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Original Article

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

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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

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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