Sleep Medicine 24 (2016) 57–62

Contents lists available at ScienceDirect

Sleep Medicine

journal homepage: www.elsevier.com/locate/sleep

Original Article

Impact of sodium oxybate, modafinil, and combination treatment on excessive daytime sleepiness in patients who have narcolepsy with or without cataplexy

Jed Black [a,b,*], Todd Swick [c], Richard Bogan [d,e,f], Chinglin Lai [a], Lawrence P. Carter [a,g]

[a] Jazz Pharmaceuticals, Palo Alto, CA, USA
[b] Stanford Sleep Medicine Center, Redwood City, CA, USA
[c] Neurology and Sleep Medicine Consultants of Houston, Houston, TX, USA
[d] University of South Carolina School of Medicine, Columbia, SC, USA
[e] SleepMed, Inc., Columbia, SC, USA
[f] Medical University of South Carolina, Charleston, SC, USA
[g] University of Arkansas for Medical Sciences, Little Rock, AR, USA

ARTICLE INFO

Article history:
Received 1 June 2016
Received in revised form 26 July 2016
Accepted 27 July 2016
Available online 22 August 2016

Keywords:
Narcolepsy
Cataplexy
Sodium oxybate
Modafinil
Excessive sleepiness
Maintenance of wakefulness

ABSTRACT

Background: Effects of sodium oxybate (SXB) on patients with narcolepsy with cataplexy (NC) or without cataplexy (NWOC) have not been separately evaluated in clinical trials.
Methods: Retrospective analysis evaluated data from a phase 3, randomized, placebo-controlled trial of SXB, modafinil, and SXB + modafinil versus placebo in adult NC patients ($n = 95$) or NWOC patients ($n = 127$). NC patients were identified based on medical history, concomitant medications, and sleep-onset REM periods on nocturnal polysomnography. The studied outcomes were changes from baseline at eight weeks on the Epworth Sleepiness Scale (ESS), the Maintenance of Wakefulness Test (MWT), and the Clinical Global Impression of Change (CGI-C).
Results: Among NC and NWOC patients, ESS improvement was significantly greater with SXB and SXB + modafinil versus placebo. In NC patients, mean MWT sleep latency was significantly increased with SXB + modafinil versus placebo. In NWOC patients, mean MWT sleep latency significantly increased in all groups versus placebo. Higher percentages of patients in the SXB and SXB + modafinil groups were "very much improved" or "much improved" on the CGI-C versus placebo in both NC and NWOC populations, although the difference did not reach statistical significance in the NWOC populations. Adverse events were consistent with previously-reported profiles for modafinil and SXB. Nausea was more common in the SXB and SXB + modafinil groups. Dizziness and tremor were more common in the SXB + modafinil group only.
Conclusions: SXB alone and in combination with modafinil improved subjective ratings of excessive sleepiness and an objective measure of the ability to stay awake to similar extents in NC patients and NWOC patients.

1. Introduction

Narcolepsy is a chronic neurologic condition that is characterized by a set of five core symptoms consisting of excessive daytime sleepiness (EDS), cataplexy, hallucinations while falling asleep or awakening (hypnagogic/hypnopompic hallucinations), sleep paralysis, and disrupted nighttime sleep. While cataplexy is considered pathognomonic for narcolepsy, it is present in approximately 60%–90% of patients [1]. Narcolepsy is subcategorized into two types: type 1 narcolepsy is characterized by EDS and the presence of cataplexy or low hypocretin levels (observed in over 90% of type 1 narcolepsy patients), and type 2 narcolepsy is characterized by EDS and the absence of cataplexy, with normal or unknown hypocretin levels [2]. Both types of narcolepsy are characterized by symptoms and objective findings of EDS, which is present in all patients with narcolepsy and is often the first presenting symptom [2].

While there is increasing recognition that the pathophysiology (eg, low hypocretin levels) and sleep architecture (eg, nocturnal sleep-onset rapid-eye movement period) may vary between type 1 and type 2 narcolepsy [3–5], studies comparing the two types of narcolepsy with regard to presentation, symptomatology, and response to treatment are lacking. Clinically, type 1 narcolepsy is often

* Corresponding author. Jazz Pharmaceuticals, Inc., 3180 Porter Drive, Palo Alto, CA 94304, USA. Fax: 650 496 2871.
E-mail address: Jed.Black@jazzpharma.com (J. Black).

http://dx.doi.org/10.1016/j.sleep.2016.07.010

distinguished from type 2 based on patient-reported cataplexy or a medical history indicating cataplectic episodes [6].

