Neurol Ther
https://doi.org/10.1007/s40120-024-00607-8

ORIGINAL RESEARCH

Dosing Optimization of Low-Sodium Oxybate in Narcolepsy and Idiopathic Hypersomnia in Adults: Consensus Recommendations

Anne Marie Morse · Richard K. Bogan · Asim Roy · Michael J. Thorpy

Received: December 15, 2023 / Accepted: March 18, 2024

ABSTRACT

Introduction: Low-sodium oxybate (LXB) is approved for treatment of narcolepsy in patients aged 7 years and older and treatment of idiopathic hypersomnia in adults. LXB contains the same active moiety with 92% less sodium than sodium oxybate (SXB). As the indication for oxybate treatment in patients with idiopathic hypersomnia is new and allows for individualized dosing optimization, guidance for beginning LXB treatment is needed. In particular, clinicians may benefit from guidance regarding treatment initiation, dosing/regimen options, potential challenges, and treatment expectations. Additionally, pharmacokinetic profiles differ slightly between both treatments, and further guidance on transitioning from SXB to LXB in patients with narcolepsy may aid clinicians.

Methods: An expert panel of five sleep specialists was convened to obtain consensus on recommendations for these topics using a modified Delphi process.

Results: Across two virtual meetings, the panel agreed on 31 recommendations with a high degree of consensus that fell into four overarching topics: (1) introducing LXB to patients; (2) initiating LXB for adult narcolepsy and idiopathic hypersomnia; (3) addressing challenges in using LXB; and (4) transitioning from SXB to LXB. The panel recommended that clinicians provide a clear overview of how LXB works for treating symptoms in narcolepsy or idiopathic hypersomnia, as appropriate for their patients, explain safety aspects, and set expectations prior to initiating LXB treatment. Strategies for initial dosing and regimen are provided. Strategies for adjusting the dose, regimen, timing, and consideration of individual factors were developed for specific instances in which patients may have trouble staying asleep or waking up, as well as guidance for addressing potential adverse events, such as nausea, dizziness, anxiety, and depression. Discussion points based on existing literature and clinical experience were included as relevant for each statement.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-024-00607-8.

A. M. Morse (✉)
Janet Weis Children's Hospital, Geisinger Medical Center, 100 North Academy Avenue, Danville, PA 17822, USA
e-mail: amorse@geisinger.edu

R. K. Bogan
University of South Carolina School of Medicine, Columbia, SC, USA

A. Roy
Ohio Sleep Medicine and Neuroscience Institute, Dublin, OH, USA

M. J. Thorpy
Albert Einstein College of Medicine, Bronx, NY, USA

Published online: 25 April 2024

Conclusion: Clinicians may use this resource to guide LXB dosing optimization with patients.

Keywords: Consensus panel; Drug therapy; Idiopathic hypersomnia; Narcolepsy; Low-sodium oxybate; Recommendations; Titration

Key Summary Points

Why carry out this study?

As a result of the recent approval of low-sodium oxybate for treating idiopathic hypersomnia, in addition to the previously approved indication for narcolepsy, expert guidance on when and how to adjust dosing, as well as detailed guidance for patients who are transitioning from sodium oxybate to low-sodium oxybate, will be of great benefit to physicians.

An expert panel of five practicing physicians with extensive expertise in treating patients with narcolepsy and/or idiopathic hypersomnia developed a set of 31 recommendation statements to guide low-sodium oxybate treatment.

What was learned from the study?

The panel's recommendation statements were organized into four overarching topics: (1) introducing low-sodium oxybate to patients; (2) initiating low-sodium oxybate for adult narcolepsy and idiopathic hypersomnia; (3) addressing challenges in using low-sodium oxybate for adult narcolepsy and idiopathic hypersomnia; and (4) transitioning from sodium oxybate to low-sodium oxybate.

The panel recommended that clinicians explain how LXB works, explain safety aspects, and set expectations with their patients prior to starting treatment.

Strategies were recommended for optimizing LXB dosage based on individual efficacy and tolerability and ensuring adequate sleep duration.

