed by the items on the NSAQ (Fig. 2) at week 6, and these effects were maintained at week 12. The "Number of cataplexy attacks" was reduced in the highest proportion of patients at both time points, 87% and 85%, respectively. The proportions of patients reporting a decrease in each of the other symptoms ranged from 61% to 73% at week 6 and 67% to 72% at week 12 (Fig. 2). When evaluated by last dose (Table 3), the majority of patients at each dose also reported improvements in the individual core narcolepsy NSAQ items except for "Number of daily inadvertent naps or sleep attacks" at week 6 and "Number of awakenings at night" at week 12 with 3 g/night.

On the "Quality of sleep" item, 87% and 85% of all patients reported "much improved" or "somewhat improved" at week 6 (Fig. 3A) and week 12 (Fig. 3B), respectively. Among all patients, 70% reported improvement in "Ability to concentrate" at week 6 (Fig. 4A) and 74% reported improvement at week 12 (Fig. 4B).

4. Discussion

This open-label study supports and extends previous clinical trial results on the safety and efficacy of SXB. The 12-week duration enabled assessment over a longer treatment period than during the 4- to 8-week registration trials. Across doses, SXB was well tolerated, and 85% of patients continued medication through the end of study with 4% of patients discontinuing due to AEs. No new safety signals were observed, and the safety and tolerability were consistent with the parent studies [19,22,24] as well as with the known safety profile of SXB [18]; the most frequent AEs were those that have previously been reported with SXB.

Assessment of doses showed that most of the adjustments were increases due to lack of efficacy, and these dose adjustments may also have been required as a result of differences in body size;

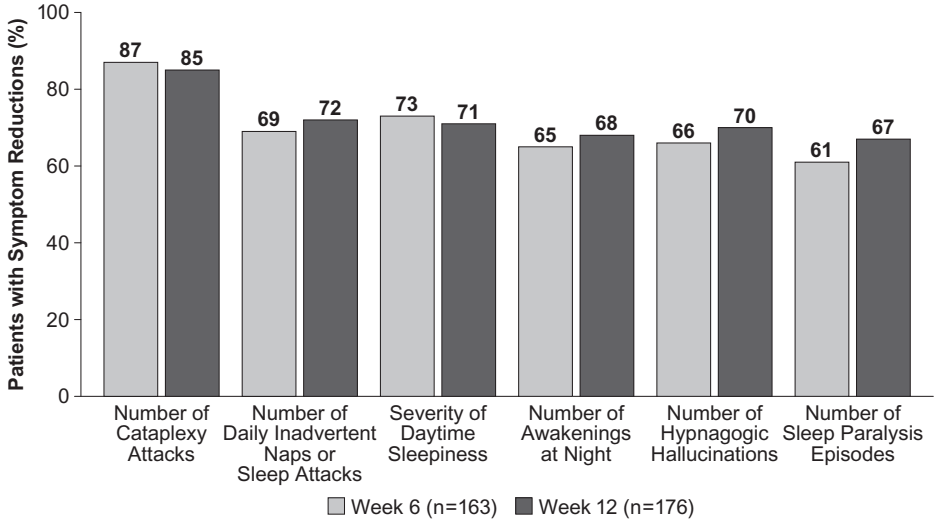

Fig. 2. Overall percentage of patients who reported reductions from baseline in core narcolepsy symptoms on the Narcolepsy Symptom Assessment Questionnaire.

Table 3
Patients who reported reductions from baseline in core narcolepsy symptoms on the Narcolepsy Symptom Assessment Questionnaire by last sodium oxybate dose.

Symptom	Patients with reduction in symptoms, *n* (%)									
	Week 6					Week 12				
	3 g (*n* = 6)	4.5 g (*n* = 17)	6 g (*n* = 64)	7.5 g (*n* = 60)	9 g (*n* = 16)	3 g (*n* = 5)	4.5 g (*n* = 24)	6 g (*n* = 69)	7.5 g (*n* = 59)	9 g (*n* = 19)
Number of cataplexy attacks	5 (83)	15 (88)	57 (89)	51 (85)	13 (81)	3 (60)	20 (83)	56 (81)	52 (88)	18 (95)
Number of daily inadvertent naps or sleep attacks	2 (33)	11 (65)	45 (70)	46 (77)	9 (56)	3 (60)	16 (67)	47 (68)	47 (80)	14 (74)
Severity of daytime sleepiness	4 (67)	12 (75)[a]	47 (75)[b]	45 (75)	9 (56)	4 (80)	17 (71)	47 (68)	44 (75)	13 (68)
Number of awakenings at night	4 (67)	10 (59)	44 (69)	39 (65)	9 (56)	2 (40)	13 (54)	48 (70)	42 (71)	15 (79)
Number of hypnagogic hallucinations	4 (67)	12 (71)	41 (64)	40 (67)	11 (69)	3 (60)	13 (54)	52 (75)	40 (68)	15 (79)
Number of sleep paralysis episodes	4 (67)	12 (71)	37 (58)	35 (59)[c]	11 (69)	3 (60)	12 (50)	50 (74)[d]	37 (64)[e]	14 (74)