Narcolepsy is associated with an economic burden resulting from high healthcare resource utilization and costs [7–10] and indirect costs associated with unemployment and lost productivity [7,9,10]. There is also a substantial patient burden arising from the greater prevalence of comorbidities and higher odds for mortality relative to those without narcolepsy [11–13] as well as significant reductions in health-related quality of life relative to the general population [9,14,15].

Treatment guidelines and best practice recommendations suggest a symptomatic approach to management, with EDS and cataplexy as the primary therapeutic targets [16–18]. Currently approved therapies for the treatment of narcolepsy also target these symptoms, and in particular, sodium oxybate (SXB) is approved to treat both EDS and cataplexy associated with narcolepsy [19], while modafinil is approved to improve wakefulness in adult patients with excessive sleepiness associated with narcolepsy [20]. There is, however, a notable absence of any published literature on the effects of modafinil on cataplexy (frequency or severity). Meta-analyses have substantiated the clinical trial efficacy and safety profile of these two medications [21–23], and the effects of SXB administered in combination with modafinil have been suggested in one study to be additive for the treatment of narcolepsy, as indicated by greater combined effects on EDS than with either drug alone [24]. However, it remains unknown whether these drugs differ in efficacy or adverse events in the treatment of EDS in patients who have narcolepsy with cataplexy versus those without. The inclusion of patients with and without cataplexy in a clinical trial of SXB, modafinil, and SXB + modafinil versus placebo provided an opportunity to retrospectively evaluate whether the presence or absence of cataplexy impacts treatment response to drugs that treat EDS.

2. Methods

2.1. Design and patients

The data for this analysis were from a phase 3, randomized, placebo-controlled trial that evaluated SXB alone and in combination with modafinil for the treatment of adults with narcolepsy (ClinicalTrials.gov identifier NCT00066170) [24,25]. Methodology and results for outcomes of excessive sleepiness, polysomnography, and safety have been previously reported [24,25]. The study included patients with narcolepsy, diagnosed using the second edition of the International Classification of Sleep Disorders [26], and who were on a stable dose of modafinil. The presence of cataplexy was not an inclusion criterion, and thus the study included patients with cataplexy (NC; $n = 95$) and without cataplexy (NWOC; $n = 127$). The patients with NC were retrospectively identified based on a medical history of cataplexy, a concomitant anticataplectic medication other than SXB, and the presence of a sleep-onset rapid-eye movement period on nocturnal polysomnography as described by Andlauer et al. [4]; patients not classified as NC were classified as NWOC.

Patients on a stable dose of modafinil were randomized to receive either: SXB + modafinil placebo (SXB group), SXB placebo + modafinil (modafinil group), SXB + modafinil, or SXB placebo + modafinil placebo (placebo group) for eight weeks. In this double-dummy trial design, all patients were randomized to treatment groups that included either SXB or SXB placebo, which was administered nightly in two equally divided doses (at bedtime and 2.5–4 hours later); patients received 6 g SXB or placebo equivalent for the initial four-week period and then 9 g of the same nightly for the second four-week period. Patients in the modafinil group continued to receive the same modafinil dosage (range: 200–600 mg/day) that they were receiving prior to randomization according to the protocol.

2.2. Outcomes

Efficacy outcomes included the Epworth Sleepiness Scale (ESS) [27] and the mean sleep latency on a four-period, 20-minute Maintenance of Wakefulness Test (MWT). Both the ESS and MWT were administered at baseline and at Weeks 4 and 8 (end of treatment) or early termination. Efficacy was evaluated as the change from baseline at Week 8 on both of these measures. Global change from the clinician's perspective was also evaluated using the Clinical Global Impression of Change (CGI-C) [28], which is scored using a seven-point Likert-type scale from 1 = "Very much improved" to 7 = "Very much worse." For the CGI-C, the percentages of patients who achieved improvement at Week 8 were determined, with improvement defined as scores of "much improved" or "very much improved." Clinical Global Impression of Severity (CGI-S) was also assessed only at baseline and was converted to numerical scores based on an ordered six-point numerical scale ranging from one (normal) to six (among the most extremely ill patients).

In addition to the efficacy outcomes, the safety profile, based on the incidence of adverse events (AEs) was evaluated according to the presence and absence of cataplexy.