INTRODUCTION

Narcolepsy and idiopathic hypersomnia are unique chronic sleep disorders with the common symptom of excessive daytime sleepiness (EDS) [1]. Narcolepsy is also associated with cataplexy (narcolepsy type 1 only), disrupted nighttime sleep, sleep paralysis, and hypnagogic/hypnopompic hallucinations [1, 2]. Idiopathic hypersomnia symptoms include sleep inertia; long, unrefreshing naps; and long sleep times (those who sleep $\geq$ 10 or 11 h per 24-h period often experience worse symptoms) [1, 3, 4]. The standard of care for patients with narcolepsy has been sodium oxybate (SXB, Xyrem® [Jazz Pharmaceuticals; Dublin, Ireland]), which is approved for treating EDS or cataplexy in people 7 years of age and older [5–9]. A new oxybate formulation (calcium, magnesium, potassium, and sodium oxybates), low-sodium oxybate (LXB, Xywav® [Jazz Pharmaceuticals; Dublin, Ireland]), was approved by the United States Food and Drug Administration (US FDA) in 2020 for patients with narcolepsy and in 2021 for adults with idiopathic hypersomnia [10–14]. Until US approval of LXB, no medication had been approved for treatment of idiopathic hypersomnia worldwide [10]. LXB has the same active moiety as the high-sodium oxybate SXB (i.e., gamma-hydroxybutyrate [GHB]) but has 92% less sodium [10, 15].

SXB and LXB are salts of GHB that are hypothesized to act on GABAergic circuits within the brain. GHB enhances sleep/wake state stability, thereby improving EDS and preventing cataplexy [9, 16]. Similar to SXB, LXB is administered as a liquid $\geq$ 2 h after eating and is taken while in bed. The pharmacokinetics of GHB are nonlinear [17], which is important to consider when assessing the pharmacodynamics of SXB and LXB. LXB meets bioequivalence criteria for area under the curve with SXB but has some pharmacokinetic/pharmacodynamic (PK/PD) differences [18]. In fasting individuals, LXB takes slightly longer than SXB to reach a maximum plasma concentration (T_{max} median 1.00 h vs 0.52 h, respectively), and the maximum plasma concentration for LXB is lower than that of SXB (C_{max} median 94.63 μg/mL vs

123.0 μg/mL, respectively). Nevertheless, LXB demonstrates robust efficacy over multiple symptoms in patients with narcolepsy or idiopathic hypersomnia [19, 20].

Although physicians have been prescribing SXB to patients with narcolepsy for 2 decades, recommendations for optimizing LXB dosing may be useful for prescribers given its newer indication for individuals with idiopathic hypersomnia, as well as its subtle PK/PD differences with SXB. LXB allows for flexible dosing paradigms, both in the titration of the dose amount in grams as well as the number of doses taken per night (for patients with idiopathic hypersomnia). The recommended maximum total nightly dose of LXB for patients with narcolepsy is 9 g, divided into two doses. For idiopathic hypersomnia, the recommended maximum dose is 6 g (once nightly) or 9 g (twice nightly) [10]. Based on experience with SXB, recommendations for LXB may include explaining to patients how LXB works and setting expectations on time to therapeutic effect.

Awareness of potential challenges with patients who are taking LXB, such as the need to individualize treatment regimens, can also be helpful. LXB, similar to SXB, should be taken twice nightly in participants with narcolepsy, and in a social media-based analysis of people with narcolepsy who took SXB, 65% of patients reported missing the second dose at least monthly [21]. FT218 is a newly approved fixed-dose high-sodium oxybate formulation (containing the same sodium per dose as SXB) that is taken once nightly for the treatment of narcolepsy [22, 23]. However, the ability to adjust dosing paradigms (either gram amount or nightly frequency), as with LXB, can be an asset in tailoring treatment to a patient's specific needs. A real-world survey of physicians treating patients with narcolepsy found that 48% of physicians adjusted their patients' nightly number of doses (e.g., from three nightly doses to two nightly doses, or from two to one) for reasons such as encouraging adherence or professional or family obligations [24]. The majority of physicians surveyed felt the ability to adjust oxybate dosing to accommodate routine changes was important or very important (88%) and had a positive impact on their ability to provide care (88%).

As a result of this degree of flexibility, physicians may benefit from expert guidance on when and how to adjust LXB dosing, as well as detailed guidance for patients who are transitioning from SXB to LXB. To address this need, an expert panel was convened to develop consensus-based guidance for the treatment of narcolepsy and idiopathic hypersomnia with LXB.

METHODS

Expert Panel Selection and Topic Development

Five practicing physicians were selected for the expert panel on the basis of their extensive expertise in treating patients with narcolepsy and/or idiopathic hypersomnia; one of the five physicians (AMM) was chosen to serve as the panel chair (Fig. 1). The consensus panel's initial objectives, formulated by Jazz Pharmaceuticals and Interactive Forums, Inc. (IFI), were to develop consensus-based guidance for initiating and achieving optimal symptom management with LXB for narcolepsy and idiopathic hypersomnia within the parameters of the prescribing information. A modified Delphi process, previously described in the literature, was used that included the development of a literature summary and limited the number of rounds of ratings to two [25]. An outline of recommendation topics (derived from the LXB prescribing label and key literature) was drafted by IFI, and this was subsequently reviewed and revised by the panel chair. The panel chair, in collaboration with IFI, generated an extensive list of questions about the recommendation topics. The panel chair then reviewed and prioritized these questions for an online survey to be completed by the panel experts prior to the first consensus panel meeting.

