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REVIEW ARTICLE

Therapeutic Use of γ-Hydroxybutyrate: History and Clinical Utility of Oxybates and Considerations of Once- and Twice-Nightly Dosing in Narcolepsy

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Abstract
Narcolepsy is a rare and chronic hypersomnolence disorder characterized by excessive daytime sleepiness, disrupted nighttime sleep, sleep paralysis, and hypnagogic hallucinations and occurs with or without cataplexy. Orexin neuron loss has been implicated in the underlying pathophysiology of narcolepsy type 1 through dysregulation of sleep/wake patterns and rapid eye movement sleep. γ-Aminobutyric acid (GABA) has been shown to play a role in modulation of orexin neuronal activity during transitions from wakefulness to sleep. γ-Hydroxybutyrate (GHB), an endogenous analog of GABA, has demonstrated therapeutic benefit in treatment of narcolepsy through early investigations, but use has historically been limited owing to existing stigma related to illicit use and abuse risk. Initial regulatory approval of its sodium salt derivative, sodium oxybate (SXB), for cataplexy in patients with narcolepsy occurred in 2002, and additional formulations have been developed. The efficacy and safety of SXB in narcolepsy have been supported by decades of clinical use and research. This review discusses the history and clinical application of GHB and its SXB derivatives in the treatment of individuals with narcolepsy, including clinical safety and effect on sleep.

Key Points

γ-Hydroxybutyrate (GHB) has been recognized as an effective treatment for narcolepsy since 1979; however, a stigma related to its illicit use remains.

The efficacy and safety of oxybates, the active moiety of GHB, in narcolepsy treatment have been supported by decades of clinical use and research.

1 Introduction

Narcolepsy is a rare and chronic neurologic/sleep disorder characterized by excessive daytime sleepiness (EDS), with an estimated prevalence of up to 44.3 per 100,000 persons in the USA [1, 2]. Globally, the prevalence of narcolepsy varies between regions, with estimated prevalence ranging from 0.14 per 100,000 in Israel to 79 per 100,000 in Finland [3]. In addition to EDS, the condition presents with other burdensome symptoms including disrupted nighttime sleep (DNS), sleep paralysis, and hypnagogic/hypnopompic hallucinations and may occur with or without cataplexy [4]. There is no cure for narcolepsy, and patients often experience significant impacts related to activities of daily living, mental health, social relationships, and performance at work or school [5]. Wakefulness and rapid eye movement (REM) sleep physiology are regulated by orexin neurons located in the lateral hypothalamus [6], and dysregulation of orexin neuronal activity is considered a contributing factor in disease pathogenesis [7]. REM sleep dissociation in narcolepsy has been associated with abnormal circadian timing and rapid, unexpected transitions into REM sleep throughout the day [6]. Narcolepsy type 1 (NT1), characterized by the

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presence of cataplexy, is caused by severe loss of orexin neurons resulting in low levels of orexin A peptide in the cerebrospinal fluid (CSF) [4]. While narcolepsy type 2 (NT2) shares similar clinical characteristics with NT1 related to REM disruption, individuals do not experience cataplexy. Although its pathogenesis remains unknown, NT2 occurs independent of significant orexin neuron loss, as CSF orexin A levels typically remain normal [4].

γ-Aminobutyric acid (GABA), a major inhibitory neurotransmitter, has been implicated in sleep-promoting systems [8, 9]. Evidence suggests that GABAergic neurons likely inhibit orexin activity during transitions from wakefulness to sleep [6, 8]. γ-Hydroxybutyrate (GHB), an analog of GABA [9], has been recognized as an effective treatment for narcolepsy since 1979 [10], although initial US Food and Drug Administration (FDA) approval of its sodium salt, sodium oxybate (SXB), for the treatment of cataplexy in narcolepsy did not occur until 2002 [11]. SXB was subsequently approved for the treatment of EDS in adults with narcolepsy in 2005 [12]. Unfortunately, GHB has historically been associated with illicit use, including reports of abuse and use as a facilitating agent in sexual assault [13]. A lingering stigma remains today, albeit less prevalent, among patients and even some clinicians. This review discusses the history and clinical use of GHB and SXB derivatives in the treatment of people with narcolepsy, including clinical safety and effects on sleep.

2 Discovery of GHB and Early Investigations in Narcolepsy

GHB was first synthesized in 1874 and, upon discovery of the compound's ability to cross the blood–brain barrier (BBB) in the 1960s, was later studied for its hypnotic properties and therapeutic potential as an endogenous precursor of GABA to induce sedation, including initial use as an adjuvant to surgical anesthesia [9, 14–16]. Notably, studies have reported lack of tolerance with prolonged use [17]. GHB is also a metabolite of GABA and exhibits a variety of pharmacologic effects ranging from euphoria and decreased inhibition to somnolence, respiratory depression, and nausea [9, 13, 14]. GHB is a substrate for both sodium- and proton-dependent monocarboxylate transporters (MCTs), with particular affinity for MCT1 at the BBB [9, 18]. GHB is present in the brain at low concentrations (μM) and coordinates its actions via two distinct receptors, $GABA_B$ and GHB (Fig. 1). The behavioral, pharmacologic, and toxicologic aspects of GHB, including sedative and hypnotic effects, are mainly mediated through its action as a weak $GABA_B$ agonist [9, 19–22]. Additionally, some physiologic effects involve specific and pH-dependent binding to the GHB receptor, which is distinct from $GABA_B$ and comprises a subset of $GABA_A$ receptors with α4, δ, and β1 subunits [9, 23, 24].

GHB was first evaluated for the treatment of narcolepsy in 1979 owing to its hypnotic properties that do not inhibit REM sleep. Initially, GHB was tested to determine if it could improve nighttime sleep and, subsequently, daytime sleepiness [10]. Multiple doses were administered (at bedtime and 1–3 times thereafter during the night) to assess effects on nighttime sleep and daytime symptoms [10]. Study participants reported rapid improvement of nocturnal sleep quality, including reductions in restlessness, nightmares, and hallucinations, along with gradual improvement of daytime symptoms, including cataplexy and ability to stay awake. Investigators noted that a key disadvantage of GHB was its relatively short duration of action and highlighted the need for an extended-release formulation to sustain therapeutic effect for 7 to 8 h overnight [10]. The effect of GHB on sleep and wake patterns was further studied in individuals with narcolepsy and cataplexy using continuous 48-h polygraph recordings [25]. GHB significantly increased nocturnal slow-wave sleep duration and REM sleep efficiency, while reducing sleep latency, sleep fragmentation, and duration of daytime sleep periods [25]. Findings from GHB studies have further supported the link between nocturnal REM fragmentation and daytime cataplexy symptoms [26].

Although SXB has been approved by the FDA for > 20 years, misperceptions remain, as does a general lack of awareness of the extensive regulatory safeguards required by the FDA to oversee safe use. Effects of illicit GHB use include euphoria, decreased inhibition, and increased sexual arousal [13, 27, 28]. Studies have shown that unresponsiveness occurs at GHB blood concentrations of approximately 300 μg/mL [27]. Further, death from respiratory depression may occur at concentrations > 500 μg/mL [27]. The average peak blood concentration of GHB after SXB administration is approximately 60–70 μg/mL [29], as shown in Fig. 2.