2.3. Statistical analysis

Analyses were conducted on the intent-to-treat population, defined as patients who received one or more doses of double blind trial medication and who had baseline and post-baseline efficacy measurements. Statistical evaluation of ESS and MWT, using a last observation carried forward imputation approach, was performed using equal slope analysis of covariance models adjusting for treatment group, pooled site, and baseline ESS or sleep latency. The primary pairwise comparisons of SXB alone and SXB + modafinil versus placebo were performed using Dunnett's test and were considered interpretable if overall $P < 0.05$. Secondary pairwise comparison of modafinil alone versus placebo did not include an adjustment for multiple comparisons. Analysis of CGI-C was based on logistic regression with effects for treatment group and study center and, similar to the other variables, pairwise comparisons of SXB alone and SXB + modafinil were considered interpretable if overall $P < 0.05$, with comparisons considered significant if $P < 0.025$ based on Bonferroni adjustment. Additionally, effect sizes versus placebo were estimated for ESS and sleep MWT based on the difference between the means of the active treatment group and the mean of the placebo divided by their pooled standard deviations (Cohen's d). Absolute values of effect sizes of 0.20 are generally considered small, 0.50 are moderate, and 0.80 are large [29].

All analyses were performed using SAS Version 9.3 (SAS Institute, Inc. Cary, NC).

3. Results

3.1. Demographics and disposition

As shown in Table 1, patients were predominantly White (83.2%), with a slightly higher percentage of males (54.7%), and a mean (standard deviation [SD]) age of 39.2 (15.8) years. The population was balanced across all treatment groups, and demographic characteristics were generally similar between patients with NC and those with NWOC.

However, patients with NC had significantly higher baseline ESS scores (15.1 versus 13.7; $P = 0.035$) and significantly shorter mean sleep latency times on the MWT (8.33 versus 12.07 minutes; $P < 0.001$) than patients with NWOC. Additionally, clinician ratings of severity at baseline indicated that NC patients had significantly more severe symptoms than patients with NWOC as rated on the

Table 1
Baseline demographic and clinical characteristics.

Variable	All patients	Placebo	SXB	Modafinil	SXB + modafinil	*P* value
With cataplexy, *n*	95	32	14	26	23	
Age, years, mean (SD)	39.2 (15.8)	41.3 (14.7)	35.1 (12.6)	37.1 (17.1)	41.3 (17.7)	0.417
Female, n (%)	43 (45.3)	19 (59.4)	6 (42.9)	10 (38.5)	8 (34.8)	0.263
Race, n (%)						0.426
Black	12 (12.6)	7 (21.9)	1 (7.1)	2 (7.7)	2 (8.7)	
White	79 (83.2)	24 (75.0)	13 (92.9)	23 (88.5)	19 (82.6)	
Other	4 (4.2)	1 (3.1)	0	1 (3.8)	2 (8.7)	
ESS score, mean (SD)	15.1 (4.9)	15.0 (5.0)	14.1 (5.4)	14.4 (4.9)	16.5 (4.4)	0.409
MWT sleep latency, minutes, mean (SD)	8.33 (6.45)	9.57 (6.75)	9.47 (7.85)	7.52 (5.41)	6.82 (6.15)	0.354
Without cataplexy, *n*	127	23	36	37	31	
Age, years, mean (SD)	38.1 (18.7)	40.7 (11.6)	35.1 (13.2)	40.1 (14.7)	37.2 (14.4)	0.482
Female, n (%)	72 (56.7)	12 (52.2)	18 (50.0)	21 (56.8)	21 (67.7)	0.500
Race, n (%)						0.218
Black	9 (7.1)	4 (17.4)	1 (2.8)	3 (8.1)	1 (3.2)	
White	116 (91.3)	19 (82.6)	34 (94.4)	34 (91.9)	29 (93.5)	
Other	2 (1.6)	0	1 (2.8)	0	1 (3.2)	
ESS score, mean (SD)	13.7 (4.9)	12.7 (5.3)	14.5 (4.5)	13.8 (5.3)	13.3 (4.8)	0.600
MWT sleep latency, minutes, mean (SD)	12.07 (5.92)	9.96 (6.46)	12.02 (5.69)	12.56 (5.62)	13.10 (6.00)	0.251

ESS, Epworth Sleepiness Scale; MWT, Maintenance of Wakefulness Test; SD, standard deviation; SXB, sodium oxybate.