As this article is based on a modified Delphi approach in which all participants originally consented to participate and author the present manuscript, no formal ethical approval was sought.

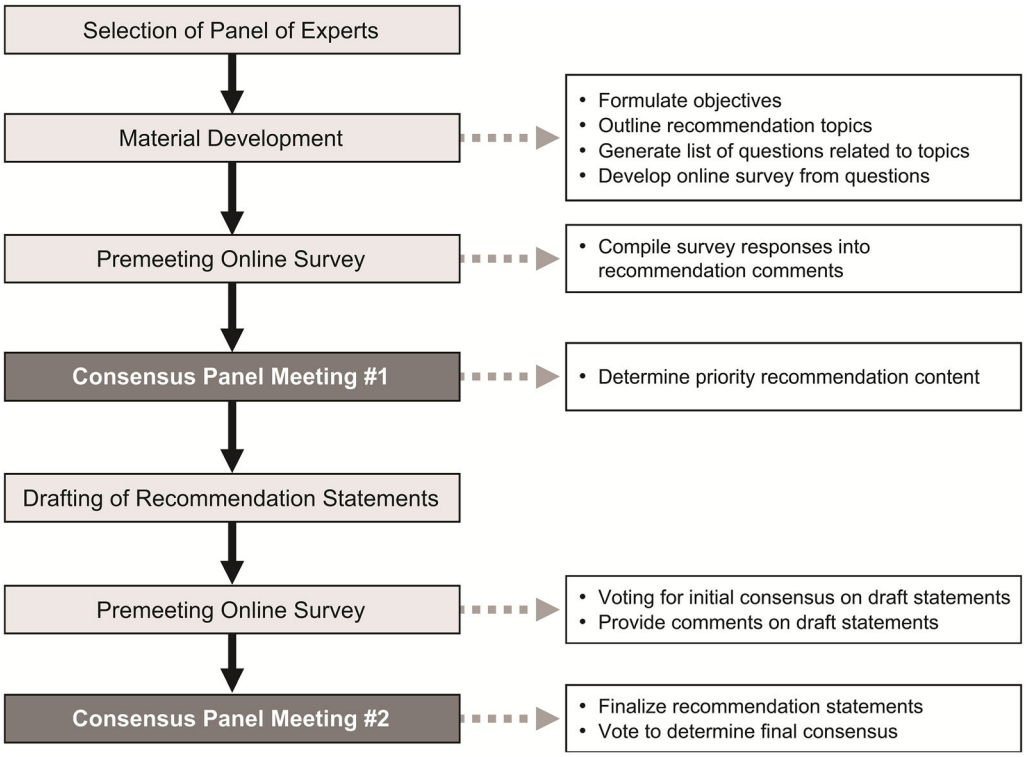

Fig. 1 Modified Delphi consensus panel process

Recommendation Statement Development

The online survey was posted and completed independently by each expert panel member prior to the first consensus panel meeting. The survey responses were compiled by IFI into recommendation comments with additional supportive comments. During the first consensus panel meeting (which was held virtually), the panel experts determined which recommendation content should receive priority. On the basis of discussions from the first consensus panel meeting, the panel chair directed the development of draft recommendation statements. Using a second online survey, the panel experts reviewed these draft statements, voted to establish initial consensus, and provided comments (based on their clinical judgment) to improve the statements. Under the direction of the panel chair, IFI revised the statements accordingly. During the second consensus panel meeting (also held virtually), the panel experts finalized the recommendation statements and voted to determine final consensus. Jazz Pharmaceuticals did not provide input on these statements during development but reviewed each statement to ensure the guidance provided was consistent with the prescribing information.

Establishing Consensus

The expert panel members voted on each recommendation statement using a scale from 0 (not at all agree) to 4 (very much agree). Voting for consensus occurred twice: first on the draft recommendation statements that were developed following the first panel meeting, and second on the revised recommendation statements during the second panel meeting.

RESULTS

The first and second consensus panel meetings were held on September 16, 2022 and October 24, 2022, respectively. During the second meeting, revisions were made to 30 recommendations and one new recommendation was added. The recommendations were organized into four broad recommendation topics (i.e., 1. introducing LXB to patients; 2. initiating LXB for adult narcolepsy and idiopathic hypersomnia; 3. addressing challenges in using LXB for adult narcolepsy and idiopathic hypersomnia; 4. transitioning from SXB to LXB), each with at least one subtopic. This resulted in eight overall recommendation topics, several of which contained multiple recommendations. The panel experts achieved a high level of agreement, including 30 statements rated 4.0 and one statement rated 3.8; additionally, ancillary guidance was generated for each recommendation and is presented below. All recommendation statements are presented together in Supplemental Table S1.