Understanding the history and current strategies for risk mitigation is crucial for clinicians and the narcolepsy patient community. In 2000, GHB was listed as a schedule I substance, defined as a controlled substance with high abuse potential and no accepted medical use, as directed by the US Congress [30, 31]. However, given the clinical benefit in narcolepsy, a path forward was achieved, and FDA-approved medications containing GHB are currently classified as schedule III substances, defined as medications with intermediate abuse potential [9, 31].

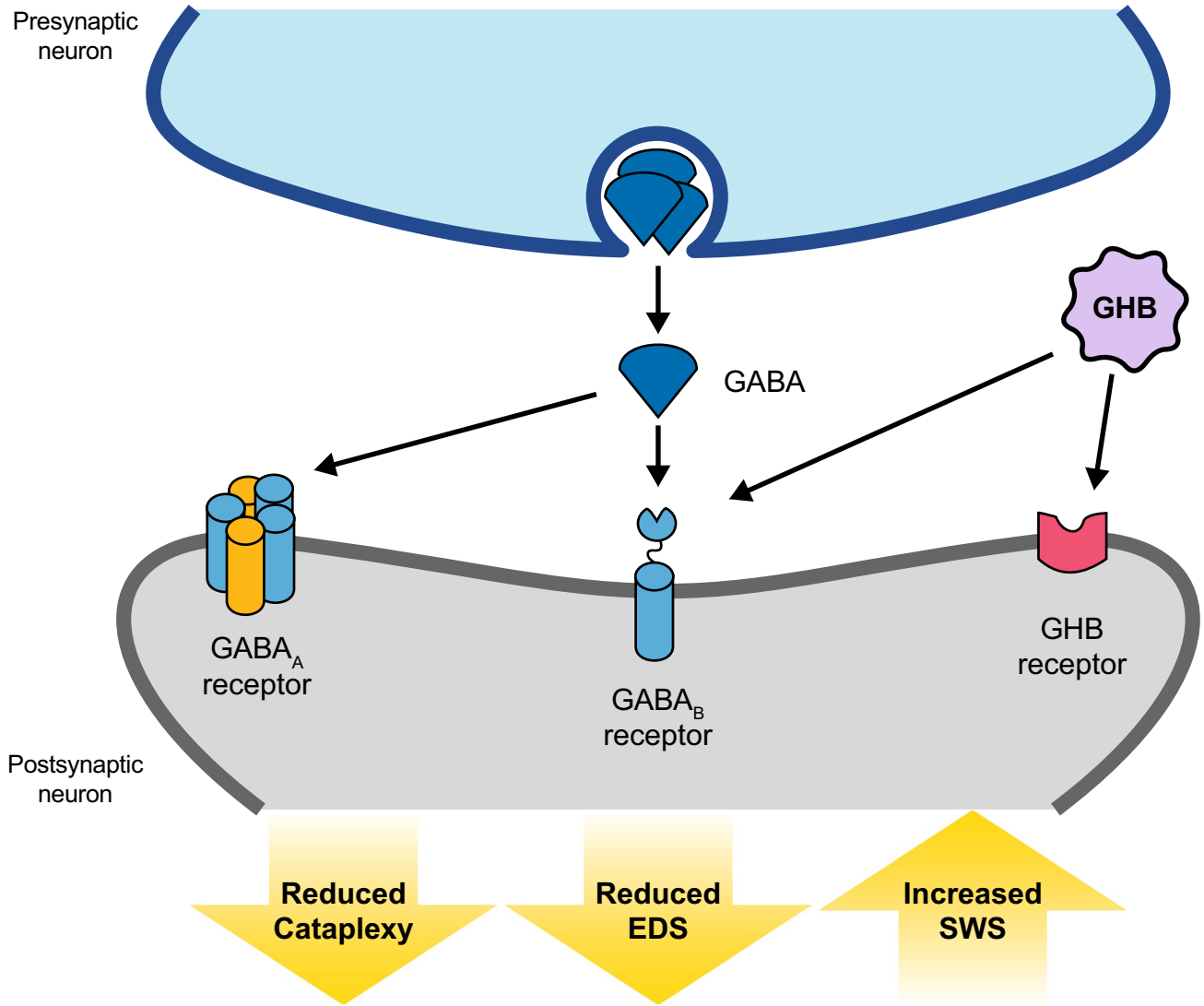


Fig. 1 Mechanism of action of GHB. *EDS* excessive daytime sleep, *GABA* γ-aminobutyric acid, *GHB* γ-hydroxybutyrate, *SWS* slow-wave sleep

3 Clinical Use of Oxybate in Narcolepsy

The clinical use of GHB as SXB for the treatment of narcolepsy began in 2002 when a twice-nightly formulation of SXB was developed by Orphan Medical [32], which was acquired by Jazz Pharmaceuticals in 2005. Developments in the clinical use of twice-nightly SXB for the treatment of narcolepsy continued during the first decade of 2000s. Clinical trials demonstrated the efficacy of SXB in the management of core narcolepsy symptoms, including cataplexy [33–36] and EDS [33, 36, 37]. In a large, international, double-blind, placebo-controlled clinical trial, twice-nightly SXB was associated with improvements in EDS, demonstrated through significant increase of Maintenance of Wakefulness Test (MWT) scores at the 4.5-g and 9-g doses, dose-related decreases in Epworth Sleepiness Scale scores at 6 g and 9 g, and improvements in Clinical Global Impression of Severity (CGI-S) scores at all doses (4.5 g, 6 g, and 9 g) [37]. Additionally, all doses of twice-nightly SXB were associated with progressive dose-dependent decreases in frequency of weekly cataplexy episodes [35]. On the basis of these findings, the FDA approved twice-nightly SXB (XYREM®) for the treatment of cataplexy associated with narcolepsy in 2002 [38] and for the treatment of EDS in 2005 [39]. SXB was subsequently added to the American Academy of Sleep Medicine (AASM) clinical practice guidelines for management of narcolepsy in 2007 [40]. Demonstrated efficacy and clinical application of SXB in narcolepsy has led to the development of alternative formulations.

