

Evaluation of Quality of Life in Patients With Narcolepsy Treated With Sodium Oxybate: Use of the 36-Item Short-Form Health Survey in a Clinical Trial

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ABSTRACT

Introduction: The present post hoc analysis was designed to evaluate health-related quality of life (HRQoL) using the 36-item Short Form

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Health Status Survey (SF-36) during an 8-week trial of sodium oxybate (SXB).

Methods: SF-36 was assessed in a phase 3 placebo-controlled trial in patients with narcolepsy ($N = 228$) randomized to placebo or SXB in doses of 4.5, 6, or 9 g nightly for 8 weeks. Changes from baseline in SF-36 (last observation carried forward) were compared between SXB and placebo, and effect sizes (ES) were estimated.

Results: Baseline SF-36 values were lower than normative values for the US general population. After 8 weeks of treatment, mean (\pm standard deviation) improvement from baseline on the Physical Component Summary (PCS) was significantly greater with SXB 9 g/night than placebo (6.3 ± 9.1 vs. 1.5 ± 6.2 ; $p = 0.005$), with moderate ES; no significant difference was found between the SXB and placebo groups on the Mental Component Summary. SXB 9 g/night resulted in significantly ($p < 0.05$) greater improvements than placebo in Physical Functioning (4.4 ± 9.2 vs. 1.0 ± 8.0), General Health (GH; 3.1 ± 7.0 vs. 0.4 ± 6.8), and Social Functioning (6.8 ± 16.8 vs. 1.1 ± 9.6). All SXB doses resulted in significant improvement ($p < 0.05$) relative to placebo for Vitality, with

moderate ES. No significant differences versus placebo were observed for Role–Physical, Role–Emotional, or Mental Health domains.

Conclusion: Treatment with SXB was associated with a dose-dependent improvement in HRQoL, with the 9-g nightly dose demonstrating a positive impact on PCS and individual SF-36 domains of Vitality, GH, and Physical and Social Functioning.

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Keywords: Narcolepsy; Sodium oxybate; Quality of life; SF-36

INTRODUCTION

Excessive daytime sleepiness (EDS) and cataplexy (intermittent partial or complete muscle paralysis) are the most frequently recognized symptoms of narcolepsy, with hallucinations upon falling asleep or awakening, sleep paralysis, and disrupted nighttime sleep completing the pentad of symptoms associated with this disease [1, 2]. While onset of narcolepsy generally occurs in childhood or early adulthood [3, 4], it has consistently been reported that there can be a delay of 10–15 years between symptom onset and confirmed diagnosis, with the lack of recognition by physicians the primary reason for this delay [5]. This failure to recognize the signs and symptoms of narcolepsy not only contributes to reported misdiagnosis [6, 7], but also delays appropriate treatment, thereby prolonging the adverse psychosocial impact of the disease [5].

Health-Related Quality of Life in Narcolepsy

In addition to the disease-related physical impairment and the recognized economic

burden of narcolepsy resulting from the direct costs of higher healthcare resource utilization and indirect costs associated with unemployment and lost productivity [8–10], there is a substantial humanistic burden. Patients with narcolepsy not only tend to have a greater prevalence of comorbidities and higher odds of mortality than those without narcolepsy [11–13], but health-related quality of life (HRQoL) has been shown to be reduced across countries and cultures [14–23]. In particular, studies using the 36-item Short Form Health Status Survey (SF-36) to assess HRQoL in patients with narcolepsy have reported lower scores in most SF-36 domains compared to the general population as well as to those experiencing obstructive sleep apnea, Parkinson’s disease, and epilepsy [14–16, 18–24].