[a] *n* = 16.
[b] *n* = 63.
[c] *n* = 59.
[d] *n* = 68.
[e] *n* = 58.

patients receiving the higher doses appeared to be heavier and taller (Table 1). There were few adjustments to a lower dose, and as expected, many of these reductions were due to AEs. Two percent of patients received the lowest dose, 3 g/night, as their final dose, indicating that down-titration to this dose due to AEs in a subset of patients may resolve issues of tolerability. It is interesting to note that all patients who received the 3 g/night dose as their final dose were female and had substantially lower weight than patients taking higher doses. However, there were few patients in this group, it was difficult to interpret these results. Nevertheless, among the other doses, 73% of patients had doses of 6–7.5 g/night, and the efficacy results further suggest that titration to effect during treatment with SXB can help achieve a response for all core narcolepsy symptoms in substantial proportions of patients.

Efficacy in this study was evaluated using the NSAQ, a patient-reported measure, which provides a perspective that may be more clinically relevant for making treatment decisions than objective assessment measures. Using the NSAQ, an overall high rate of response to treatment was observed after 6 weeks and was maintained at 12 weeks, at which time 60% had also reported they were "much improved" relative to baseline. Additionally, patients reported improvement across the range of individual core and associated symptoms. Several of the symptoms evaluated by the NSAQ, including nocturnal awakenings (DNS) and quality of sleep, are primary sources of patient complaints and contribute to the patient burden. Of note is that there was a high response rate at 6 weeks for improvement in ability to concentrate, 59–84% across the doses (Fig. 4A), which was maintained at the lower doses and increased at the higher doses at 12 weeks. There are few data on the ability to concentrate among patients with narcolepsy, but studies have suggested that narcolepsy patients have attention deficits including alterations in the executive control of attention [25,26]. Thus, these preliminary results regarding concentration and the effects of SXB warrant further investigation. Although symptoms other than cataplexy and EDS are less frequently assessed, the results reported are consistent with the few data that are available on the effects of SXB on those other symptoms [19,22,27–29].

4.1. Limitations

The main limitation of the current study is that it was of open-label design with no comparator group. As subjective outcome

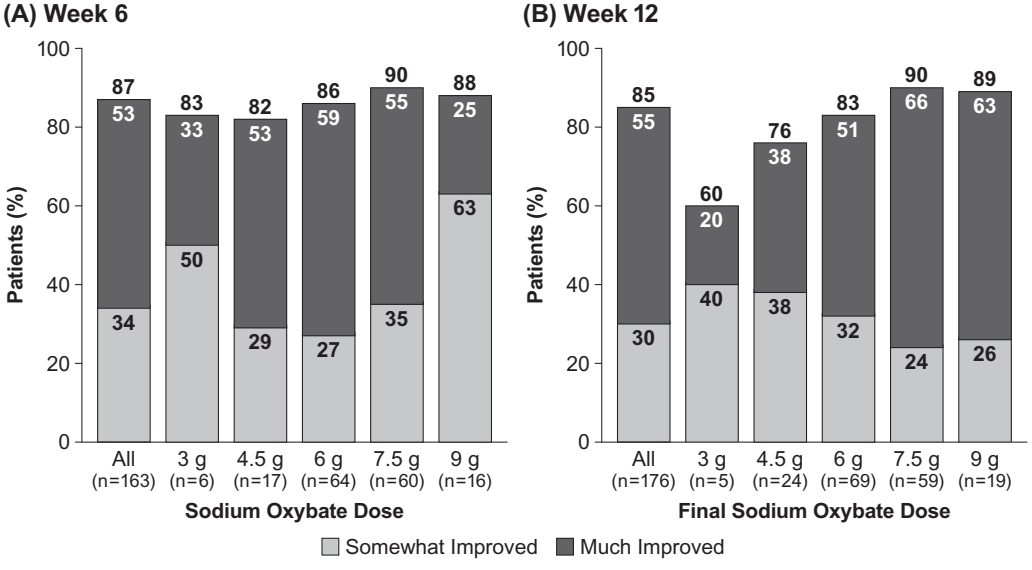

Fig. 3. Patients who reported improvements from baseline on the Quality of Sleep item of the Narcolepsy Symptom Assessment Questionnaire: (A) Week 6; (B) Week 12.