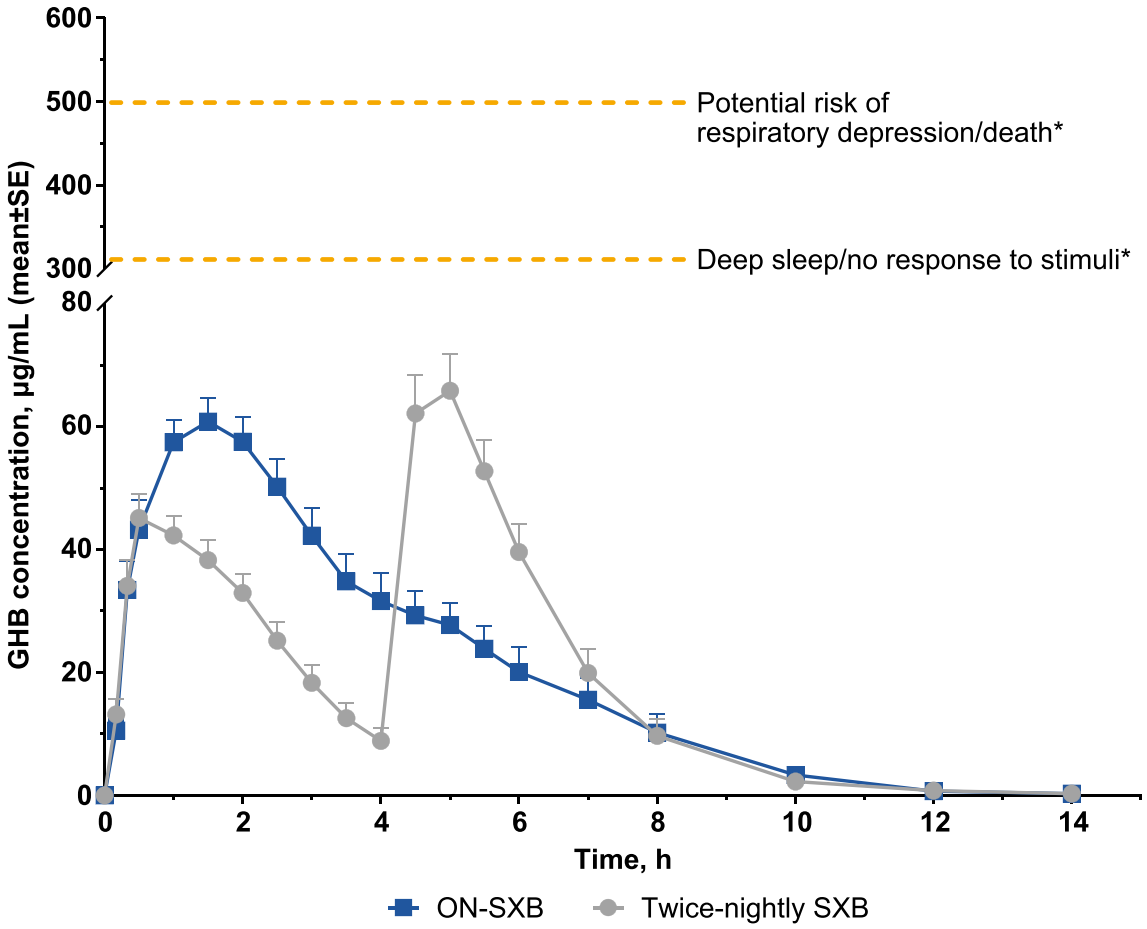


Fig. 2 Mean plasma concentrations of orally administered SXB formulations in healthy volunteers. Mean plasma concentrations of 6-g ON-SXB and twice-nightly SXB formulations over a 14-h period in 25 healthy adult volunteers (adapted from Bogan R, et al. *Sleep Medicine.* 2022;100:442–447 [88]). *Published GHB plasma levels associated with lack of arousability are illustrated (Busardò FP, Jones AW. *Curr Neuropharmacol*. 2015;13(1):47–70 [27]). The estimated plasma concentration of GHB at which there is a risk of death due to respiratory depression is approximately > 500 mg/L (Busardò FP, Jones AW. *Curr Neuropharmacol*. 2015;13(1):47–70 [27]). In a study of 16 healthy adult volunteers who were assessed 20–300 min following intravenous administration of GHB, the mean plasma concentration associated with deep sleep/no response to stimuli was approximately 311 mg/L (Helrich M, et al. *Anesthesiology.* 1964;25:771–775 [15]). *GHB* γ-hydroxybutyrate, *ON-SXB* once-nightly sodium oxybate, *SXB* sodium oxybate

Calcium/magnesium/potassium/sodium oxybate (mixed-salt oxybates; XYWAV®) was approved for the treatment of narcolepsy in 2020 and idiopathic hypersomnia (IH) in 2021 [41] on the basis of positive efficacy and safety data from randomized withdrawal trials [42, 43]. Although this formulation contains less sodium owing to the inclusion of additional cations, twice-nightly dosing is still required [41]. Although a small proportion of the narcolepsy population may be sensitive to sodium, > 20 years of use in clinical practice, as well as an extensive review of published data, have not identified a signal for increased risk of cardiovascular disease, including hypertension, underscoring that clinicians appropriately manage utilization [44].

Flamel Pharmaceuticals (later Avadel Pharmaceuticals) began development of an extended-release, once-nightly formulation of SXB (ON-SXB) in 2013 and has completed a total of 11 pharmacokinetic studies in nearly 300 healthy volunteers. Positive efficacy and safety data from the phase 3 REST-ON trial were published in 2022 [45], and ON-SXB (LUMRYZ™) was approved by the FDA to treat cataplexy and EDS in adults with narcolepsy in 2023 and in patients 7 years of age and older with narcolepsy in 2024 [46]. ON-SXB demonstrated statistically significant and clinically meaningful improvement versus placebo at all doses tested (6 g, 7.5 g, and 9 g) on the coprimary endpoints of mean sleep latency on the MWT, Clinical Global Impression of Improvement (CGI-I) rating, and mean number of weekly cataplexy episodes.

Additional sponsors have described efforts to develop extended-release oxybate formulations for once-nightly dosing (XW10172, XW Pharma; Tris Pharma; JZP324, Jazz

Pharmaceuticals) [47–49]. To date, only preliminary data from XW10172 have been presented [47]. Jazz Pharmaceuticals and Concert Pharmaceuticals conducted a phase 1 study of JZP-386, a deuterium-modified SXB analog, but scant information is available aside from the results not supporting advancement into a later stage clinical trial [50].

When it was introduced into the AASM clinical practice guidelines in 2007, SXB was initially classified as a standard recommendation, defined as a patient-care strategy that reflects a high degree of clinical certainty, for treatment of cataplexy, daytime sleepiness, and DNS associated with narcolepsy [40]. Notably, the updated 2021 AASM guidelines classify SXB as a strong recommendation, defined as an intervention that almost all patients should receive if clinically appropriate, for treatment of narcolepsy, owing to clinically significant improvements in EDS, cataplexy, and disease severity [51]. Additional medications that received a strong recommendation by AASM for narcolepsy include modafinil, solriamfetol, and pitolisant; only pitolisant and SXB are recognized to significantly reduce cataplexy [51]. SXB was also recommended as a first-line treatment in clinical guidelines developed by European entities (European Academy of Neurology, European Sleep Research Society, European Narcolepsy Network) in 2021 and is the only first-line monotherapy recommended for management of concurrent cataplexy, EDS, and DNS symptoms. European guidelines also recommend pitolisant for treatment of EDS (strong recommendation) and cataplexy (weak recommendation) symptoms [52]. Use of SXB is suggested for treatment of moderate to severe sleep paralysis and/or sleep-related hallucinations, but available evidence is limited given the relatively low basal frequency of these symptoms [35, 52].