Because there is no cure for narcolepsy, treatment occurs over the lifetime of the patient, with EDS and cataplexy the main targets of most current therapies [25, 26]. Sodium oxybate (SXB) is the sodium salt of gamma hydroxybutyrate, an endogenous metabolite of gamma-aminobutyric acid; SXB is approved for the treatment of cataplexy and EDS in narcolepsy [27]. Randomized controlled trials have demonstrated the efficacy of SXB for reducing EDS and the frequency of cataplexy attacks in patients with narcolepsy [28–30]. Improvements in functional outcomes, assessed using the Functional Outcomes of Sleep Questionnaire (FOSQ) [31], have also been suggested [32]. However, no studies to date have reported on the effects of SXB on HRQoL using a standard assessment measure such as the SF-36.

Objective

The purpose of this analysis is to provide data on the effect of SXB on HRQoL collected during an 8-week randomized controlled trial.

METHODS

Design and Patients

This analysis of HRQoL in patients with narcolepsy treated with SXB is based on data obtained during an 8-week phase 3 randomized placebo-controlled trial. Details of the study design and methods were published previously [29]. Patients ≥ 16 years of age with a diagnosis of narcolepsy with cataplexy, based on clinical history, an overnight polysomnogram, and multiple sleep latency test, were randomized to 8 weeks of treatment with placebo or with SXB in doses of 4.5, 6, or 9 g, administered as two equally divided nightly doses; the second dose was taken 2.5–4 h after the first dose. For patients receiving 6 and 9-g doses of SXB, the doses were titrated in weekly 1.5-g increments. The use of stable doses of stimulants for the treatment of EDS was allowed.

Medical Outcomes Survey 36-Item Short Form

To assess changes in HRQoL associated with treatment, the Medical Outcomes Survey SF-36 [33, 34] was administered during the study as an exploratory efficacy endpoint. The SF-36 is a widely used generic instrument for evaluating HRQoL, consisting of eight subscales evaluating specific health status domains and two summary scales, a Physical Component Summary (PCS) and a Mental Component Summary (MCS). The domain subscales include Physical Functioning (ability to perform physical activity); Role–Physical, which assesses the impact of physical function on daily roles (work, daily activities); Bodily Pain (presence of pain and its impact on limiting activities); General Health (GH; overall health status); Vitality

(energy and tiredness); Social Functioning (ability to perform social activities); Role–Emotional (impact of emotional problems on participation in life activities such as work and other daily activities); and Mental Health (general mood, i.e., anxiety, depression). The PCS is derived from positively weighting the domains of Physical Functioning, Role–Physical, Bodily Pain, and GH, while the MCS weights the domains of Vitality, Social Functioning, Role–Emotional, and Mental Health. Scores on the SF-36 range from 0 to 100, with higher scores indicating better health status. Normative values for the US population have been published [35], and a change of five points is generally accepted as the minimum clinically important difference (MCID) [36].

Statistical Analyses

The SF-36 was administered at baseline and at weeks 4 and 8, with efficacy measured as change from baseline at the end of double-blind treatment (week 8) using a last-observation-carried-forward analysis on the intent-to-treat population. Scores were transformed to norm-based scoring using 1998 SF-36 US population norms [37].

Within-group change from baseline was evaluated using a paired *t* test, and differences in the change from baseline between groups were evaluated using an analysis of variance model with adjustment for treatment and site. Pairwise comparisons versus placebo were performed if the overall *p* was less than 0.05. Effect sizes (ES) versus placebo were estimated based on the difference between the mean change from baseline in the active treatment group and the mean change in the placebo group divided by the pooled standard deviation (SD) of the active and

placebo treatment groups (Cohen's *d*); ES of 0.20 are generally considered small, 0.50 are moderate, and 0.80 are large [38].

Statistical analyses were performed using SAS version 9 software (SAS Institute, Inc., Cary, NC, USA).

Compliance with Ethics Guidelines

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for inclusion in the study (ClinicalTrials.gov identifier NCT00049803).