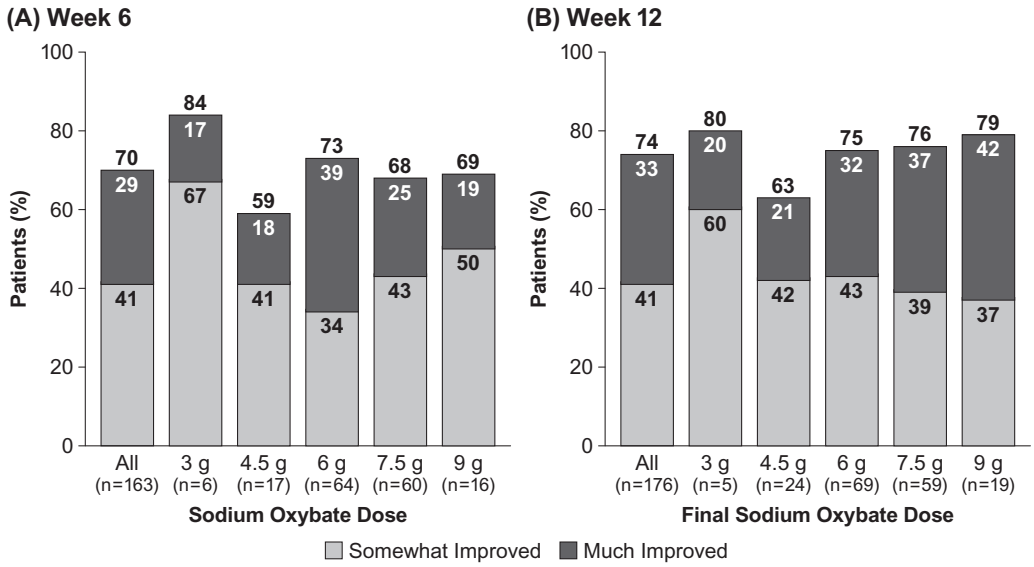

Fig. 4. Patients who reported improvements from baseline on the Ability to Concentrate item of the Narcolepsy Symptom Assessment Questionnaire: (A) Week 6; (B) Week 12.

measures were used, it is not possible to identify the component of change due to treatment effect versus that due to "placebo" effect, regression to the mean, or some other effect. Another key limitation results from the flexible dose-titration process; patients' doses were increased or decreased as needed to optimize efficacy and tolerability. Consequently, this study provides no capacity to allow definitive conclusions regarding the potential dose–response function of SXB for either efficacy or safety. Additionally, the NSAQ has not been formally validated and provides qualitative data only. However, the NSAQ does include items covering all core narcolepsy symptoms as well as two items on outcomes of importance to patients (sleep quality and attention), and has been previously used with results similar to those reported here [19]. Another limitation is that patient responses may be subject to recall bias, since the recall period for NSAQ responses was the previous week, and was with respect to baseline, 6 weeks, and 12 weeks prior to the assessment; longer recall periods have a greater risk for bias than shorter recall periods. Finally, evaluable data for the 3 g/night dose were limited by the small sample size, although the low number of patients in this dose group also suggests that there were few patients who required such a dose reduction due to AEs.

5. Conclusions

The safety profile of SXB in this open-label study was consistent with previous safety findings from double-blind clinical trials. Patient self-report indicated improvement at 6 and 12 weeks across the range of narcolepsy symptoms, with most patients deemed responders based on the predefined NSAQ response definition; the majority of patients were much improved, and this improvement was dose dependent. Additionally, patients reported improvement in sleep quality and ability to concentrate, outcomes that generally have not been evaluated in clinical trials.

Conflict of interest

Dr Mamelak has received consultancy fees from Jazz Pharmaceuticals, Inc. Dr Swick has received consultancy fees and/or honoraria from Aerial BioPharma, LLC, Jazz Pharmaceuticals, Inc., Merck, UCB, Vanda Pharmaceuticals, and XenoPort Pharmaceuticals; and has received research funding from Aerial BioPharma, LLC, GSK Pharmaceuticals, Jazz Pharmaceuticals, Inc., Otsuka Pharmaceuticals, Teva Pharmaceuticals, and Vanda Pharmaceuticals. Dr Emsellem has received consultancy fees from and/or has been a Speakers' Bureau member for GLG Research, Jazz Pharmaceuticals, Inc., and Vanda Pharmaceuticals; and has received research funding from Aerial BioPharma, LLC, ApniCure, GSK, Jazz Pharmaceuticals, Inc., Merck, Vanda Pharmaceuticals, and Xenon. Dr Montplaisir has received consultancy fees from Jazz Pharmaceuticals, Inc., Merck, UCB, and Valeant Pharmaceuticals; and has received research funding from GSK and Merck. Dr Lai is an employee of Jazz Pharmaceuticals, Inc., who in the course of this employment has received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc. Dr Black is a part-time employee of Jazz Pharmaceuticals, Inc.

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2014.10.004.

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Appendix: Supplementary Material

Supplementary data to this article can be found online at doi:10.1016/j.sleep.2014.10.004.

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