3.1 Safety and Tolerability of Oxybate Use in Narcolepsy

The FDA requires that all oxybate medications follow a Risk Evaluation and Mitigation Strategy (REMS) [51], which is a drug safety program reserved for certain medications with serious safety concerns to help ensure that the benefits of the medication outweigh the risks [53]. For oxybates, the primary safety concerns are abuse, misuse or diversion, and central nervous system (CNS) depression [38, 41, 46]. As such, oxybate REMS programs require that (i) healthcare providers who prescribe the drug be specially certified, (ii) the drug is dispensed only by specially certified pharmacies, and (iii) the drug be dispensed and shipped only to patients who are enrolled in the REMS with documentation of safe use conditions [38, 41, 46]. Similarly, the European Medicines Agency requires a risk management plan (RMP) for twice-nightly SXB, which aims to identify, characterize, and minimize risks of a medication to ensure safe and effective use [54, 55]. As part of the RMP, the European Medicines Agency requires (i) a controlled distribution program and (ii) physician and patient education materials [56]. The French Monitoring Program requires additional measures, including (i) a 24 h/7 day phone number for questions; (ii) a 24 h/7 day coordinating center with specialized staff; (iii) a physician, pharmacist, and patient registry; (iv) annual, initial, and first monthly prescription renewal forms; and (v) annual postauthorization reports [56]. This safety oversight includes careful review of concomitant medications and potential drug–drug interactions by pharmacists. Notably, alcohol and sedative hypnotics are contraindicated in combination with oxybates [38, 41, 46]. In cases that require concurrent use of oxybates with medications that cause CNS depression, dose reductions of one or both treatments may be required [38, 41, 46].

When used appropriately, adverse reactions with oxybates are generally issues related to tolerability (nausea, vomiting, headache, enuresis, and dizziness), which are usually transient and mild to moderate in severity [45, 57–59]. Patient counseling is important to help set patient expectations that these side effects typically subside over time. Serious risks such as CNS depression, respiratory depression, seizure, and bradycardia have typically been reported by individuals who took the second dose of twice-nightly SXB too early (< 2.5 h), but such risks are not described in the labeling [60, 61]. Psychiatric adverse events following twice-nightly SXB treatment have been observed at low rates [57]. In a post-marketing, real-world evidence study in the European Union involving 730 individuals, only one event was reported [57]. As per product labeling, clinicians should inform patients that oxybates can cause behavioral or psychiatric adverse reactions, including confusion, anxiety, and psychosis [38, 41, 46].

4 Clinical Use of Oxybate in Other Conditions

Potential clinical application of SXB has been evaluated for the treatment of other medical and sleep-related disorders (Table 1). SXB has been investigated as a therapeutic option in alcohol use disorder [62, 63], and further research is warranted. Sleep disturbance plays a key role in the pathophysiology of fibromyalgia, and nonrestorative sleep has been linked to hyperalgesia and bodily hypersensitivity [64]. Twice-nightly SXB (4.5 g or 6 g) demonstrated significant improvement of pain, fatigue, and tenderness, as well as general health, in patients with fibromyalgia [64]. However, despite evidence of potential therapeutic value reported in large, multicenter studies, approval of SXB for the treatment of fibromyalgia was denied by the FDA owing to an inadequate benefit/risk profile [65]. In an open-label study of four patients with chronic cluster headache and disrupted sleep,

Table 1 Summary of clinical use of oxybate in other conditions

Study	Study design	Study population	Key outcomes
Khatami et al., 2011 [66]	Case series of TN-SXB with treatment periods ranging from 8–29 months	Individuals with chronic cluster headache residing in Switzerland ($N = 4$; age range, 21–47 years)	TN-SXB reduced the intensity and frequency of headaches, improved sleep quality, and increased slow-wave sleep
Spaeth et al., 2012 (NCT00423813) [64]	Phase 3, randomized, double-blind, placebo-controlled, multicenter trial of TN-SXB with a 14-week treatment period	Individuals age ≥ 18 years with fibromyalgia residing in the United States and Europe[a] ($N = 573$)	The proportions of individuals with VAS pain reductions of ≥ 30% (4.5 g, $P = 0.002$; 6 g, $P < 0.001$) and ≥ 80% (6 g, $P = 0.003$) were significantly greater with TN-SXB versus placebo
Hidalgo et al., 2013 [67]	Case report of TN-SXB with a 2-week treatment period	Individual age 60 years with episodic cluster headache residing in Germany ($N = 1$)	TN-SXB treatment improved sleep onset, sleep efficiency, and TST; no headaches were reported over the treatment period
Buchele et al., 2018 (NCT02111122) [68]	Phase 2, randomized, double-blind, placebo-controlled, single-center, crossover trial of TN-SXB with a 6-week treatment period	Individuals with Parkinson's disease with EDS residing in Switzerland ($N = 12$; mean age, 62 years)	TN-SXB significantly improved EDS according to the MSLT ($P = 0.002$) and ESS ($P = 0.001$)
Guiraud et al., 2022 (NCT04648423) [63]	Phase 3/4, randomized, double-blind, placebo-controlled, multicenter trial of SXB with a 6-month treatment period followed by a 6-month treatment-free period	Individuals aged 21–75 years with alcohol dependence residing in Austria, Germany, Italy, and Poland ($N = 314$)	During the treatment period, cumulative abstinence duration was higher with SXB compared with placebo (fixed-effect model: $P = 0.001$; random-effect meta-analysis: $P = 0.014$)
During et al., 2023 (NCT04006925) [70]	Phase 2, randomized, double-blind, placebo-controlled, parallel-group, single-center trial of TN-SXB	Individuals aged 40–85 years with isolated RBD or Parkinson's disease with clinical history of presumed RBD residing in the United States ($N = 24$)	While reduction of RBD episodes per month was not significantly different between TN-SXB and placebo ($P = 0.13$), TN-SXB was associated with significant improvements across subjective measures of RBD activity (frequency of monthly episodes, severe episode burden, and overall severity burden; all $P < 0.05$)

EDS excessive daytime sleepiness, *ESS* Epworth Sleepiness Scale, *MSL* mean sleep latency, *MSLT* Multiple Sleep Latency Test, *RBD* REM sleep behavior disorder, *REM* rapid eye movement, *SXB* sodium oxybate, *TN-SXB* twice-nightly sodium oxybate, *TST* total sleep time, *VAS* visual analog scale

[a]France, Germany, Italy, the Netherlands, Poland, Spain, and the United Kingdom