RESULTS

Demographics and Clinical Characteristics

Demographic characteristics of the intent-to-treat population were similar across the study groups (Table 1). Overall, patients were predominantly female (65.4%) and white (86.0%), with a mean \pm SD age of 40.5 ± 15.3 years. The clinical characteristics of narcolepsy in these patients were also similar across groups, and showed that the population was characterized by moderate-to-severe disease. In particular, the mean Epworth Sleepiness Scale (ESS) score ranged from 17.3 to 18.2 across treatment groups (scores ≥ 10 are considered to represent clinically important sleepiness [39]). Additionally, patients reported the frequent occurrence of other narcolepsy symptoms (Table 1). The mean values of all SF-36 domains at baseline showed impaired QoL (Table 1) and were not significantly different across treatment groups, except for the PCS ($p = 0.040$).

Changes from Baseline

Significant changes from baseline on the PCS were observed with all SXB doses ($p < 0.05$) but not with placebo (Fig. 1). The 9-g dose resulted in the greatest change (mean \pm SD), 6.3 ± 9.1 points, which exceeded the MCID. This change was also significantly greater relative to the 1.5 ± 6.2 points with placebo ($p = 0.005$), and the difference demonstrated a moderate ES (0.616). In contrast, only the SXB 6-g dose resulted in a significant change from baseline on the MCS, and none of the changes with SXB was significant relative to placebo (Fig. 1).

Among the individual domains (Fig. 2), all SXB doses resulted in significant changes from baseline in Physical Functioning ($p < 0.05$) and Vitality ($p < 0.001$), with the 9-g dose observed to have greatest effect. The changes from baseline in Vitality exceeded the MCID for all SXB doses.

The 9-g dose also resulted in significant changes from baseline on Role-Physical ($p < 0.05$), Bodily Pain ($p < 0.05$), GH ($p < 0.001$), and Social Functioning ($p < 0.05$), with the changes of 6.4 and 6.8 exceeding the MCID for Role-Physical and Social Functioning, respectively (Fig. 2). A significant change from baseline was observed with placebo only for Role-Physical ($p < 0.05$).

In pairwise comparisons, Vitality was the only domain where all SXB doses showed significant differences relative to placebo (Fig. 2), and while the ES for the 4.5-g dose was small, at 0.394, the ES for the 6.5 and 9-g doses were moderate, at 0.518 and 0.728, respectively. The SXB 4.5 and 6-g doses did not show significant differences compared to placebo for any of the other domains. However, the mean \pm SD change from baseline with the 9-g SXB dose was significantly greater than with placebo in the domains of Physical Functioning