Introducing LXB to Patients

Recommendations comprising statements 1–3 are shown in Table 1.

Introducing LXB as a Therapeutic Option

A discussion of LXB PK/PD and oxybate mechanism of action will be beneficial to the patient's understanding of details such as nighttime administration in bed, safety precautions, and multiple-dose administration. LXB takes an average of 1.3 h to reach C_{max} (in fasting individuals) and is metabolized quickly (the mean terminal elimination half-life of GHB is 0.66 h) [10]. Although the mechanism of action of LXB is not completely understood, it is hypothesized to exert its therapeutic effect through the $GABA_B$ receptor during sleep at noradrenergic and dopaminergic neurons, as well as at thalamocortical neurons [10].

Helping Patients Understand the Safety of LXB

Typical illicit GHB doses (11–18 g and usually repeated administrations) are higher than therapeutic oxybate doses (6–9 g oxybate salts, divided) [26, 27]; however, the risk for oxybates to be abused remains and warrants monitoring [10]. The Risk Evaluation and Mitigation Strategy (REMS) program, which has a central pharmacy that distributes oxybate prescriptions, tracks volumes of LXB and SXB dispensed and utilized, concomitant medications, illicit drug use, and medical problems [28]. In the postmarketing period from December 2016 through December 2017, 31 instances of oxybate abuse were reported through the REMS program, out of 17,037 enrolled individuals who received at least one SXB shipment during that period [29]. Additionally, there were 343 instances of misuse and 22 instances of diversion. As LXB was approved after the reporting period for the REMS program, the postmarketing study did not include people who were prescribed LXB.

LXB, along with other oxybates, is contraindicated with alcohol or sedative hypnotics as the combined use can increase the CNS depressant effects of LXB [9, 10, 23]. In cases where patients would like to consume an alcoholic beverage (e.g., at a party or event), they may discuss temporary dosing adjustments with their physician [24]. Concomitant use of LXB and divalproex sodium increases the systemic exposure to GHB [10]. For patients already taking LXB who are initiating divalproex sodium treatment, the LXB dose should be decreased by at least 20%. For patients already taking divalproex sodium who are initiating LXB treatment, a lower starting dosage of LXB is recommended (e.g., < 4.5 g per night).

Presenting Information Regarding Label Warnings

Symptoms of CNS depression that can occur from LXB treatment include decreased alertness, loss of consciousness, hypotension, respiratory depression, profound sedation, and death [10]. Patients are instructed not to drive (or do anything that requires them to be fully awake or is dangerous) for at least 6 h after taking LXB [10]. Rates of respiratory depression in clinical trials of SXB were relatively low: in one trial, 2 of 128 patients with narcolepsy had profound CNS depression that resolved after respiratory intervention [10], and in two controlled trials,

Table 1 Introducing LXB to patients

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
Introducing LXB to patients	1	Prior to initiating LXB, discuss rationale for its use in narcolepsy and idiopathic hypersomnia and implications of its PK/PD profile. Explain that LXB contains oxybate, which is identical to an endogenous molecule made in the human brain, GHB. Oxybate has an inhibitory effect on alerting pathways in the brain, which enables it to improve the quality of sleep. In addition, oxybate is rapidly absorbed and metabolized, which is why LXB is taken in bed and typically in two doses (the recommended regimen for patients with narcolepsy, and a regimen option for patients with idiopathic hypersomnia), separated by 2.5–4 h. Due to its mechanism of action, patients with narcolepsy can expect improvement in both EDS and cataplexy; patients with idiopathic hypersomnia can expect improvement in their EDS and overall symptom burden	N/A[b], 4.0
Helping patients understand the safety of LXB	2	(a) When introducing LXB to patients, emphasize prescribing parameters that ensure its safe use, including the REMS program and guidance to avoid use with alcohol or other CNS depressants. Mention data demonstrating safety and FDA approval of therapeutic oxybate in children and adults when used as prescribed (b) Consider explaining key differences between LXB and illicit GHB, including comparative doses utilized and common recreational use of GHB in combination with other substances	2.8, 4.0