Table 2 Summary of effects of SXB treatment on sleep

Study	Study design	Study population	Key sleep architecture outcomes
Mamelak et al., 2004 [76, 77]	Open-label, dose-escalation, multicenter pilot study of TN-SXB with a 10-week treatment period	Individuals age ≥ 18 years with NT1 residing in the United States and Canada ($N = 25$)	TN-SXB significantly improved change from baseline in sleep latency ($P < 0.001$), SWS ($P < 0.05$), and number of awakenings ($P < 0.01$)
Black et al., 2010 [86]	Double-blind, placebo-controlled, parallel group, multicenter study of TN-SXB with an 8-week treatment period	Individuals age ≥ 16 years with NT1 residing in Canada, Europe[a], and the United States ($N = 228$)	TN-SXB significantly improved TST ($P = 0.049$), SWS ($P < 0.001$), and nocturnal awakenings ($P = 0.009$) versus placebo
Alshaikh et al., 2011 [80]	Case series of TN-SXB	Individuals with NT1 ($N = 4$; age range, 11–65 years)	SXB was associated with decreased N1 and arousal index, as well as increased REM, SWS, and sleep latency
Donjacour et al., 2011 [79]; Donjacour et al., 2011 [78]; Donjacour et al., 2012 [99]	In-laboratory, matched-controlled study of TN-SXB with a 5-night treatment period	Individuals with NT1 and matched controls residing in the Netherlands ($N = 16$; mean age, 38 years)[b]	Compared with controls, SXB treatment in patients with narcolepsy was associated with decreased N1/N2 ($P = 0.005$) and REM ($P = 0.032$) during the day and reduced number of awakenings ($P = 0.002$)
Poryazova et al., 2011 [81]	Long-term, single-center study of TN-SXB over an approximately 2-year period	Individuals with NT1 residing in Switzerland ($N = 18$; mean age, 43 years)	TN-SXB was associated with significant improvements in sleep latency ($P < 0.001$)
van der Heide et al., 2016 [83]	Real-world, matched-controlled, ambulatory study of TN-SXB over a 5-year period	Individuals aged 18–70 years with narcolepsy residing in the Netherlands and Switzerland ($N = 25$)	TN-SXB significantly increased SWS ($P = 0.023$)
Xu et al., 2019 [85]	Systematic review and meta-analysis	Individuals age ≥ 16 years with narcolepsy from 15 randomized clinical trials ($N = 2104$)	GHB was associated with decreased N1 ($P = 0.04$), REM ($P = 0.0006$), number of sleep stage shifts ($P = 0.005$), and nocturnal awakenings ($P = 0.004$) and increased SWS ($P = 0.003$) compared with placebo
Roth et al., 2022 (NCT02720744) [92]	Phase 3, randomized, double-blind, placebo-controlled, multicenter trial of ON-SXB with a 13-week treatment period	Individuals age ≥ 16 years with NT1 or NT2 residing in Australia, Canada, the United States, and Europe[c] ($N = 190$)	ON-SXB significantly improved DNS compared with placebo, reducing sleep stage shifts ($P < 0.001$) and nocturnal arousals ($P < 0.001$) regardless of concurrent stimulant use
Peraita-Adrados et al., 2023 [84]	Longitudinal, observational study of TN-SXB over a 3-year period	Individuals with NT1 residing in Spain ($N = 23$; mean age, 42 years)	TN-SXB increased N2 at year 1 ($P = 0.03$) and N1 at year 3 ($P = 0.03$) compared with month 6

DNS disrupted nighttime sleep, *NT1* narcolepsy type 1, *NT2* narcolepsy type 2, *ON-SXB* once-nightly sodium oxybate, *REM* rapid eye movement, *SWS* slow-wave sleep, *TN-SXB* twice-nightly sodium oxybate, *TST* total sleep time

[a]The Czech Republic, France, Germany, the Netherlands, Switzerland, and the United Kingdom

[b]Donjacour et al 2012 report $N = 14$ [99]

[c]The Czech Republic, Denmark, Finland, France, Germany, the Netherlands, Switzerland, and the United Kingdom

SXB demonstrated reduction in the frequency and intensity of nocturnal headaches, improved daytime headaches, and improved sleep [66]. SXB also demonstrated efficacy in reducing daytime and nocturnal headaches in an individual with episodic cluster headache [67]. In individuals with Parkinson's disease, SXB improved EDS and nocturnal sleep disturbances, which are common and burdensome non-motor manifestations of the disease [68]. The 2021 AASM guidelines include a conditional recommendation for SXB to treat hypersomnia secondary to Parkinson's disease in adults [69]. A double-blind trial investigating SXB in REM sleep behavior disorder (RBD) did not demonstrate SXB superiority over placebo; however, significant improvement across subjective outcomes of RBD activity, including frequency of monthly episodes, severe episode burden, and overall severity burden, was observed [70].

5 Effects of SXB Treatment on Sleep

Individuals with narcolepsy have fragmented sleep with frequent nocturnal awakenings and shortened periods of consolidated sleep, owing to sleep instability (elevated number of stage sleep shifts to wake and lighter sleep stages, along with limited slow-wave and REM sleep). While total sleep time (TST) in narcolepsy may be decreased during the sleep period, it remains normal over a 24-h period [71]. TST in healthy adults, as measured by polysomnography (PSG), has been estimated to range between 6.5 and 7 h [72]. People with narcolepsy also have shorter nocturnal sleep latencies than individuals without narcolepsy, irrespective of subtype [73]. People with NT1 show longer stage 1 (N1) bouts and elevated arousability with shorter bouts in N2 and REM sleep compared with individuals who report problematic daytime sleepiness but do not meet PSG and multiple sleep latency test criteria for NT1, NT2, or IH [74]. Subsequently, people with narcolepsy experience difficulty maintaining continuous sleep throughout the night and wakefulness during the day [75].

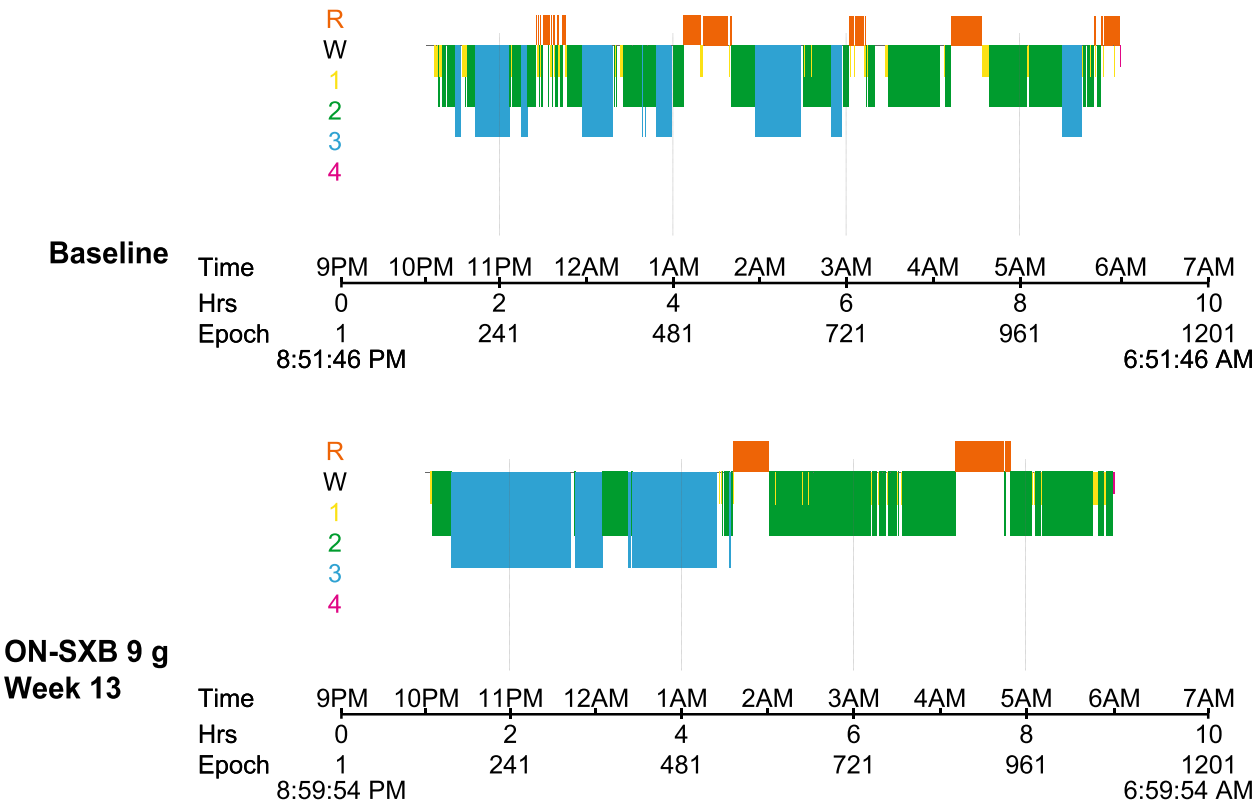


Fig. 3 Illustrative hypnogram: sleep architecture of a 24-year-old female patient with NT1 before and after treatment with ON-SXB. Illustrative hypnogram of sleep cycles assessed using overnight polysomnography performed in clinic (Kushida CA, et al. *Sleep*. 2022;45(6):zsab200 [45]) of an individual with NT1 before and after 13-week treatment with ON-SXB. 1, N1 sleep stage; 2, N2 sleep stage; 3, N3 sleep stage; 4, N4 sleep stage, *NT1* narcolepsy type 1, *ON-SXB* once-nightly sodium oxybate, *R* rapid eye movement sleep stage, *W* wake sleep