CGI-S; mean (SD) scores of 4.0 (0.9) and 3.6 (0.9) for NC and NWOC, respectively ($P < 0.001$) (data not shown).

3.2. Epworth Sleepiness Scale

Among patients with NC, the mean change in ESS from modafinil-treated baseline was not statistically significant at Week 8 for patients who stayed on the same dose of modafinil or who switched from modafinil to SXB. However, the mean change in ESS from baseline at Week 8 for patients who received SXB + modafinil was significant ($P = 0.002$) and showed improvement. Relative to the placebo group, which had a mean ESS increase of 0.8, the reductions in ESS scores in both the SXB and SXB + modafinil groups were significant, –2.9 ($P = 0.011$) and –3.8 ($P = 0.002$), respectively (Fig. 1). Effect sizes relative to placebo were large for the SXB group (–0.80) and for the SXB + modafinil group (–1.15). There was no effect in the group that stayed on modafinil relative to placebo (0.7; $P = 0.733$, with a negligible effect size of –0.03).

Among patients with NWOC, the mean changes in ESS from baseline at Week 8 for both the SXB group and for the SXB + modafinil group were significant (both $P < 0.001$). Relative to the placebo group, which had a mean ESS increase of 0.8, the reductions in ESS scores were similar in the SXB group (–3.0; $P = 0.021$) and the SXB + modafinil group (–2.8; $P = 0.015$) (Fig. 1). Effect sizes relative to placebo were large, –0.89 for the SXB group and –0.99 for SXB + modafinil group. There was no effect in the group that stayed on modafinil (0.3; $P = 0.775$), which had an effect size of –0.175.

3.3. Maintenance of Wakefulness Test

On the MWT (Fig. 2), the mean sleep latency decreased by –2.58 minutes from baseline to Week 8 among the patients with NC who were switched from modafinil to placebo (the placebo group), indicating that those patients stayed awake for a significantly shorter period of time ($P < 0.05$). In contrast, the MWT mean sleep latency in the SXB + modafinil group increased by 3.34 minutes from baseline to Week 8, indicating that those patients were able to stay awake for a significantly longer period of time when SXB was added to their dose of modafinil ($P < 0.05$), and was also significantly greater

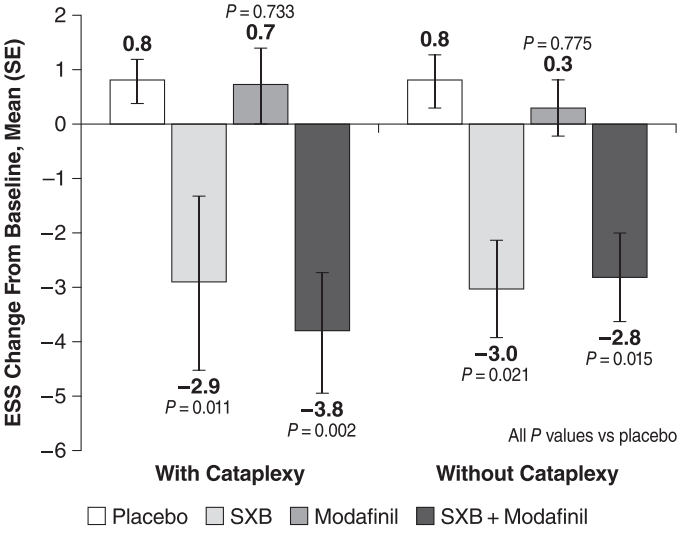

Fig. 1. Change from baseline in excessive daytime sleepiness assessed using the Epworth Sleepiness Scale (ESS). The study was of double-dummy design (see Methods for details). SE, standard error; SXB, sodium oxybate.

