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COMMENTARY

Implications of Oxybate Dosing Regimen for Sleep, Sleep Architecture, and Disrupted Nighttime Sleep in Patients with Narcolepsy: A Commentary

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ABSTRACT

Narcolepsy is associated with disrupted nighttime sleep (DNS). Sodium oxybate (SXB; Xyrem®), administered twice nightly, is indicated for the treatment of cataplexy and excessive daytime sleepiness in patients 7 years or older with narcolepsy. Recently, low-sodium oxybate (LXB, Xywav®; for people 7 years of age and older), which contains 92% less sodium than SXB and is dosed twice nightly, and sodium oxybate for extended release (SXB-ER; Lumryz™; for adults), which contains equal sodium to SXB and is dosed once nightly, have also been approved to treat cataplexy or excessive daytime sleepiness in narcolepsy. This paper reviews the evidence regarding the overall impact of oxybate administration, and impact of different oxybate dosing regimens (once nightly, SXB-ER; twice nightly, SXB), on DNS in narcolepsy utilizing polysomnographic data from five clinical trials (three assessing SXB in adults [referred to here as SXB trials 1, 2, and 3], one assessing SXB in children [referred to as the pediatric SXB trial], and one assessing SXB-ER in adults [REST-ON]). Both once-nightly and twice-nightly oxybate regimens similarly improved symptoms of DNS. Regardless of dosing regimen, people with narcolepsy treated with oxybate experience roughly 42–53 arousals and 9–38 awakenings each night, with one of these awakenings on twice-nightly oxybate being due to the second dosing requirement in studies of SXB. Additionally, for SXB, but not SXB-ER, polysomnographic data has been analyzed by half of the night, demonstrating a greater positive impact on sleep architecture in the second half of the night, which might be related to its nonlinear pharmacokinetic profile. We conclude that while once-nightly and twice-nightly oxybate dosing regimens differ in their pharmacokinetic profiles, both improve DNS in patients with narcolepsy to a similar degree.

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PLAIN LANGUAGE SUMMARY

Narcolepsy causes daytime sleepiness and difficulty sleeping (commonly called disrupted nighttime sleep). Sodium oxybate (Xyrem®) and low-sodium oxybate (Xywav®, which contains 92% less sodium than sodium oxybate), are taken twice nightly in patients with narcolepsy. Sodium oxybate for extended release (Lumryz™), which contains as much sodium as sodium oxybate, is taken once per night. All three medications improve narcolepsy symptoms and have the same active ingredient. It is important to understand how well they improve nighttime sleep.

This review examined results of five clinical studies looking at disrupted nighttime sleep in people with narcolepsy: three of twice-nightly sodium oxybate in adults (called SXB trials 1, 2, and 3 here), one of twice-nightly sodium oxybate in children (called the pediatric SXB trial here), and one of once-nightly sodium oxybate for extended release in adults (called REST-ON here). No studies specifically investigated disrupted nighttime sleep with twice-nightly low-sodium oxybate in people with narcolepsy. Although the trial designs for these studies were different, both twice-nightly and once-nightly oxybate medications improved sleep similarly, and neither eliminated arousals or awakenings. Certain aspects of sleep improved more during the second half of the night in SXB trials 1 and 3 compared with the first half of the night. Both once-nightly and twice-nightly oxybate medications similarly improve nighttime sleep in people with narcolepsy. Twice-nightly oxybate may be particularly helpful in improving sleep in the second half of the night.

Keywords: Narcolepsy; Sodium oxybate; Low-sodium oxybate; Polysomnography; Disrupted nighttime sleep; Nocturnal

Key Summary Points

Why carry out this study?

Multiple oxybate medications (sodium oxybate [SXB], sodium oxybate for extended release [SXB-ER], and low-sodium oxybate [LXB]) are approved to treat narcolepsy, a central hypersomnolence disorder.

These medications differ in their dosing regimens (SXB and LXB are dosed twice nightly and SXB-ER is dosed once nightly), but there is no evidence that these different regimens have different effects on disrupted nighttime sleep (DNS) in narcolepsy.

This commentary critically examines the effects of two different oxybate dosing regimens (once nightly or twice nightly) on sleep, sleep architecture, and sleep disruption in key clinical trials in narcolepsy.

What was learned from the study?

While no head-to-head trials exist and the impact of LXB on DNS has not been examined in narcolepsy, SXB and SXB-ER were found to similarly improve DNS across five key clinical trials.

Although once-nightly dosing may be perceived as more convenient than twice nightly, the evidence suggests that once-nightly and twice-nightly oxybate regimens impart substantial and highly similar medical benefit on subjective and objective measures of sleep and daytime function.