Data demonstrating improvements in various sleep parameters for both twice-nightly SXB and ON-SXB have been published (Table 2) [76–85]. Although some data from twice-nightly oxybates are presented as a continuous endpoint, effects on sleep must be evaluated in light of the bifurcated regimen required by twice-nightly oxybate dosing, such as the "first half" and "second half" of the night measurements presented by Black et al. [86]. Interestingly, twice-nightly SXB was associated with greater slow-wave sleep during the second half of the night at the 9-g dose [86], in contrast to the more typical sleep architecture in which slow-wave sleep occurs early in the nocturnal sleep period following homeostatic regulation [87]. While temporal PSG assessment data are not available for ON-SXB, early peak concentrations may theoretically correspond to more slow-wave sleep in the first half of the night [88], as occurs in a more "normal" sleep pattern. An illustrative hypnogram of sleep cycles assessed using overnight PSG performed in clinic [45] of an individual with NT1 before and after treatment with ON-SXB is depicted in Fig. 3.

While PSG assessments are important in clinical trials, real-world effectiveness of medications is based upon how an individual feels after a night's sleep. As the importance of sleep health and regularity is increasingly recognized, some individuals with sleep disorders may mistakenly believe they need to conduct their own assessments to confirm achievement of the recommended 7 to 9 h of nocturnal sleep [89, 90]. However, individual needs for optimal sleep time differ between patients, and parameters related to reported sleep quality and refreshing nature of sleep are important to consider. To help evaluate treatment response, clinicians should educate patients with narcolepsy to assess how they feel about their sleep and how they function the next day. Individuals with narcolepsy sleep a similar number of hours, on average, to those without narcolepsy [71]. In clinical trials of both twice-nightly SXB and ON-SXB, TST ranged from approximately 6–7 h prior to initiation of the study medication and remained so throughout the trials (twice-nightly SXB, 358.0–380.9 min; ON-SXB, 393.5–403.1 min) [86, 91]. Clinically significant improvements in objective and subjective measures of sleep architecture have been consistently observed with ON-SXB, regardless of concomitant alerting agent use (Fig. 4) [92].

While there are no published data on the effect of mixed-salt oxybates on sleep architecture, the effect should theoretically be similar. However, it is noteworthy that mixed-salt oxybate is not bioequivalent to twice-nightly SXB, likely owing to less sodium, which is required for sodium-dependent MCT transport [93].

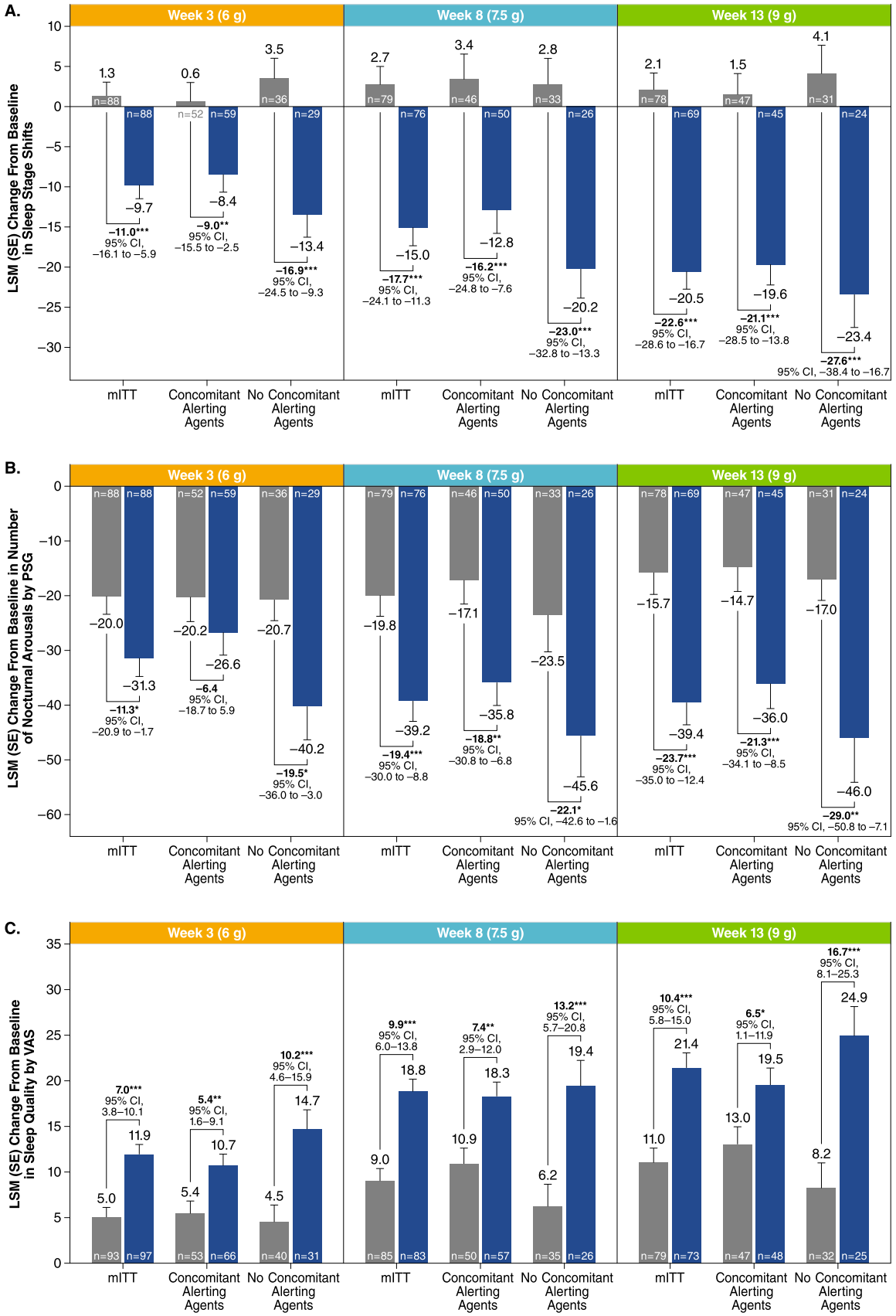
6 SXB Pharmacokinetic Profile

ON-SXB was developed to improve pharmacokinetic parameters and potential therapeutic benefit in narcolepsy treatment. The pharmacokinetics of twice-nightly SXB and ON-SXB were compared in a bioavailability study (Table 3) [88]. The maximum serum concentration (C_{max}) with a single dose of ON-SXB at 6 g (65.8 mg/mL) was bioequivalent to that of the second dose of twice-nightly SXB 3 g, given 4 h after the first 3-g dose (77.1 mg/mL) [88]. Median time to reach maximum plasma concentrations (T_{max}) was 0.5 h after the first dose and 1 h after the second dose of twice-nightly SXB and 1.5 h after ON-SXB administration. Notably, the mean plasma concentration of GHB with ON-SXB at 0.5 h after dosing was comparable to the C_{max} after the first dose of twice-nightly SXB (Fig. 2) [88].