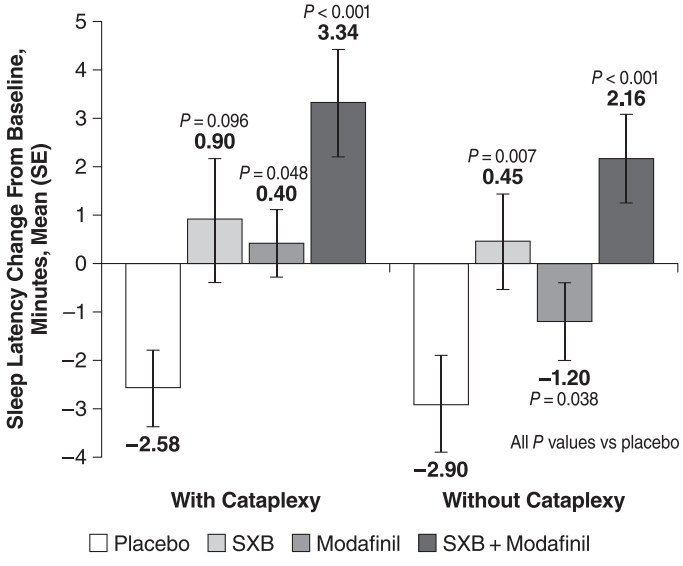

Fig. 2. Change from baseline in sleep latency assessed using the Maintenance of Wakefulness Test. The study was of double-dummy design (see Methods for details). SE, standard error; SXB, sodium oxybate.

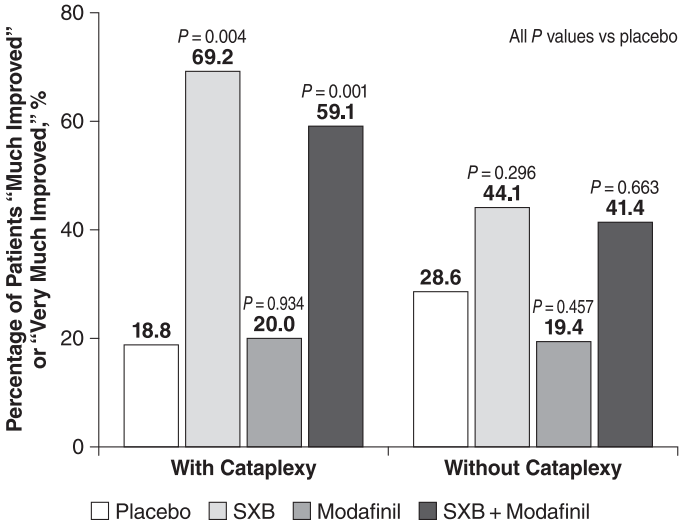

Fig. 3. Treatment response assessed using the Clinical Global Impression of Change, defined as patients who achieved "much improved" or "very much improved." The study was of double-dummy design (see Methods for details). SXB, sodium oxybate.

compared with placebo ($P < 0.001$) resulting in a large effect size of 1.19. There was a trend toward greater improvement in the SXB group relative to placebo (0.90 minutes; $P = 0.096$), with a moderate effect size of 0.76 (the lack of statistical significance, even in the presence of robust effect size, is likely due to the small number of patients in the SXB group [n = 14] versus the modafinil group [n = 26]). The 0.40-minute increase observed in the modafinil group was significant compared with placebo ($P = 0.048$), and resulted in an effect size of 0.71.

Similar patterns were generally observed in patients with NWOC (Fig. 2), with a significant worsening from baseline to Week 8 when patients were switched from modafinil to placebo, and improvement when SXB was added to modafinil (both $P < 0.05$). Relative to the change in the placebo group (–2.90 minutes), both the SXB group and the SXB + modafinil group had significant increases in mean MWT sleep latency time; 0.45 minutes in the SXB group ($P = 0.007$) and 2.16 minutes in the SXB + modafinil group ($P < 0.001$), with moderate and large effect sizes of 0.62 and 1.07, respectively. While the mean MWT sleep latency from baseline to Week 8 numerically decreased in the modafinil group, the difference relative to placebo was significantly smaller ($P = 0.038$) and resulted in a small effect size of 0.37.

3.4. Clinical Global Impression of Change

Among the patients with NC, the percentage who were improved on the CGI-C, defined as ratings of "very much improved" or "much improved," was significantly higher in the SXB group (69.2%; $P = 0.004$) and the SXB + modafinil group (59.1%; $P = 0.001$) relative to placebo (18.8%) (Fig. 3). For patients with NC who stayed on modafinil, the percentage who were improved on the CGI-C (20.0%) from baseline was similar to placebo ($P = 0.934$).

Although a numerically higher percentage of the NWOC patients who were treated with SXB (44.1% SXB) and combination therapy (41.4%) were rated as "very much improved" or "much improved" on CGI-C relative to placebo (28.6%), the differences did not reach statistical significance (Fig. 3). The percentage of NWOC patients who stayed on modafinil who achieved these levels of improvement (19.4%) was not significantly different than placebo (28.6%, $P = 0.457$).