INTRODUCTION

Narcolepsy is a central hypersomnolence disorder [1, 2]. Symptoms include excessive daytime sleepiness, cataplexy, disrupted nighttime sleep

(DNS), hypnopompic/hypnagogic hallucinations, and sleep paralysis [3]. Excessive daytime sleepiness is experienced by all people with narcolepsy, and cataplexy and DNS are common [4]. There is no agreed upon definition of DNS, but it can be described both objectively, in terms of changes in polysomnographic (PSG) measures of sleep architecture and sleep stage transitions, and subjectively, in terms of self-report measures [5].

Sodium oxybate (SXB; Xyrem®), administered twice nightly and originally approved by the US Food and Drug Administration (FDA) in 2002, is an established and effective treatment for cataplexy and excessive daytime sleepiness in narcolepsy [6–8]. Recently, new oxybate therapies have been approved by the FDA for the treatment of these symptoms. Low-sodium oxybate (calcium, magnesium, potassium, and sodium oxybates; LXB; Xywav®; approved in 2020), which contains 92% less sodium than SXB and is dosed twice nightly, is indicated for patients 7 years of age and older with narcolepsy [9–12]. Sodium oxybate for extended release (SXB-ER; Lumryz™; approved in 2023), which is dosed once nightly but has the same high sodium content as SXB, is indicated for adults with narcolepsy [13].

Although head-to-head trials have not been conducted, clinical trial data from the individual clinical development programs demonstrate that once-nightly and twice-nightly oxybate regimens are associated with similar improvements in DNS (sleep architecture, stage shifts, arousals or awakenings, and patient-reported sleep quality) [14–20]. Importantly, no oxybate product is approved for the treatment of DNS, and approval of all oxybate products was based on clinically relevant endpoints of cataplexy rates and subjective and objective measures of excessive daytime sleepiness. Although waking one fewer time to take a second dose seems intuitively more convenient, there are no data to suggest that once-nightly regimens lead to a more favorable effect on sleep architecture, nor are there any data to suggest that waking for a second dose has an adverse impact on daytime symptoms.

In this paper, we briefly review the scientific literature regarding the effects of oxybates on DNS in people with narcolepsy, critically examine these effects between two different oxybate dosing regimens (once nightly or twice nightly) in key clinical trials, and evaluate the impact of oxybate administration with both dosing regimens on sleep, sleep architecture, and sleep disruption. The available scientific evidence demonstrates an expected, highly similar, and substantial benefit on these parameters, without an identifiable additional benefit of a once-nightly regimen.

DISRUPTED NIGHTTIME SLEEP IN NARCOLEPSY AND HEALTHY INDIVIDUALS

Although DNS is not included in the most recent diagnostic criteria for narcolepsy [21], nighttime sleep is dysregulated in many people with narcolepsy, commonly manifesting as early entry into rapid eye movement (REM) sleep after sleep onset, disordered sleep/wake stages, and sleep state instability, including frequent shifts from deeper to lighter stages of sleep and increased awakenings and arousals, resulting in poor sleep quality [5]. PSG studies of people with narcolepsy compared with healthy controls have shown that total sleep time is decreased [22–24], wake after sleep onset (WASO) is increased [22, 23, 25–28], awakenings are increased [25, 29], arousals are increased [29], N1 sleep is increased [22, 23, 25], N2 sleep is decreased [22, 23, 25], N3 sleep is decreased [29–31], sleep efficiency is lower [22, 23, 25], and transitions between sleep stages are increased [5]. No medications are currently indicated for the treatment of DNS in narcolepsy.

Brief disruptions in sleep are normal within a range of approximately 29–130 arousals and 4–40 awakenings per night, generally increasing in frequency with age, in people without diagnosed sleep disorders [29, 32]. It should be noted, however, that definitions of arousals and awakenings have changed over time, and may vary across studies; additionally, many studies fail to describe criteria used. Per American Sleep Disorders Association (ASDA) [33] criteria and, more recently, American Academy of Sleep

Medicine (AASM) [34] criteria for PSG scoring, an arousal is defined as an abrupt shift in electroencephalogram (EEG) frequency lasting ≥ 3 s, which may include theta, alpha, and/or frequencies > 16 Hz, but not spindles, occurring after ≥ 10 continuous seconds of any sleep stage. Wakefulness was described as being characterized by EEG containing alpha activity and/or a low-voltage, mixed-frequency activity in the early ASDA scoring [35]; AASM criteria now define an awakening as alpha activity over the occipital region and/or other findings consistent with wake (eye blinks, REM associated with normal or high chin muscle tone, or reading eye movements) lasting ≥ 15 s [34].

In a study of untreated adults with narcolepsy, arousals and awakenings were found to be 2.7 and 9.3 times more common, respectively, than in healthy controls [29]. Specifically, people with narcolepsy experienced approximately 80 arousals and 35 awakenings (< 3 min each) per night, whereas healthy controls experienced approximately 30 arousals and 4 awakenings [29]. In a study of untreated people evaluated for chronic sleepiness, nocturnal awakenings were significantly increased in people diagnosed with narcolepsy type 1 (NT1) compared with people who did not meet diagnostic criteria for a sleep disorder (mean, 33.5 vs 20.3 per night during the second of two consecutive nights of PSG recording; $P < 0.00001$) [25]. Consistent with this, people with narcolepsy self-report significantly more nocturnal awakenings and poorer sleep quality than the general population [36]. Although the impact of SXB on sleep architecture was studied by half of night in trials 1 and 3 [14, 17], the studies described here do not assess differences between patients with narcolepsy and healthy controls by half of night.