Table 1 Baseline demographic and clinical characteristics

| Variable | Value ^a | | | | <i>p</i> value |
|---|-----------------------------|-------------------------------|-----------------------------|-----------------------------|----------------|
| | Placebo (<i>n</i> = 59) | SXB 4.5 g (<i>n</i> = 64) | SXB 6 g (<i>n</i> = 58) | SXB 9 g (<i>n</i> = 47) | |
| Gender, <i>n</i> (%) | | | | | 0.582 |
| Male | 17 (28.8) | 21 (32.8) | 22 (37.9) | 19 (40.4) | |
| Female | 42 (71.2) | 43 (67.2) | 36 (62.1) | 28 (59.6) | |
| Age, years, mean (SD) | 40.8 (15.5) | 41.8 (16.7) | 39.2 (15.9) | 39.9 (12.5) | 0.822 |
| Race, <i>n</i> (%) | | | | | 0.306 |
| White | 54 (91.5) | 50 (78.1) | 49 (84.5) | 43 (91.5) | |
| Black | 3 (5.1) | 11 (17.2) | 7 (12.1) | 4 (8.5) | |
| Other | 2 (3.4) | 3 (4.7) | 2 (3.4) | 0 | |
| ESS, mean (SD) | 17.3 (3.7) | 18.0 (4.0) | 18.2 (3.0) | 17.8 (4.0) | 0.462 |
| Narcolepsy symptom episodes per week, mean (SD) | | | | | |
| Cataplexy attacks | 18.9 (14.8) | 38.0 (121.0) | 26.5 (27.4) | 25.6 (29.3) | 0.408 |
| Awakenings | 28.0 (61.3) | 19.2 (11.7) | 32.5 (45.7) | 23.3 (19.4) | 0.362 |
| Hypnagogic hallucinations | 4.1 (4.8) | 5.1 (8.0) | 6.4 (7.4) | 4.7 (6.0) | 0.258 |
| Sleep paralysis | 2.9 (3.7) | 2.9 (4.8) | 5.3 (7.9) | 3.7 (4.7) | 0.052 |
| Inadvertent naps/sleep attacks | 14.6 (9.1) | 18.6 (15.7) | 21.0 (11.9) | 18.5 (17.7) | 0.077 |
| SF-36 Score, mean (SD) | | | | | |
| Physical Component Summary | 42.2 (8.3) ^b | 45.1 (8.5) | 46.3 (9.0) | 42.7 (8.9) | 0.040 |
| Mental Component Summary | 40.5 (10.6) ^b | 42.7 (12.0) | 38.5 (10.2) | 40.6 (11.3) | 0.236 |
| Physical Functioning | 44.5 (9.9) ^b | 45.9 (10.8) | 46.1 (8.0) | 43.6 (10.9) | 0.509 |
| Role–Physical | 34.7 (9.4) ^b | 38.0 (11.4) | 37.8 (11.1) | 35.3 (11.3) | 0.230 |
| Bodily Pain | 47.8 (10.6) ^b | 50.6 (10.3) | 50.9 (10.0) | 49.3 (10.1) | 0.348 |
| General Health | 43.0 (9.1) ^b | 47.5 (10.0) | 45.1 (11.4) | 45.0 (9.7) | 0.124 |
| Vitality | 37.4 (8.9) ^b | 38.9 (10.8) | 37.7 (8.9) | 36.6 (10.6) | 0.673 |
| Social Functioning | 34.3 (13.2) ^b | 38.1 (12.8) | 37.1 (11.7) | 33.6 (13.9) | 0.194 |
| Role–Emotional | 40.8 (13.4) ^b | 45.8 (12.3) | 39.9 (13.1) | 41.7 (13.9) | 0.065 |
| Mental Health | 46.2 (9.2) ^b | 45.7 (11.6) | 43.5 (10.2) | 46.6 (10.5) | 0.410 |

ESS Epworth Sleepiness Scale, SD standard deviation, SXB sodium oxybate

^a Values are for the intent-to-treat population defined as patients who received at least one dose of study medication and had baseline and post-baseline efficacy measurements

^b *n* = 58

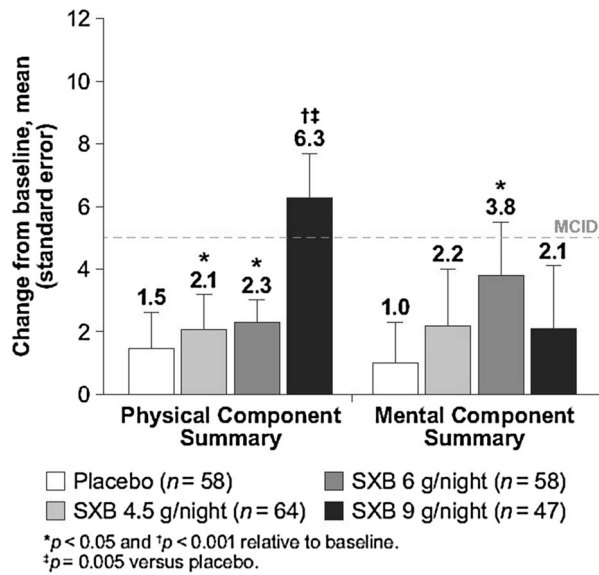


Fig. 1 Change from baseline at 8 weeks in SF-36 component summary scores. Data are for the intent-to-treat population using last observation carried forward; *broken horizontal line* represents the minimum clinically important difference (MCID)

(4.4 ± 9.2 vs. 1.0 ± 8.0 ; $p = 0.016$), GH (3.1 ± 7.0 vs. 0.4 ± 6.8 ; $p = 0.036$), and Social Functioning (6.8 ± 16.8 vs. 1.1 ± 9.6 ; $p = 0.033$; Fig. 2); these differences resulted in small ES of 0.394, 0.395, and 0.417, respectively.