3.5. Safety

Among the patients with NC, there was a significant difference across treatments in the incidence of any AEs ($P = 0.040$), which was likely driven by the higher incidence of AEs among those treated with SXB + modafinil (Table 2). The incidence of AEs was similar across treatments among patients with NWOC.

AEs were generally consistent with the profiles for modafinil and SXB [19,20]. The most common AEs, defined as having an incidence ≥5% in either of the cataplexy status groups, in the patients with NC were headache (17.9%), nasopharyngitis (10.5%), nausea (7.4%), dizziness (6.3%), and somnolence (6.3%) (Table 2). For nausea, there was a significant difference across treatments ($P = 0.026$), with the highest incidence in the SXB group (21.4%). Similarly, the most common AEs in patients with NWOC were nausea (15.7%), headache (14.2%), dizziness (11.0%), vomiting (10.2%), tremor (7.1%), arthralgia (6.3%), and somnolence (5.5%) (Table 2). Significant differences across treatments among NWOC were observed for nausea,

Table 2
Adverse events (AEs) ≥ 5%.

AE	Incidence, n (%)					*P* value
	All patients	Placebo	SXB	Modafinil	SXB + modafinil	
With cataplexy, *n*	95	32	14	26	23	
Any AE	56 (58.9)	20 (62.5)	8 (57.1)	10 (38.5)	18 (78.3)	0.040
Most common AEs*						
Headache	17 (17.9)	7 (21.9)	2 (14.3)	2 (7.7)	6 (26.1)	NS
Nasopharyngitis	10 (10.5)	3 (9.4)	4 (28.6)	2 (7.7)	1 (4.3)	NS
Nausea	7 (7.4)	1 (3.1)	3 (21.4)	0	3 (13.0)	0.026
Dizziness	6 (6.3)	2 (6.3)	1 (7.1)	0	3 (13.0)	NS
Somnolence	6 (6.3)	4 (12.5)	1 (7.1)	0	1 (4.3)	NS
Without cataplexy, *n*	127	23	36	37	31	
Any AE	93 (73.2)	19 (82.6)	24 (66.7)	24 (64.9)	26 (83.9)	NS
Most common AEs*						
Nausea	20 (15.7)	0	9 (25.0)	2 (5.4)	9 (29.0)	0.002
Headache	18 (14.2)	5 (21.7)	3 (8.3)	5 (13.5)	5 (16.1)	NS
Dizziness	14 (11.0)	1 (4.3)	3 (8.3)	2 (5.4)	8 (25.8)	0.044
Vomiting	13 (10.2)	0	7 (19.4)	2 (5.4)	4 (12.9)	NS
Tremor	9 (7.1)	0	2 (5.6)	0	7 (22.6)	< 0.001
Arthralgia	8 (6.3)	1 (4.3)	4 (11.1)	3 (8.1)	0	NS
Somnolence	7 (5.5)	0	3 (8.3)	2 (5.4)	2 (6.5)	NS

NS, not significant; SXB, sodium oxybate.
* Defined as occurring in ≥5% of all patients for either of the cataplexy status groups by the Medical Dictionary for Regulatory Activities preferred term.

dizziness, and tremor, all of which were highest in the combination therapy treatment group.

4. Discussion

To our knowledge, this is the first study to evaluate the effects of SXB, or any narcolepsy treatment, on patients based on cataplexy status. In the current analysis, significant differences were observed at baseline in sleepiness and wakefulness between patients with NC and patients with NWOC. Patients with NC were sleepier on the ESS and stayed awake for shorter periods of time on the MWT. These differences have implications for differentially characterizing type 1 and type 2 narcolepsy, especially considering that there is also increased recognition that these two narcolepsy types may be objectively characterized by differences in sleep architecture, CSF hypocretin levels, and HLA type [4,5].

The data reported here show that regardless of cataplexy status, treatment with SXB alone and in combination with modafinil resulted in greater improvements relative to placebo in EDS as assessed by the ESS, ability to stay awake as assessed by mean sleep latency on the MWT, and global improvement in overall symptom status as rated by the clinician. The effects were generally similar in the patients with NC or with NWOC, and the combination of SXB + modafinil consistently resulted in improvements that were significantly greater than placebo and resulted in large effect sizes. Except for the change in ESS score in the patients with NWOC, the combination of SXB + modafinil resulted in the greatest effect across outcomes and the effect sizes were consistently greater in that group than in any of the other groups. These results further support previous observations that have led to the suggestion that there may be an additive effect of SXB and modafinil when used together to treat EDS associated with narcolepsy [24]. This effect appears to be independent of the presence of cataplexy.