STUDIES OF THE EFFECTS OF OXYBATE ON NIGHTTIME SLEEP IN NARCOLEPSY

Studies examining the effect of oxybate on sleep in people with narcolepsy include several small-scale studies that were published in the 1980s and 1990s [37–41], which administered gamma-hydroxybutyrate (the active moiety in all oxybate products) [10, 13, 42] per non-standard dosing regimens and as such are not described here, as well as more recent, large-scale, well-controlled clinical trials of twice-nightly administration of SXB [14–19]. These key clinical trials are referred to here as SXB trial 1 [14, 18, 43], trial 2 [15, 19, 44], trial 3 [17], and the pediatric SXB trial [16, 45]; the PSG data from SXB trials 1 and 2 are published in two manuscripts each. There are currently no published studies directly examining the effects of twice-nightly LXB on objective measures of DNS in narcolepsy. The effects of a once-nightly regimen (SXB-ER) on sleep in adults with narcolepsy were examined in the double-blind, placebo-controlled REST-ON study [20]. There are no studies comparing once-nightly to twice-nightly dosing regimens.

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors. The designs, treatment allocations, and objective sleep assessments of the relevant trials are summarized in Table 1. It must be emphasized that these studies are not directly comparable because of important differences in treatment duration, dose titration, and data presentation, among other features.

BOTH TWICE-NIGHTLY AND ONCE-NIGHTLY OXYBATE REGIMENS IMPROVE PSG MEASURES OF DNS, WITH A SIMILAR MAGNITUDE OF EFFECT

In adult and pediatric patients with narcolepsy, SXB was associated with decreased stage 1 sleep, increased slow-wave sleep (SWS), decreased REM sleep, and increased delta power (Table 2) [14–17]. Similarly, in the REST-ON study, SXB-ER was associated with decreased N1 sleep, increased SWS, decreased REM sleep, and increased delta power during non-REM (NREM) sleep in adults with narcolepsy. Bearing in mind the caveats related to cross-study comparisons, the effects of SXB and SXB-ER on these measures appear remarkably similar: following

Table 1 Overview of key studies of the effects of oxybate on nighttime sleep in narcolepsy

Reference	Study design	Treatment	Objective sleep assessments
SXB trial 1			
Xyrem International Study Group, 2005 [43]	8-week, double-blind, placebo-controlled, parallel-group trial Adult patients (> 16 years of age) with narcolepsy with cataplexy (N = 228; intent-to-treat)	8 weeks of treatment (4 weeks dose titration, then 4 weeks stable dose) with 1 of the following:	
Black et al. 2010 [14] Roth et al. 2017 [18]		SXB 4.5 g nightly SXB 6 g nightly SXB 9 g nightly Placebo nightly	PSG and MWT were performed: At end of lead-in period (before withdrawal of cataplexy medications) At end of baseline period (after withdrawal of cataplexy medications and subsequent washout period) After 4-week titration period At end of trial (after 8 weeks of treatment)
SXB trial 2			
Black et al. 2006 [44]	8-week, double-blind, placebo-controlled, multicenter study Adult patients (≥ 18 years of age) with narcolepsy currently taking stable doses of modafinil (N = 222; intent-to-treat)	8 weeks of treatment (SXB 6 g nightly for first 4 weeks, then 9 g nightly for final 4 weeks) with 1 of the following:	
Black et al. 2009 [15] Dauvilliers et al. 2017 [19]		Placebo SXB and placebo modafinil SXB and placebo modafinil Modafinil and placebo SXB SXB and modafinil	PSG and MWT were performed: Before end of baseline period At end of baseline period After 4 weeks of treatment After 8 weeks of treatment
Pediatric SXB trial			
Plazzi et al. 2018 [45]	Double-blind, placebo-controlled, randomized-withdrawal study Pediatric patients (7–17 years of age) with narcolepsy with cataplexy who were on SXB treatment or were SXB-naive (N = 106; enrolled)	3 weeks (patients already on SXB) or 2 weeks (SXB-naive patients; titrated over 3–10 weeks) on stable-dose SXB treatment	