GHB exposure, as determined by area under the concentration-time curve (AUC), was also bioequivalent between the single dose of ON-SXB and two doses of twice-nightly SXB (geometric least squares mean $AUC_{0\text{-inf}}$, 241.8 versus 235.1 µg·h/mL; geometric mean ratio [90% CI] 102.9% [98.0–108.0]), with low intrapatient variability between the two treatments [88]. Although bioequivalence was demonstrated through C_{max} and AUC, plasma concentrations 8 hours after dosing (C_{8h}) were lower with ON-SXB compared with twice-nightly SXB and below the bioequivalence threshold (geometric least squares mean, 2.3 versus 3.7 µg/mL; geometric mean ratio [90% CI], 61.7% [45.8–83.0]). These findings suggest that ON-SXB may result in less next-day sleepiness or grogginess after wakening [88]. The pharmacokinetics of ON-SXB may follow an ideal drug exposure, with a fast onset reaching peak concentrations early in the evening to encourage sleep onset, maintenance through the night, and dissipation from the circulation by morning. ON-SXB, which has a calculated half-life of 2.25 h [91], may provide pharmacokinetic advantages over twice-nightly SXB, which requires patients to administer the second dose overnight, interrupting nighttime sleep for individuals with narcolepsy and their bed partners. ON-SXB demonstrates a pharmacokinetic profile consistent with those of sedative hypnotics for sleep that similarly demonstrate high initial concentrations that progressively decline over time, corresponding to waking hours [94]. Therefore, ON-SXB may theoretically produce a more "normal" sleep pattern in people with narcolepsy [45, 88].

7 Conclusions

Early studies from nearly 50 years ago demonstrated that GHB was a promising treatment for narcolepsy owing to its ability to modulate sleep/wake patterns and promote


A.
Week 3 (6 g)
Week 8 (7.5 g)
Week 13 (9 g)
LSM (SE) Change From Baseline in Sleep Stage Shifts
1.3
n=88
n=88
−9.7
−11.0*** 95% CI, −16.1 to −5.9
0.6
n=52
n=59
−8.4
−9.0** 95% CI, −15.5 to −2.5
3.5
n=36
n=29
−13.4
−16.9*** 95% CI, −24.5 to −9.3
2.7
n=79
n=76
−15.0
−17.7*** 95% CI, −24.1 to −11.3
3.4
n=46
n=50
−12.8
−16.2*** 95% CI, −24.8 to −7.6
2.8
n=33
n=26
−20.2
−23.0*** 95% CI, −32.8 to −13.3
2.1
n=78
n=69
−20.5
−22.6*** 95% CI, −28.6 to −16.7
1.5
n=47
n=45
−19.6
−21.1*** 95% CI, −28.5 to −13.8
4.1
n=31
n=24
−23.4
−27.6*** 95% CI, −38.4 to −16.7
mITT
Concomitant Alerting Agents
No Concomitant Alerting Agents
B.
Week 3 (6 g)
Week 8 (7.5 g)
Week 13 (9 g)
LSM (SE) Change From Baseline in Number of Nocturnal Arousals by PSG
n=88 n=88
−20.0
−31.3
−11.3* 95% CI, −20.9 to −1.7
n=52 n=59
−20.2
−26.6
−6.4 95% CI, −18.7 to 5.9
n=36 n=29
−20.7
−40.2
−19.5* 95% CI, −36.0 to −3.0
n=79 n=76
−19.8
−39.2
−19.4*** 95% CI, −30.0 to −8.8
n=46 n=50
−17.1
−35.8
−18.8** 95% CI, −30.8 to −6.8
n=33 n=26
−23.5
−45.6
−22.1* 95% CI, −42.6 to −1.6
n=78 n=69
−15.7
−39.4
−23.7*** 95% CI, −35.0 to −12.4
n=47 n=45
−14.7
−36.0
−21.3*** 95% CI, −34.1 to −8.5
n=31 n=24
−17.0
−46.0
−29.0** 95% CI, −50.8 to −7.1
mITT
Concomitant Alerting Agents
No Concomitant Alerting Agents
C.
Week 3 (6 g)
Week 8 (7.5 g)
Week 13 (9 g)
LSM (SE) Change From Baseline in Sleep Quality by VAS
7.0*** 95% CI, 3.8–10.1
5.0
11.9
n=93 n=97
5.4** 95% CI, 1.6–9.1
5.4
10.7
n=53 n=66
10.2*** 95% CI, 4.6–15.9
4.5
14.7
n=40 n=31
9.9*** 95% CI, 6.0–13.8
9.0
18.8
n=85 n=83
7.4** 95% CI, 2.9–12.0
10.9
18.3
n=50 n=57
13.2*** 95% CI, 5.7–20.8
6.2
19.4
n=35 n=26
10.4*** 95% CI, 5.8–15.0
11.0
21.4
n=79 n=73
6.5* 95% CI, 1.1–11.9
13.0
19.5
n=47 n=48
16.7*** 95% CI, 8.1–25.3
8.2
24.9
n=32 n=25
mITT
Concomitant Alerting Agents
No Concomitant Alerting Agents

◀ **Fig. 4** Effects of ON-SXB treatment on sleep architecture parameters with and without concomitant alerting agent use. Change from baseline in (**A**) sleep stage shifts, (**B**) nocturnal arousals, (**C**) VAS sleep quality, and (**D**) VAS refreshing nature of sleep, for participants with or without concomitant alerting agent use (mITT population; Roth T, et al. *CNS Drugs*. 2022;36(4):377–387 [92]). *$P < 0.05$, **$P \leq 0.01$, ***$P \leq 0.001$. VAS was on a scale of 1–100. *LSM* least squares mean, *mITT* modified intent to treat, *ON-SXB* once-nightly sodium oxybate, *PSG* polysomnography, *VAS* visual analog scale