Physician assessment of global improvement (CGI-C) showed numerically greater percentages of patients who improved in the SXB and SXB + modafinil groups relative to placebo, also independent of cataplexy status, although only in the patients with NC were the differences statistically significant. There may have also been a greater placebo effect on CGI-C in the NWOC group. While categorization of patients by NC or NWOC status was based on reasonable information, full information about cataplexy was not available and thus some patients may have been misclassified. In this regard, the presence of a sleep-onset rapid-eye movement period on nocturnal polysomnography was one of the criteria for identifying NC patients. While a specificity of 82% for this criterion has been reported in patients who have been diagnosed only on the basis of multiple sleep latency test results, the specificity is as high as 99% in patients who have documented low hypocretin levels, clear cataplexy, and HLA-DQB1*06:02 positivity, and it is likely that some of the patients in this study had been diagnosed on the basis of these assessments [4]. Nevertheless, it is possible that a small percentage of patients with NC may have been misclassified as patients with NWOC. This potential misclassification is not expected to substantially impact the current analysis since the likelihood of this is low. Additionally, differences in baseline levels of subjective sleepiness and objective ability to remain awake suggest that cataplexy status was largely accurately identified.

It should be noted that since all subjects had been previously treated with modafinil, the interpretability of the results in the modafinil only treatment group may be limited. Additionally, it is possible that patients who enrolled in this study may not have been adequately treated by modafinil alone.

5. Conclusions

In patients with narcolepsy, treatment with SXB alone and in combination with modafinil resulted in significantly greater improvements in EDS and wakefulness relative to placebo regardless of cataplexy status. The effects of SXB combined with modafinil on these outcomes were greater than either drug alone regardless of cataplexy status, suggesting additive therapeutic effects of the two drugs. Further evaluation of differences between these populations, and the implications for treatment is warranted.

Conflict of interest

Dr. Black is a part-time employee of Jazz Pharmaceuticals, Inc, and shareholder of Jazz Pharmaceuticals plc. Dr. Swick is an employee of Neurology and Sleep Medicine Consultants; has received consultancy fees and/or honoraria from Jazz Pharmaceuticals, Inc, Vanda Pharmaceuticals, XenoPort Pharmaceuticals, UCB Pharma, Merck, and Aerial BioPharma; has received grant/research funding from Jazz Pharmaceuticals, Inc, Aerial BioPharma, GSK Pharmaceuticals, Otsuka Pharmaceuticals, Teva Pharmaceuticals, Vanda Pharmaceuticals, UCB Pharma, XenoPort Pharmaceuticals, and Merck; and is on the Speakers Bureau for Jazz Pharmaceuticals, Inc, XenoPort Pharmaceuticals, Teva Pharmaceuticals, Merck, and UCB Pharma. Dr. Bogan is a shareholder and an employee of SleepMed, Inc.; has received consultancy fees from Jazz Pharmaceuticals, Inc, UCB Pharma, and XenoPort; has received industry-funded research support from Jazz Pharmaceuticals, Inc., Phillips, ApniCure, and Fisher & Paykel; and has been on the Speakers Bureau for Teva Pharmaceuticals, Jazz Pharmaceuticals, Inc, UCB Pharma, and XenoPort. Dr. Carter and Dr. Lai are employees of Jazz Pharmaceuticals, Inc, who, in the course of their employment, have received stock options exercisable for, and other stock awards of, ordinary shares of Jazz Pharmaceuticals plc.

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.2015.12.017.

Acknowledgments

This study was funded by Jazz Pharmaceuticals, Inc. Under the direction of the authors, E. Jay Bienen, PhD, of The Curry Rockefeller Group, LLC (CRG), provided medical writing support for this publication. Editorial assistance in formatting, proofreading, copy editing, and fact checking was also provided by CRG. Jazz Pharmaceuticals, Inc, provided funding to CRG in support of this manuscript.