Table 1 continued

Reference	Study design	Treatment	Objective sleep assessments
Mignot et al. 2019 [16]		2-week, double-blind, placebo-controlled, randomized-withdrawal period 2-year open-label period	PSG was performed: During screening At end of stable-dose period (SXB-naive only) After 1 year of SXB treatment
SXB trial 3			
Mamelak et al. 2004 [17]	14-week, open-label pilot study Adult patients (≥ 18 years of age) diagnosed with narcolepsy (N = 25; enrolled)	Following 2-week withdrawal from antidepressants and sedative-hypnotic drugs and additional 2-week washout, 10 weeks of treatment with twice-nightly SXB: Initiated at 4.5 g nightly (4 weeks) 6 g nightly (2 weeks) 7.5 g nightly (2 weeks) 9 g nightly (2 weeks)	PSG was performed: Before the washout period At the end of the washout period On the first night of treatment After 4 weeks of treatment At the end of each dosing period
REST-ON trial			
Roth et al. 2022 [20]	17-week, double-blind, placebo-controlled, randomized, multicenter study Adult patients (≥ 16 years of age) diagnosed with NT1 or NT2 (N = 190; modified intent-to-treat)	Following a 3-week screening period, 13 weeks of treatment once nightly with SXB-ER sequentially ascending doses or placebo: 4.5 g (1 week) 6 g (2 weeks) 7.5 g (5 weeks) 9 g (5 weeks)	PSG was performed: At baseline At week 3 At week 8 At week 13

MWT Maintenance of Wakefulness Test, *NT1* narcolepsy type 1, *NT2* narcolepsy type 2, *PSG* polysomnography, *SXB* sodium oxybate, *SXB-ER* sodium oxybate for extended release

8 weeks of SXB treatment (titrated to 9 g) in two separate studies [14, 15], or 13 weeks of SXB-ER treatment (titrated to 9 g) in REST-ON [20], change from baseline in duration of stage 1 sleep was − 16 min and − 22.5 min with SXB [14, 15] and − 13.2 min with SXB-ER [20]; change from baseline in duration of SWS was + 43.5 min and + 52.5 min with SXB (median change from baseline in stage 3 and stage 4 sleep) [14, 15] and + 39.5 min with SXB-ER (least squares mean [LSM] change from baseline in N3 sleep) [20]; and change from baseline in

Table 2 Effects of oxybate treatment on PSG measures of DNS

	Twice-nightly oxybate (SXB)				Once-nightly oxybate (SXB-ER)
	SXB trial 1	**SXB trial 2**	**Pediatric SXB trial**	**SXB trial 3**	**REST-ON trial**
PSG measures of DNS	Median change from baseline to 8 weeks	Median change from baseline to 4 weeks (6 g) or 8 weeks (9 g)	Median change from baseline to end of study (individual doses)	Mean at 4 weeks (4.5 g), 6 weeks (6 g), 8 weeks (7.5 g), or 10 weeks (9 g)	LSMD vs placebo at week 3 (6 g), week 8 (7.5 g), or week 13 (9 g)
TST, min	Increased Placebo: 0.3 SXB 4.5 g: 0 SXB 6 g: 13.0 SXB 9 g: 18.0†	Not significant Placebo: − 5.5 SXB 6 g: − 5 Placebo: − 0.5 SXB 9 g: − 4.5	–	Not significant (4.5 g decreased) Baseline: 383.4 SXB 4.5 g: 364.8* SXB 6 g: 363.0 SXB 7.5 g: 374.1 SXB 9 g: 380.8	–
WASO, min	Decreased Placebo: 2.0 SXB 4.5 g: − 5.8 SXB 6 g: − 3.8 SXB 9 g: − 22.0†	–	–	–	–
N1, min (except pediatric data)	Decreased Placebo: − 2.3 SXB 4.5 g: − 9.5 SXB 6 g: − 13.5††† SXB 9 g: − 22.5†††	Decreased Placebo: 3.25 SXB 6 g: − 9.5 Placebo: 1.5 SXB 9 g: − 16†††	Decreased SXB-naive: − 4.6% Taking SXB at study entry: − 0.6%	Not significant Baseline: 74.8 SXB 4.5 g: 72.3 SXB 6 g: 68.1 SXB 7.5 g: 69.4 SXB 9 g: 62.6	Decreased SXB-ER 6 g: − 5.9† SXB-ER 7.5 g: − 11.0††† SXB-ER 9 g: − 13.4†††
N2, min	Not significant Placebo: 3.5 SXB 4.5 g: 9.5 SXB 6 g: 13.0 SXB 9 g: 31.5	Not significant Placebo: − 5.25 SXB 6 g: 0.5 Placebo: − 8.25 SXB 9 g: 3.5	No change Values not reported	Not significant Baseline: 217.8 SXB 4.5 g: 216.9 SXB 6 g: 216.9 SXB 7.5 g: 224.1 SXB 9 g: 238.0	Not significant SXB-ER 6 g: − 6.6 SXB-ER 7.5 g: 3.6 SXB-ER 9 g: − 13.5
SWS, min (except pediatric data)	Increased Placebo: 0 SXB 4.5 g: 3.0† SXB 6 g: 21.0††† SXB 9 g: 52.5†††	Increased Placebo: 0 SXB 6 g: 11† Placebo: 0 SXB 9 g: 43.5†††	Increased SXB-naive: 12.6% Taking SXB at study entry: − 1.0%	Increased Baseline: 3.0 (1st half), 0.6 (2nd half) SXB 4.5 g: 3.5 (1st half), 0.7 (2nd half) SXB 6 g: 5.5 (1st half), 4.5 (2nd half) SXB 7.5 g: 9.8 (1st half), 4.5* (2nd half) SXB 9 g: 14.2 (1st half), 12.6* (2nd half)	Increased SXB-ER 6 g: 22.1††† SXB-ER 7.5 g: 26.8††† SXB-ER 9 g: 38.4†††