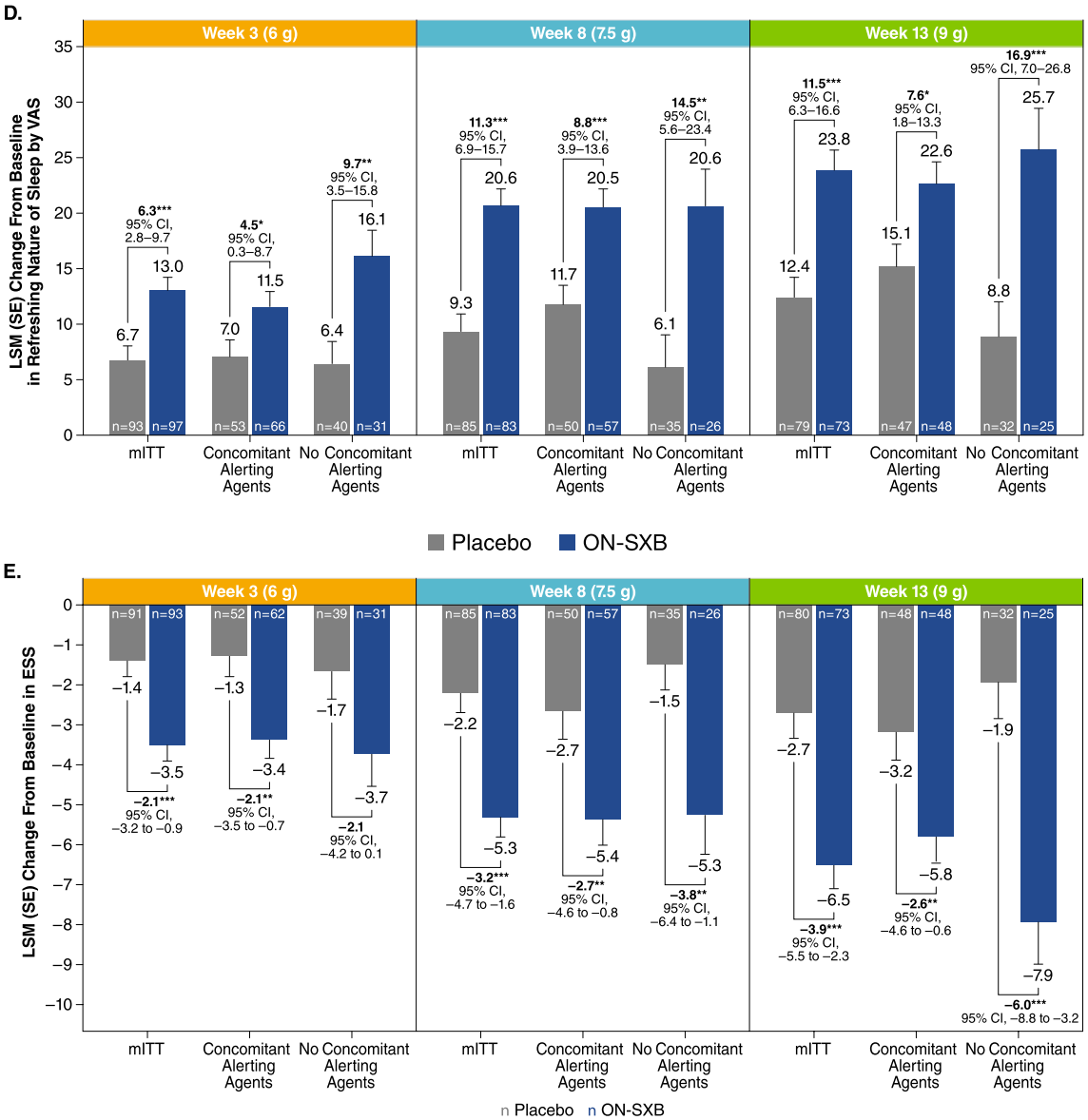


Fig. 4 (continued)

Table 3 Summary of SXB pharmacokinetic profile

Study	Study design	Study population	Key pharmacokinetic parameters
Chen et al., 2021 [93]	Analysis of two phase 1, open-label, randomized, single-dose crossover studies of TN-SXB and mixed-salt oxybates	Healthy volunteers aged 18–50 years ($N = 108$)	Mixed-salt oxybates and TN-SXB met bioequivalence criteria for AUC; however, mixed-salt oxybates had a lower C_{max}
Seiden et al., 2021 [29]	Pilot study Randomized, open-label, crossover study of ON-SXB and TN-SXB Dose-proportionality study Open-label, single-dose, 3-sequential period study of ON-SXB Relative bioavailability study Randomized, open-label, crossover study of ON-SXB and TN-SXB Food-effect study Open-label, 2-period, crossover, single-dose study of ON-SXB	Healthy volunteers aged 18–65 years Pilot study ($N = 16$) Dose-proportionality study ($N = 20$) Relative bioavailability study ($N = 28$) Food-effect study of ON-SXB ($N = 16$)	Pilot study $AUC_{0\text{-inf}}$ of ON-SXB was comparable to that of TN-SXB Dose-proportionality study ON-SXB had similar overall pharmacokinetic profile at all tested doses and C_{max} and $AUC_{0\text{-inf}}$ increased in a dose-proportional manner Relative bioavailability study $AUC_{0\text{-inf}}$ and interpatient variability of ON-SXB were similar to those of TN-SXB Food-effect study $AUC_{0\text{-inf}}$ met bioequivalence criteria between the fed and fasted states, with lower C_{max} in the fed state
Bogan et al., 2022 [88]	Phase 1, randomized, crossover, open-label single-center study of ON-SXB 6 g versus TN-SXB 6 g (two 3-g doses)	Healthy volunteers aged 18–65 years residing in the United States ($N = 28$)	Pharmacokinetic properties of ON-SXB and TN-SXB, including C_{max}, $AUC_{0\text{–inf}}$, and $AUC_{0\text{–t}}$ were bioequivalent; however, C_{8h} for ON-SXB fell below bioequivalence criteria when compared with TN-SXB

$AUC_{0–inf}$ area under the concentration-time curve from time 0 extrapolated to infinity, $AUC_{0–t}$ area under the concentration-time curve from time 0 to the time of the last observed/measured nonzero concentration, C_{8h} plasma concentration 8 h after dosing, C_{max} maximum plasma concentration, *ON-SXB* once-nightly sodium oxybate, *TN-SXB* twice-nightly sodium oxybate

slow-wave sleep [25]. Following establishment of SXB, the sodium salt of GHB, as an FDA-approved treatment for narcolepsy, safety and efficacy of SXB in narcolepsy management have been supported by decades of utilization and AASM clinical practice guideline recommendations [40, 44, 51]. Despite this, many sleep clinicians are reluctant or avoid incorporating oxybates into their treatment armamentarium. Currently, the AASM strongly recommends four medications for narcolepsy: modafinil, solriamfetol, sodium oxybate, and pitolisant [51]. However, only two medications are both FDA-approved and strongly recommended by the AASM for treating cataplexy: sodium oxybate and pitolisant [46, 51, 95]. Treatment decisions should be individualized for each patient, with ongoing assessments. Many patients will require polypharmacy, and combining drugs with different mechanisms of action may be helpful. Notably, findings from a recent post hoc analysis of REST-ON demonstrated that the 37% of the overall trial population, who received ON-SXB monotherapy, experienced significant improvements across multiple domains [96].

When treated with twice-nightly oxybates, individuals must chronically awaken to take a second dose during nighttime sleep, which is already disrupted in the majority of people with narcolepsy [2, 97]. Although all oxybates are effective at treating EDS and cataplexy, ON-SXB only requires one dose at bedtime, which is recognized as a major contribution to patient care [98]. With > 20 years of efficacy and safety data in the treatment of narcolepsy from twice-nightly SXB and > 3 years of ON-SXB data from the long-term RESTORE study, clinicians can rely upon a well-characterized safety profile for the drug moiety, along with the advantage of a single bedtime dose provided by ON-SXB.

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Conflict of interest Thomas Roth is a consultant for Avadel Pharmaceuticals, Eisai, Idorsia, Jazz Pharmaceuticals, Merck & Co., Orexo, and Takeda Pharmaceutical Co.

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Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

Author Contributions Thomas Roth contributed to the conceptualization and refining of the review, analysis and interpretation, and writing of the original draft, as well as reviewing and editing the manuscript.

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