References

[1] Ahmed I, Thorpy M. Clinical features, diagnosis and treatment of narcolepsy. Clin Chest Med 2010;31:371–81.
[2] American Academy of Sleep Medicine. The international classification of sleep disorders – third edition (ICSD-3). Darien, IL: American Academy of Sleep Medicine; 2014.
[3] Baumann CR, Mignot E, Lammers GJ, et al. Challenges in diagnosing narcolepsy without cataplexy. A consensus statement. Sleep 2014;37:1035–42.
[4] Andlauer O, Moore HT, Jouhier L, et al. Nocturnal rapid eye movement sleep latency for identifying patients with narcolepsy/hypocretin deficiency. JAMA Neurol 2013;70:891–902.
[5] Pizza F, Vandi S, Iloti M, et al. Nocturnal sleep dynamics identify narcolepsy type 1. Sleep 2015;38:1277–84.
[6] American Psychiatric Association. Sleep-wake disorders: narcolepsy. Diagnostic and statistical manual of mental disorders fifth edition (DSM-5). Arlington, VA: American Psychiatric Association; 2013. p. 372–8.
[7] Dodel R, Peter H, Walbert T, et al. The socioeconomic impact of narcolepsy. Sleep 2004;27:1123–8.
[8] Black J, Reaven NL, Funk S, et al. The burden of narcolepsy disease (BOND) study: healthcare utilization and cost findings. Sleep Med 2014;15:522–9.
[9] Jennum P, Ibsen R, Petersen ER, et al. Health, social, and economic consequences of narcolepsy: a controlled national study evaluating the societal effect on patients and their partners. Sleep Med 2012;13:1086–93.
[10] Jennum P, Knudsen S, Kjellberg J. The economic consequences of narcolepsy. J Clin Sleep Med 2009;5:240–5.
[11] Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. Sleep Med 2013;14:488–92.

[12] Jennum P, Ibsen R, Knudsen S, et al. Comorbidity and mortality of narcolepsy: a controlled retro- and prospective national study. Sleep 2013;36:835–40.
[13] Ohayon MM, Black J, Lai C, et al. Increased mortality in narcolepsy. Sleep 2014;37:439–44.
[14] Daniels E, King MA, Smith IE, et al. Health-related quality of life in narcolepsy. J Sleep Res 2001;10:75–81.
[15] Dodel R, Peter H, Spottke A, et al. Health-related quality of life in patients with narcolepsy. Sleep Med 2007;8:733–41.
[16] Billiard M, Bassetti C, Dauvilliers Y, et al. EFNS guidelines on management of narcolepsy. Eur J Neurol 2006;13:1035–48.
[17] Morgenthaler TI, Kapur VK, Brown T, et al. Practice parameters for the treatment of narcolepsy and other hypersomnias of central origin. Sleep 2007;30:1705–11.
[18] Thorpy MJ, Dauvillers Y. Clinical and practical considerations in the pharmacologic managment of narcolepsy. Sleep Med 2015;16:9–18.
[19] Xyrem® [sodium oxybate] oral solution US prescribing information. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2015.
[20] Provigil® [modafinil] tablets US prescribing information. North Wales, PA: Teva Pharmaceuticals USA, Inc; 2015.
[21] Golicki D, Bala MM, Niewada M, et al. Modafinil for narcolepsy: systematic review and meta-analysis. Med Sci Monit 2010;16:RA177–86.
[22] Alshaikh MK, Tricco AC, Tashkandi M, et al. Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis. J Clin Sleep Med 2012;8:451–8.
[23] Boscolo-Berto R, Viel G, Montagnese S, et al. Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials. Sleep Med Rev 2012;16:431–43.
[24] Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. Sleep 2006;29:939–46.
[25] Black J, Pardi D, Hornfeldt CS, et al. The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy. Sleep Med 2009;10:829–35.
[26] American Academy of Sleep Medicine. The international classification of sleep disorders – revised: diagnostic and coding manual. 2nd ed. Rochester, MN: American Academy of Sleep Medicine; 2005.
[27] Johns MW. A new method for measuring daytime sleepiness: the Epworth Sleepiness Scale. Sleep 1991;14:540–5.
[28] Guy W. ECDEU assessment manual for psychopharmacology, revised. US Department of Health, Education, and Welfare publication (ADM 76–338). Rockville, MD: National Institute of Mental Health; 1976.
[29] Cohen J. Statistical power analysis for the behavioral sciences. 2nd ed. Hillsdale, NJ: Lawrence Erlbaum Associates; 1988.