Table 2 continued

	Twice-nightly oxybate (SXB)				Once-nightly oxybate (SXB-ER)
	SXB trial 1	**SXB trial 2**	**Pediatric SXB trial**	**SXB trial 3**	**REST-ON trial**
REM, min (except pediatric data)	Decreased Placebo: − 1.0 SXB 4.5 g: − 6.0 SXB 6 g: − 7.0 SXB 9 g: − 22.0†	Decreased Placebo: 6.25 SXB 6 g: − 14.5†† Placebo: 10 SXB 9 g: − 38.5†††	Decreased SXB-naive: − 6.0% Taking SXB at study entry: not reported	Decreased Baseline: 31.2 (1st half), 56.0 (2nd half) SXB 4.5 g: 29.7 (1st half), 43.5* (2nd half) SXB 6 g: 26.3 (1st half), 42.7*** (2nd half) SXB 7.5 g: 31.3 (1st half), 34.9*** (2nd half) SXB 9 g: 22.9 (1st half), 30.5*** (2nd half)	Decreased SXB-ER 6 g: − 16.7††† SXB-ER 7.5 g: − 27.2††† SXB-ER 9 g: − 24.5†††
Shifts from N2/N3/REM to N1/wake	Decreased (LSM change from baseline in shifts per hour) Placebo: − 0.8 SXB 4.5 g: − 1.7 SXB 6 g: − 2.7† SXB 9 g: − 4.4†††	Decreased (LSM change from baseline in shifts per night) Placebo: − 0.6 SXB 9 g: − 16.5†††	–	–	Decreased (LSMD change from baseline in shifts per night to wake or N1 from N1, N2, N3, and REM) SXB-ER 6 g: − 11.0††† SXB-ER 7.5 g: − 17.7††† SXB-ER 9 g: − 22.6†††
Shifts from N2/N3 to N1/wake	Decreased (LSM change from baseline in shifts per hour) Placebo: − 0.3 SXB 4.5 g: − 0.9 SXB 6 g: − 1.7† SXB 9 g: − 3.1†††	–	–	–	
Shifts from REM to N1/wake	Decreased (LSM change from baseline in shifts per hour) Placebo: − 1.9 SXB 4.5 g: − 3.8 SXB 6 g: − 5.0 SXB 9 g: − 7.6†	Decreased (LSM change from baseline in shifts per night) Placebo: − 0.6 SXB 9 g: − 6.0†††	–	–	

Table 2 continued

	Twice-nightly oxybate (SXB)				Once-nightly oxybate (SXB-ER)
	SXB trial 1	**SXB trial 2**	**Pediatric SXB trial**	**SXB trial 3**	**REST-ON trial**
Arousals	–	–	Decreased SXB-naive: − 43.0 Taking SXB at study entry: − 1.0	–	Decreased SXB-ER 6 g: − 11.3† SXB-ER 7.5 g: − 19.4††† SXB-ER 9 g: − 23.7†††
Awakenings	Decreased Placebo: − 0.5 SXB 4.5 g: − 5.0 SXB 6 g: − 8.0†† SXB 9 g: − 12.0††	Decreased Placebo: − 0.5 SXB 6 g: − 1 Placebo: − 0.5 SXB 9 g: − 6††	No change SXB-naive: − 4.0 awakenings Taking SXB at study entry: 1.5 awakenings	Decreased Baseline: 50.2 SXB 4.5 g: 50.0 SXB 6 g: 45.1 SXB 7.5 g: 37.3*** SXB 9 g: 37.8**	–
Patient-reported sleep quality	Improved (4-point Likert scale)[a] Placebo: − 0.10 SXB 4.5 g: − 0.41† SXB 6 g: − 0.31† SXB 9 g: − 0.46†††	Improved (LSM change from baseline on question 6 of the PSQI) Placebo: − 0.07 SXB 9 g: − 0.52†††	–	Improved (Self-reported degree of change) Baseline: 0% (much), 14% (somewhat) SXB 4.5 g: 19% (much), 57% (somewhat) SXB 6 g: 24% (much), 67% (somewhat) SXB 7.5 g: 24% (much), 62% (somewhat) SXB 9 g: 24% (much), 57% (somewhat)	Improved (Visual analog scale from 0–100)[b] SXB-ER 6 g: 7.0††† SXB-ER 7.5 g: 9.9††† SXB-ER 9 g: 10.4†††