Table 1 continued

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
Presenting information regarding label warnings	3a: CNS depression, respiratory depression	(i) CNS depression: explain the potential for CNS depression with LXB and emphasize the importance of taking the medicine only when in bed and never in combination with alcohol or other CNS depressants. Discuss the REMS program and ongoing monitoring	i. 3.6, 4.0
		(ii) Respiratory depression: explain that respiratory depression and sleep-disordered breathing can occur. Inform the patient that starting dose is low and that therapeutic response and adverse effects will be monitored. Patients with sleep-disordered breathing should be counseled and monitored when appropriate	ii. 3.2, 4.0
	3b: abuse/misuse	Explain the potential for abuse, misuse, and diversion of the medication. Discuss the REMS program, role of central pharmacy, and ongoing monitoring	3.4, 4.0
	3c: depression, suicidality, or psychiatric effects	Explain that depression, anxiety, or suicidality could emerge or intensify during treatment, and that these symptoms will be carefully assessed and monitored. Patients should be advised to report any worsening of these symptoms	3.2, 3.8
	3d: parasomnias	If the patient has a history of parasomnias, counsel that events can worsen or reemerge. Rarely, events may emerge in patients without a prior history of parasomnias. Educate patients in maintaining a safe sleep environment. Patients should report any abnormal behavior during sleep	3.2, 4.0

CNS central nervous system, *EDS* excessive daytime sleepiness, *FDA* US Food and Drug Administration, *GHB* gamma-hydroxybutyrate, *LXB* low-sodium oxybate, *PD* pharmacodynamics, *PK* pharmacokinetic, *REMS* Risk Evaluation and Mitigation Strategy

[a]On a scale of 0–4

[b]This statement was derived from comments and suggestions made by the panel during meeting #2. It was reviewed during a follow-up panel meeting and achieved a consensus agreement rating of 4.0

none of 40 patients with a baseline apnea–hypopnea index of 16–67 events per hour experienced clinically significant worsening of their sleep-disordered breathing [10]. In 50 patients with obstructive sleep apnea (OSA), 3 patients (6%) had oxygen desaturation $\leq$ 55% when taking 9 g of SXB [10]. A trial of pharmacotherapy (including SXB) in participants with OSA found that central apneas increased in those taking SXB, with clinically significant oxygen desaturations observed in three participants [30]. Approaches to managing obstructive versus central apneas vary somewhat. Management of OSA can involve

behavioral measures (e.g., abstaining from alcohol, weight loss), positive airway pressure, mandibular repositioning devices, or surgery [31]. Management of central sleep apnea includes positive pressure therapy (e.g., continuous positive airway pressure, adaptive servo-ventilation, and noninvasive positive pressure ventilation), phrenic nerve stimulation, and low-flow supplemental oxygen administration [32].

Most dangers associated with oxybate products, including LXB, are related to its combination with other substances. As mentioned in Sect. "Helping Patients Understand the Safety of LXB", the REMS central pharmacy tracks volumes of SXB and LXB dispensed and utilized, concomitant medications, illicit drug use, and medical problems [28]. Withdrawal symptoms associated with oxybate products can sometimes occur when a drug is suddenly stopped after being taken for a period of time. Several patients in clinical trials have reported insomnia after abruptly stopping LXB treatment (narcolepsy with cataplexy, $n = 1$; idiopathic hypersomnia, $n = 8$), and one patient with idiopathic hypersomnia reported visual/auditory hallucinations [10]. Although tolerance to oxybate medications has not been systematically studied, in long-term clinical studies of SXB in patients with narcolepsy, or LXB in patients with idiopathic hypersomnia, clinical efficacy was maintained without requiring subsequent dose increases [33, 34].

Before and during LXB treatment, it is critical to assess for depression, anxiety, and suicidality. Depression and depressive symptoms are more prevalent in people with narcolepsy or idiopathic hypersomnia than in the general population [35–38]. Presence or development of these symptoms may warrant co-management with psychiatry or psychology for added safety. In clinical trials for LXB, although current or past major depression was a trial exclusion criterion, depression and depressed mood were reported by 3% and 4% of participants with narcolepsy, and 1% and 3% of participants with idiopathic hypersomnia, respectively [10]. There were no reports of suicide or suicidal ideation by participants taking LXB in the idiopathic hypersomnia clinical trial [20]; however, it must be noted that two participants in the narcolepsy trial endorsed items on the Columbia-Suicide Severity Rating Scale (one each before and after discontinuing study medication) [19]. Four of 781 participants with narcolepsy (< 1%) taking SXB in clinical trials discontinued as a result of depression. Two suicides and two suicide attempts occurred in adult patients taking SXB in clinical trials ($N = 781$) [10]. Some instances of depression and of depression with suicidal ideation have been reported in individuals with narcolepsy who started taking SXB; these symptoms resolved upon either reducing the SXB dose or stopping SXB completely [39, 40]. Psychotic symptoms (e.g., daytime hallucinations) have occurred in people with narcolepsy, which also resolved upon reducing dose or stopping SXB [41–43]. One case of psychosis followed by suicidal ideation and a near-fatal suicide attempt was reported in an adolescent with narcolepsy; following cessation of SXB treatment, this individual's psychotic symptoms and suicidal ideations did not recur [44].