DISCUSSION

Dose-Dependent HRQoL Response

This study found that SXB treatment in patients with narcolepsy was associated with improved HRQoL in a dose-dependent manner, and that the 9-g dose provided the greatest benefits. Consistent with other studies [18–20, 22, 24], these patients were characterized by impaired HRQoL, as shown by baseline values across all SF-36 domains that were lower than normative SF-36 values for the US population [35]. SF-36

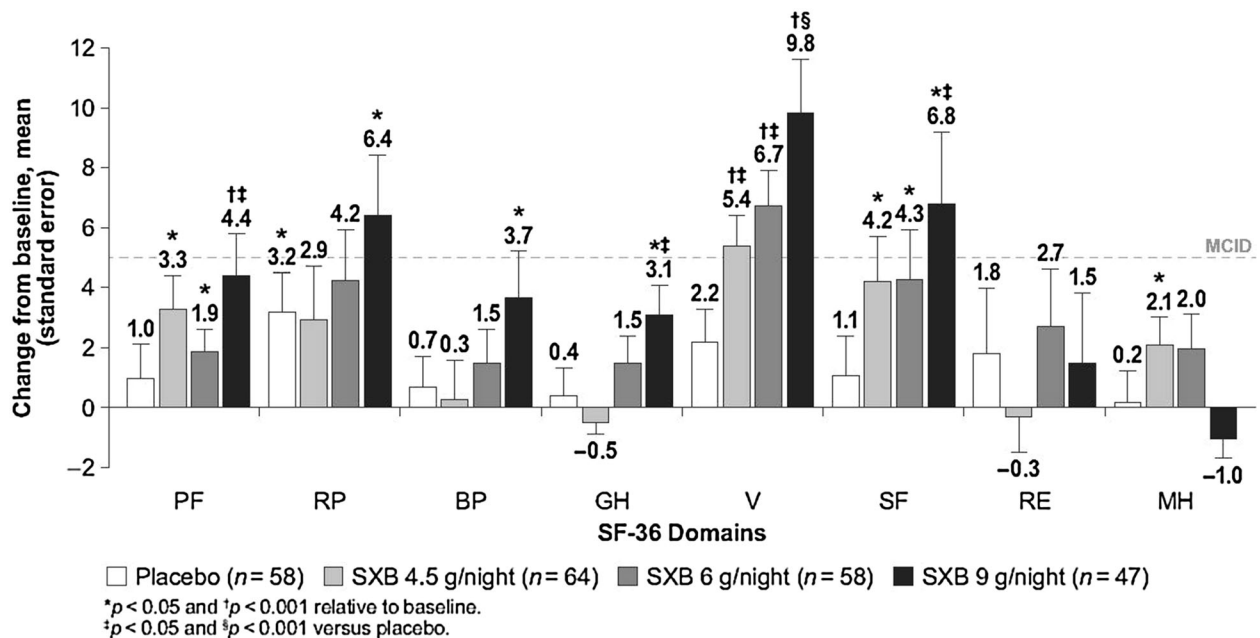


Fig. 2 Change from baseline at 8 weeks in SF-36 domain scores. Data are for the intent-to-treat population using last observation carried forward; *broken horizontal line* represents the minimum clinically

important difference (MCID). *PF* Physical Functioning, *RP* Role–Physical, *BP* Bodily Pain, *GH* General Health, *V* Vitality, *SF* Social Functioning, *RE* Role–Emotional, *MH* Mental Health

domain scores were also generally lower than those reported in most other narcolepsy studies that used this measure [14, 18–24], indicating greater impairment of HRQoL at baseline. In these patients, the frequency of narcolepsy symptoms and the high ESS scores are consistent with moderate-to-severe narcolepsy.