DNS disrupted nighttime sleep, *LSM* least squared mean, *LSMD* least squared mean difference, *N1/2* stage 1/2 non-rapid eye movement sleep, *ns* not significant, *PSG* polysomnography, *REM* rapid eye movement, *S3/S4* stage 3/4, *SWS* slow-wave sleep, *SXB* sodium oxybate, *SXB-ER* sodium oxybate for extended release, *TST* total sleep time, *WASO* wake after sleep onset

[a]Assessed with 4-point Likert-type scale (0, excellent; 1, good; 2, fair; 3, poor)

[b]Baseline scores were 53.8 and 55.9 in ON-SXB and placebo groups, respectively

$^{\dagger}P < 0.05$ vs placebo. $^{\dagger\dagger}P < 0.01$ vs placebo. $^{\dagger\dagger\dagger}P < 0.001$ vs placebo. $^{*}P < 0.05$ vs baseline. $^{**}P < 0.01$ vs baseline. $^{***}P < 0.005$ vs baseline. – denotes a variable not assessed in this trial. No statistical testing was performed in the pediatric trial

REM sleep was − 38.5 min and − 22.0 min with SXB [14, 15] and − 22.8 min with SXB-ER [20]. All of these changes were statistically significantly greater with oxybate compared with placebo ($P < 0.05$).

Oxybate is also associated with reduced frequency of sleep stage shifts associated with DNS (i.e., shifts from deeper to lighter stages of sleep or to wake) [16–19]. It is important to note, however, that stage shifts were measured differently across studies (either as shifts per night or as shifts per hour). In SXB trial 1 [18], there were significant reductions from baseline in the number of shifts per hour from N2/3/REM to N1/wake (LSM, − 4.4), from N2/3 to N1/wake (LSM, − 3.1), and from REM sleep to N1/wake (LSM, − 7.6), following 8 weeks of SXB treatment (9 g/night). Translating this to shifts per night based on an average total sleep time of 7 h (based on the approximate baseline TST reported in SXB trial 2 as SXB trial 1 does not report TST) [15], this would be equivalent to a decrease

of roughly 30.8, 21.7, and 53.2 shifts per night for N2/3/REM to N1/wake, N2/3 to N1/wake, and REM sleep to N1/wake, respectively. It should be noted that this is a very crude transformation of the data based on TST (to help contextualize the results of the study) and does not take into account time spent in individual sleep stages. Similarly, in SXB trial 2 [19], there were significant reductions from baseline in total shifts per night from N2/3/REM to N1/wake (LSM, − 16.5) and from REM sleep to N1/wake (LSM, − 6.0) following 8 weeks of SXB treatment (9 g/night). SXB-ER was also associated with a reduced frequency of sleep stage shifts in the REST-ON study. Following 13 weeks of SXB-ER treatment (titrated to 9 g), total shifts per night from N1/2/3/REM to wake and N2/3/REM to N1 decreased significantly from baseline (LSM, − 20.5); this trial did not report stage shifts broken down by sleep stage as were reported in SXB trials 1 and 2 [20].

NEITHER TWICE-NIGHTLY NOR ONCE-NIGHTLY OXYBATE REGIMENS ELIMINATE NOCTURNAL AROUSALS OR AWAKENINGS

As noted earlier, even healthy individuals experience nocturnal arousals and awakenings [29], and no oxybate formulation has been associated with arousal/awakening-free sleep across the treated patient population. However, SXB is associated with marked reductions in arousals and awakenings after sleep onset [16]. In the pediatric SXB trial (which included both SXB-naive participants and participants taking SXB at study entry), participants taking SXB at study entry experienced a median of 47.5 nocturnal arousals per night at baseline [16]. After 1 year of taking SXB, the median number of nocturnal arousals (defined according to AASM criteria) declined from 78.0 per night at baseline to 42.0 per night in the previously SXB-naive participants, but remained relatively stable at 53.0 per night in the established SXB participants [16]. In the REST-ON study of SXB-ER, adult participants experienced a decline in mean nocturnal arousals from 81.8 per night to 43.5 per night (defined according to AASM criteria) after 13 weeks of SXB-ER treatment [20].

Awakenings (scored according to AASM criteria) were also assessed in the pediatric SXB study and remained stable (at approximately 8–12 per night) through 1 year of SXB treatment during the study period in both SXB-naive and established SXB participants [16]. In SXB trial 3, awakenings (scored according to ASDA criteria) in adults declined over 10 weeks of SXB treatment from a mean of 54.7 per night at baseline to 37.8 per night at week 10 [17]. No study has formally analyzed the time required to awaken for a second dose of SXB.