Parasomnias, such as sleep paralysis and sleepwalking, occur in the general population. Sleep paralysis has a prevalence of 7.5–35% [1], and a systematic review indicated that approximately 20% of individuals have experienced at least one episode of sleep paralysis [45]. A lifetime prevalence of 6.9% has been reported for sleepwalking from a systematic review of studies including more than 100,000 individuals [46]. In clinical trials for LXB, 6% of patients with narcolepsy and 5% of patients with idiopathic hypersomnia reported parasomnias such as sleepwalking (although the presence of clinically significant parasomnias was an exclusion criterion for participating in these trials) [10].

General guidance for managing parasomnias includes avoiding sleep deprivation, maintaining a regular sleep–wake schedule, and limiting or eliminating the use of alcohol and recreational drugs [47]. For sleep paralysis, sleeping in a lateral or prone (abdominal) position, as opposed to supine (on the back), may reduce episodes [48]. For patients who sleep with a partner, their partner may be able to rouse them from sleep paralysis, which may be indicated if the patient is heard uttering low vocalizations

in their sleep during the morning [48]. For sleepwalking, it is important to maintain a safe sleep environment using the following guidance: sleep on the lowest floor in the house; use a mattress on the floor; sleep alone or consider a larger (king-size) bed for co-sleeping; minimize or pad any furniture near the bed and ensure the floor is free from objects or debris that could lead to tripping or injury; place any lights above the bed and out of reach; use plastic cups or bottles if bedside water is necessary; consider using childproof door knobs, door wedges, or alarms; and remove or lock any weapons or dangerous household items [47].

It should be noted that label warnings for LXB are typically related to class effects of oxybate treatment. In particular, warnings regarding abuse and misuse; CNS and respiratory depression; depression, anxiety, and suicidality; and parasomnias are present in the prescribing information for all three approved oxybate medications [9, 10, 23].

Initiating LXB for Adult Narcolepsy and Idiopathic Hypersomnia

Recommendations comprising statements 4 and 5a–c are shown in Table 2.

Developing an Initial Schedule for Timing of Doses

In all cases, LXB should be taken $\geq$ 2 h after eating, with the first dose taken at bedtime, while the patient is in bed. However, a variety of dosing titration options and regimen adjustments may be considered to tailor the treatment. For patients with narcolepsy, LXB should be taken twice nightly in equal or unequal doses, with the second dose scheduled (using an alarm) for 2.5 to 4 h after the first dose and taken while the patient is still in bed. Patients can set the alarm for 4 h after the first dose, but, if they wake spontaneously after at least 2.5 h, the second dose can be taken then. Approaches for adding the second dose in these patients include splitting the single dose into two equal or unequal doses followed by titration as appropriate (per the label guidance, the total dose should not be increased in an increment > 1.5 g per night per week). Only one participant took LXB thrice nightly in a clinical trial setting, but this is also an option for patients with idiopathic hypersomnia [49]. For patients with idiopathic hypersomnia who take a single dose and spontaneously wake 2.5 to 4 h after dosing, a second dose may be considered.

Setting Expectations for Therapy

In the phase 3 clinical trials, the median (range) time to reach stable dose in participants analyzed for efficacy was 29.0 (1, 84) days in participants with narcolepsy and 48.5 (1, 97) days in participants with idiopathic hypersomnia [19, 49]; a substantial proportion (55/134 in the efficacy population) of participants in the narcolepsy trial transitioned from SXB, which may have contributed to shorter titration times. Some patients may not need to be titrated above the minimum approved doses of 4.5 g/night (divided into two doses) and 3 g/night (once nightly, idiopathic hypersomnia only) [10]. In participants with idiopathic hypersomnia, the greatest improvements in Epworth Sleepiness Scale (ESS) and Idiopathic Hypersomnia Severity Scale (IHSS) scores occurred during the first 4 weeks of LXB treatment [49]. Although time to therapeutic effect for LXB in patients with narcolepsy has not been formally assessed, analysis of two trials of SXB in participants with narcolepsy found a median (95% CI) time to therapeutic effect of 37 (31–50) days for EDS and 25 (17–29) days for cataplexy [50]. Median (95% CI) time to maximum effect was 106 (85–164) and 213 (94–279) days for EDS and cataplexy, respectively.

For patients with idiopathic hypersomnia, in addition to the overall IHSS score, analysis of the three IHSS component scores (i.e., component 1: items 5, 9, 10, 11, 12, 13, 14; component 2: items 1, 2, 3, 4, 8; and component 3: items 6 and 7) can provide more granular information on changes in daytime functioning, long sleep duration and sleep inertia, and napping, respectively, with LXB treatment [51]. LXB improved all three IHSS components similarly in patients with idiopathic hypersomnia [34].