Significant improvements with SXB relative to placebo were observed on the PCS and in four of the eight SF-36 subscales, including Physical Functioning, GH, Vitality, and Social Functioning. Notably, the greatest changes from baseline with SXB were consistently observed in the Vitality domain across all doses, also exceeding the MCID by a five-point change. This domain was also the only one that showed statistically significant differences compared to placebo for all SXB doses. Vitality, which is interpreted as a measure of energy and fatigue, is the subscale that is often reported to have the lowest value among the SF-36 domains in patients with narcolepsy as well as in the general population [18, 22, 24]. Although fatigue has not been considered a core symptom of narcolepsy, it is frequently reported by patients with narcolepsy [40, 41].

The significant changes from baseline in the SF-36 Role–Physical and Social Functioning domains, which also exceeded the MCID and were significantly greater relative to placebo, are consistent with previously reported improvements in functional outcomes with SXB as measured by the FOSQ [32]. The SF-36 Role–Physical would be analogous to the General Productivity domain on the FOSQ, and SF-36 Social Functioning would be analogous to the FOSQ Social Outcomes; both FOSQ functional outcomes showed dose-dependent improvements for the 6-g and 9-g SXB doses and large ES relative to placebo [32].

There were some improvements in MCS with SXB, but these were not statistically

significantly different from placebo. This lack of an effect may suggest that the MCS is more a measure of mental health (i.e., anxiety/depression) than cognitive function [41, 42]. It should be noted that a previous analysis from this study that used the FOSQ did report that 6-g and 9-g SXB doses were associated with significantly greater improvements relative to placebo in the Vigilance domain [32]. This domain assesses the cognitive functions of attention and concentration.

Limitations

Limitations of this study include the 8-week study duration. This observational period may not be long enough to capture changes in patient-reported QoL outcomes that may be associated with narcolepsy treatment [24]. Clinically meaningful changes in EDS and cataplexy with SXB may require 2 months or more, and a longer period is required to achieve maximum response [43]. Another limitation is that the SF-36 is a disease-independent assessment, and while it may be appropriate for an overall understanding of HRQoL in patients with narcolepsy relative to other populations, it may not be fully responsive to changes in domains associated with narcolepsy treatment effects. Consequently, a disease-specific measure is needed that could more sensitively capture changes in outcomes that impact HRQoL in patients with this disorder. Nevertheless, the results of the current study showed improvements in several SF-36 subscales at the 9-g/day dose of SXB. Finally, the use of the generally accepted MCID of five points to indicate clinically meaningful improvements could be criticized, since the MCID is likely to vary across conditions. However, in the absence of disease-specific values, this threshold provides a relative

measure for interpreting the observed improvements.

CONCLUSIONS

SXB appears to improve QoL measures in a dose-dependent manner, with the largest impact at the 9-g/night dose, which had a significant effect on the Vitality, GH, and Physical and Social Functioning domains of the SF-36. Studies of longer duration may be needed to more fully evaluate the effects of SXB on HRQoL in patients with narcolepsy, and the results reported here also highlight the need for a narcolepsy-specific measure of HRQoL.

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employee of Jazz Pharmaceuticals, and holds stock in Jazz Pharmaceuticals plc. J. Montplaisir has received consultancy fees from Jazz Pharmaceuticals, Merck, UCB, and Valeant Pharmaceuticals; and has received research funding from GSK and Merck.

Compliance with Ethical Standards. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. Informed consent was obtained from all patients for inclusion in the study.

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