BOTH TWICE-NIGHTLY AND ONCE-NIGHTLY OXYBATE REGIMENS IMPROVE PATIENT-REPORTED SLEEP QUALITY, WITH A SIMILAR MAGNITUDE OF EFFECT

Sleep quality is often assessed in terms of subjective evaluations of a person's sleep experience [46]. In SXB trials 1 and 2, participant-reported nocturnal sleep quality (assessed using a 4-point Likert scale and question 6 of the Pittsburgh Sleep Quality Index, respectively) improved significantly with SXB treatment and was correlated with the number of shifts from deeper to lighter stages of sleep in SXB trial 1 [18, 19]. In a separate study examining the experience of patients with narcolepsy transitioning from SXB treatment to LXB treatment (Transition Experience of persons with Narcolepsy taking Oxybate in the Real-world; TENOR), improvements in participant-reported sleep quality (rated using a 5-point scale in a sleep diary) were maintained following transition from SXB to LXB [47]. SXB-ER was also associated with improvements in participant-reported sleep quality (assessed using a visual analog scale ranging from 1 to 100 in a sleep diary) in the REST-ON study [20].

DAYTIME SYMPTOMS OF NARCOLEPSY

Improvement in nighttime sleep is associated with improvement in daytime symptoms of narcolepsy, including excessive daytime sleepiness and cataplexy, as well as overall symptom severity. One or more of these daytime measures was included in each of the oxybate studies described in Table 1, as well as the pivotal, double-blind, placebo-controlled, randomized withdrawal study of LXB in narcolepsy [9]. SXB, LXB, and SXB-ER all demonstrated highly similar efficacy in treating excessive daytime sleepiness, assessed using the Epworth Sleepiness Scale (or, in the pediatric study of SXB, the Epworth Sleepiness Scale for Children and Adolescents) [9, 17, 20, 43–45, 48], and cataplexy in patients with narcolepsy [9, 20, 45, 49]. Following treatment with SXB, LXB, or SXB-ER, clinician-rated impressions of disease severity and change improved similarly for patients treated with SXB and SXB-ER, and worsened in those randomized to placebo in the LXB trial [9, 20, 44, 48, 50].

OXYBATE DOSE–RESPONSE, PHARMACOKINETICS, AND SLEEP DURING THE FIRST AND SECOND HALVES OF THE NIGHT

The recommended dosage range for SXB, LXB, and SXB-ER is 6 g to 9 g per night [10, 13, 42]. In clinical studies of SXB and SXB-ER in narcolepsy, a potential dose–response relationship was assessed. With respect to improvement in daytime symptoms of narcolepsy, the dose–response of SXB-ER showed substantial improvements from baseline at the 4.5 g dose, but plateaued between 6 and 9 g, with minimal to no difference between the 7.5 g and 9 g dose on the Maintenance of Wakefulness Test, Clinical Global Impression of Improvement, and change from baseline in cataplexy attacks [13, 50]. This is in contrast to SXB, which demonstrated substantial improvements on these parameters between the 6 g and 9 g doses [17, 43]. Effects on sleep architecture were dose related (i.e., more pronounced with higher doses) with both once-nightly and twice-nightly oxybate regimens [14, 20].

The pharmacokinetics and bioavailability of SXB-ER 6 g (administered as a single 6 g dose) and SXB 6 g (administered as two divided doses of 3 g each, separated by 4 h [42]) were compared in a study in healthy individuals [51]. For SXB-ER, mean plasma concentration of oxybate peaked 1–2 h after administration at approximately 60 μg/mL, then declined, returning to near zero within 8–10 h. For SXB, mean plasma concentration of oxybate peaked within 1 h of the first dose at approximately 40 μg/mL, declining thereafter over a 4-h period until the second SXB dose was taken, then peaked again within 1 h after the second dose at approximately 65 μg/mL and declined again, returning to near zero within 4–5 h (i.e., 8–10 h after the first dose). Hence, the mean plasma concentration of oxybate was greater with SXB-ER compared with SXB during the first half of the night (hours 0–4) and was greater with SXB during the second half of the night (hours 5–8). Overall, for SXB-ER 6 g and SXB 6 g, median (range) time (hours) to peak drug concentration (t_{max}) was 1.5 (0.3–3.5) and 0.5 (0.3–2.0), respectively; mean (SE) maximum concentration (C_{max}; μg/mL) was 64.6 (5) and 70.9 (4), respectively; and mean $AUC_{0–inf}$ (h·μg/mL) was 273 (27) and 259 (22), respectively [51]. In previous studies of SXB, C_{max} was similar following administration of each of two 2.25 g doses taken 4 h apart under fasting conditions, and t_{max} ranged from 0.5 to 1.25 h [42]. Plasma oxybate levels increased more than dose-proportionally, increasing 3.7-fold as total daily SXB dose is doubled from 4.5 to 9 g. With increasing doses of SXB-ER (4.5 g, 6 g, and 9 g) and LXB (2.25 g and 4.5 g), mean C_{max} and $AUC_{0–inf}$ increased [51, 52]. Although the prescribing information instructs patients to fast for 2 h before either dose of SXB, a potentially greater fasting effect prior to the second dose may in part lead to increased exposure [52].