Table 2 Initiating LXB for adult narcolepsy and idiopathic hypersomnia

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
Developing an initial schedule for timing of doses	4	(a) In developing a schedule for LXB administration, ensure that total sleep opportunity is at least 7.5–8 h and that sleep and wake times are regular. For twice-nightly dosing, initiate LXB at 4.5 g divided into two equal doses. Both doses should be taken in bed, with the first dose administered at bedtime. Set an alarm to awaken for second administration 4 h later. If the patient wakes spontaneously at least 2.5 h after the first dose, the second dose can be administered. Advise food avoidance for at least 2 h before each dose	3.0, 4.0
		(b) Once-nightly consideration in idiopathic hypersomnia: if patient prefers or is unlikely to wake for second dose, consider once-nightly dosing (starting at $\leq$ 3 g at bedtime) and titrate to a maximum dose of 6 g according to label instructions. If the patient wakes spontaneously 2.5–4 h after first dose, consider addition of a second dose	
Setting expectations for therapy	5a: therapeutic effect	Inform that the dose and timing may need to be adjusted over weeks or months to achieve the optimal therapeutic effect. Time to initial therapeutic effect may be up to 6 weeks; time to optimal therapeutic effect may be up to 12 weeks	3.2, 4.0
	5b: signals of effectiveness	(i) Narcolepsy: establish baseline ESS and/or cataplexy frequency and impact of symptoms on daily function and overall quality of life. Monitor for reduced severity and frequency of symptoms and improvement in daily functioning (e.g., reduced frequency of naps, cataplexy-free days, improved school/job performance, increased alertness, improved driving performance, increased overall patient satisfaction)	3.6, 4.0
		(ii) Idiopathic hypersomnia: establish baseline daytime and nighttime symptoms. Obtain baseline ESS and determine impact of symptoms on daily function and overall quality of life. Consider obtaining baseline and subsequent IHSS scores. Monitor for severity and frequency of symptoms and improvement in daily functioning (e.g., improved sleep inertia, improved nocturnal sleep duration, reduced frequency of naps, improved school/job performance, increased alertness, improved driving performance, improved brain fog, increased overall patient satisfaction)	
	5c: follow-up and monitoring	(i) Follow-up (in-person or virtual) should occur at least every 4–6 weeks after initiation of LXB and throughout the titration period. Subsequent visits should occur at least every 3 months until the patient is stable on therapy. After 1 year, routine visits depend on patient stability but should be at least every 6 months	3.2, 4.0
		(ii) Monitoring includes adherence and response to therapy, timing and adjustment of doses, sleep effects, adverse events, review of concomitant medications, adherence to behavioral therapies, and changes of medical and psychiatric status/conditions	

ESS Epworth Sleepiness Scale, *IHSS* Idiopathic Hypersomnia Severity Scale, *LXB* low-sodium oxybate

[a]On a scale of 0–4

In relation to recommendation statement 5, monitoring for "sleep effects" refers to pharmacodynamic effect of treatment including time to sleep onset, response of rapid eye movement (REM) dissociative symptoms (e.g., dream enactment, vocalizations, and motor behaviors during sleep), and duration of dose. Adherence to behavioral therapies includes adherence to a regular sleep schedule and other lifestyle approaches for symptom management. Electronic medical record messaging can be used as needed to augment follow-ups.

Addressing Challenges in Using LXB for Adult Narcolepsy and Idiopathic Hypersomnia

Recommendations comprising statements 6a–f and 7a–n are shown in Table 3. Any recommendation to change (e.g., increase or decrease) one dose implies that the alternate dose remains the same. Clinicians should note that the troubleshooting strategies listed in statements 6 and 7 are options, not stepwise guidance. Any adverse event that does not subside after 5 to 7 days warrants action. For all adverse events, clinicians should consider scenarios that qualify for discontinuation of LXB and strategies for rechallenging.

Sleep Initiation and Maintenance

Cognitive behavioral therapy for insomnia (CBT-I) typically consists of weekly meetings between the client and the therapist for approximately 6 to 8 weeks [52]. Two major foci of CBT-I are stimulus control therapy (limiting the amount of time spent awake in bed) and sleep restriction therapy (limiting the amount of time in bed to a duration during which the patient is most likely to sleep). These therapies can increase the drive for sleep. Additionally, CBT-I aims to reduce the anxiety and worry associated with not being able to fall asleep and often employs relaxation techniques. More recently, strategies for CBT for hypersomnia (CBT-H) have begun to be developed (e.g., using sleep–wake diaries to help structure daytime and nighttime activities, anxiety management), but these have not yet been validated or thoroughly studied [53]. Nevertheless, CBT strategies such as sleep hygiene and delaying of bedtime may be helpful to patients with narcolepsy or idiopathic hypersomnia who have difficulty falling or remaining asleep.