Differences in the pharmacokinetic profile of twice-nightly oxybate and SXB-ER may lead to differences in sleep staging within specific portions of the night, not captured by summarizing PSG activity across the entire night. Hence, a

reasonable consideration is to evaluate the effects of oxybate on sleep architecture by half of the night, as this may differ between oxybate formulations, perhaps as a result of the unique pharmacokinetic profiles of each. The effects by half of the night are not yet available for SXB-ER, but have been evaluated for SXB [14, 17]. In these studies, SXB showed effects on improving sleep architecture in both the first and second half of the night [14, 17], with greater magnitudes of effect (expressed as median changes from baseline) relative to placebo observed for total sleep time (increased), total REM sleep time (decreased), stage 1 sleep (decreased), SWS (increased), and delta power (increased) in the second half [14]. Additionally, WASO and nocturnal awakenings were decreased to a greater extent in the second half of the night compared with the first [14]. These observations, taken together with the steep dose response relationship between 6 and 9 g of SXB in terms of the magnitude of reduction of cataplexy and excessive daytime sleepiness, may suggest that the second dose of SXB, and subsequent exposure in the second half of the night, imparts clinically relevant effects. The benefit of increased exposure during the second half of the night may counter any disruption associated with waking to take a second dose of a twice-nightly regimen, although this is speculative.

DISCUSSION AND CRITICAL APPRAISAL

Recognizing its clinically meaningful benefit, the AASM recommended SXB as an effective treatment for DNS in patients with narcolepsy in 2007 [6, 7]. In the setting of baseline high rates of arousals and awakenings in patients not treated with oxybate (approximately 80 arousals per night [16, 20] and approximately 12–55 awakenings per night [16, 17]), which are not eliminated with chronic oxybate treatment (approximately 42–53 arousals per night [16, 20] and approximately 9–38 awakenings per night [16, 17]), there is no scientific evidence to suggest that eliminating a single nighttime awakening with a once-nightly oxybate regimen (SXB-ER) offers any additional benefit over twice-nightly oxybate regimens (SXB and LXB) in the form of reducing sleep fragmentation or disruption of sleep architecture, or in improving patient-reported sleep quality or daytime symptoms.

On the basis of a review of the published literature, once-nightly and twice-nightly oxybate regimens appear to be equally effective in improving sleep in narcolepsy. Both SXB and SXB-ER demonstrate beneficial effects on PSG measures of DNS, including sleep architecture and sleep stage shifts, and the magnitude of those effects appear to be similar overall; however, the observation of greater magnitude of effects during the second half of the night with twice-nightly oxybate may be clinically relevant [14–20]. Both dosing regimens also similarly improve patient-reported subjective sleep quality, though this was assessed using different rating scales in each study [18–20, 47].

Finally, a supposed benefit of once-nightly oxybate regimens for DNS should be reflected by a meaningful difference from twice-nightly oxybate regimens in the level of improvement in daytime symptoms of narcolepsy. However, this is not supported by the available data. In pivotal clinical trials, SXB, LXB, and SXB-ER all demonstrated significant and comparable efficacy on measures of excessive daytime sleepiness, cataplexy, and overall disease severity, compared with placebo [9, 43, 50, 53].

In short, we have found no scientific evidence for a clinical advantage associated with once-nightly oxybate regimens, relative to twice-nightly regimens, for the treatment of narcolepsy. In contrast to this, the available data on SXB may suggest that an additional benefit of the second dose is possible, as a greater reduction in awakenings and WASO, and increase in SWS occur in the second half of the night [14, 17], when there is a greater peak in plasma oxybate concentration with SXB but waning plasma oxybate concentration with SXB-ER [51]. This finding, especially if unique to twice-nightly oxybate regimens, may help offset the required awakening to take the second dose, but additional research is needed to validate this possibility. The relationship between oxybate PK and therapeutic effects on DNS has yet

to be studied within the same trial, and no study has assessed the impact of SXB-ER on DNS in different portions of the night.

CONCLUSION

Although the lack of head-to-head trials precludes direct comparisons, the available evidence demonstrates that, in people with narcolepsy, SXB and SXB-ER similarly improve measures of DNS, including sleep architecture, stage shifts, arousals or awakenings, and patient-reported sleep quality. Twice-nightly and once-nightly oxybate regimens also show similar and substantial efficacy in treating daytime symptoms of narcolepsy, including excessive daytime sleepiness, cataplexy, and overall symptom severity. Following administration of the second dose of SXB, the oxybate PK profile characterized by sustained exposure to oxybate in the second half of the night is associated with greater improvement on measures of DNS, which may be clinically important for the consolidation of sleep during this period. In conclusion, although once-nightly dosing may be perceived as more convenient to patients, several lines of scientific evidence suggest that both once-nightly oxybate and twice-nightly oxybate regimens impart substantial and highly similar medical benefit on subjective and objective measures of sleep and daytime function.

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Declarations

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