For individuals with idiopathic hypersomnia who have difficulty waking for a second dose, one approach may be to titrate to 6 g once nightly until the patient is able to awaken to an alarm, at which time the dose may be split (equally or unequally) to achieve longer sleep duration. An additional approach may be to titrate to < 4.5 g once nightly until the patient is able to awaken to an alarm, at which time a second (unequal) dose may be added within the parameters of label guidance (titration increment should not exceed 1.5 g per night per week, to a maximum dose of 9 g per night).

Difficulty awakening in the morning could be related to the condition (i.e., sleep inertia) or treatment (i.e., lingering sedation). Sleep inertia would most likely be present before treatment was initiated, while lingering sedation would begin after initiation of LXB. These scenarios should be addressed differently: difficulty awakening from suboptimal treatment (i.e., incomplete titration to efficacy) should be addressed with uptitration, whereas difficulty awakening from lingering sedation from treatment (i.e., a side effect due to the second dose being too high or too late in the night) should be addressed with decreased dosing or earlier administration of the second dose. In particular, unequal dosing (when the second dose is lower than the first) may help to address lingering sedation from treatment.

Adverse Events in Narcolepsy and Idiopathic Hypersomnia

Nausea, headache, and dizziness are among the most common side effects observed with LXB treatment [10]. A study of the duration of treatment-emergent adverse events (TEAEs) during the phase 3 clinical trial in participants with narcolepsy found most TEAEs occurred early and decreased in incidence over the course of the study [54]. In the case of headache, any other medical condition that may be causing headaches (e.g., morning headache due to development of OSA [55]) must first be ruled

Table 3 Addressing challenges in using LXB for adult narcolepsy and idiopathic hypersomnia

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
Addressing challenges in sleep initiation and maintenance	6a: difficulty falling asleep after first dose	Evaluate medical, psychiatric, social, behavioral, and environmental factors	3.8, 4.0
		Evaluate role of food intake	
		Evaluate and align timing of natural sleep/wake schedule with LXB administration	
		Increase first dose	
		Consider CBT-I/H	
	6b: difficulty falling asleep after second dose	Evaluate medical, psychiatric, social, behavioral, and environmental factors	3.6, 4.0
		Evaluate role of food intake	
		Evaluate and align timing of natural sleep/wake schedule with LXB administration	
		Increase second dose or decrease duration between doses	
		Consider CBT-I/H	
	6c: inability to sleep long enough after first dose	Evaluate medical, psychiatric, social, behavioral, and environmental factors	3.6, 4.0
		Evaluate role of food intake	
		Evaluate and align timing of natural sleep/wake schedule with LXB administration	
		Increase first dose	
		Allow for initial sleep period prior to administration of first dose	
		Consider CBT-I/H	
	6d: inability to sleep long enough after second dose	Evaluate medical, psychiatric, social, behavioral, and environmental factors	3.6, 4.0
		Evaluate role of food intake	
		Evaluate and align timing of natural sleep/wake schedule with LXB administration	
		Delay second dose if patient is not waking spontaneously within 4 h of first dose	
		Increase second dose	
		Increase first dose and delay second dose	
		Consider CBT-I/H	

Table 3 continued

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
	6e: difficulty awakening for second dose	Ensure full 4 h between doses	3.4, 4.0
		Evaluate and align timing of natural sleep/wake schedule with LXB administration	
		Decrease first dose	
		For idiopathic hypersomnia: switch to once nightly and titrate to maximum of 6 g. If patient awakens earlier than desired or becomes able to awaken by alarm, restart twice-nightly dosing	
	6f: difficulty awakening at morning wake time	If condition-related:	3.8, 4.0
		Evaluate and align timing of natural sleep/wake schedule with LXB administration	
		Titrate to maximum dose	
		Administer second dose earlier	
		If treatment-related:	
		Evaluate and align timing of natural sleep/wake schedule with LXB administration	
		Decrease second dose	
		Administer second dose earlier	
Addressing adverse events in narcolepsy and idiopathic hypersomnia	7a: headache	Evaluate/treat for headache disorder or other medical conditions	3.8, 4.0
		Optimize headache hygiene (e.g., caffeine, hydration, skipped meals)	
		Give time for resolution if mild or moderate in severity	
		Titrate more slowly	
		Evaluate other medications	
		Decrease total dose	
		Decrease second dose	

Table 3 continued

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
	7b: nausea at bedtime	Advise staying in bed after dose	3.4, 4.0
		Give time for resolution	
		Titrate more slowly	
		Evaluate other medications	
		Consume noncaffeinated beverage or crackers	
		Decrease first dose	
		Increase first dose (if prolonged sleep onset, i.e., $\geq$ 20–30 min)	
		If refractory, consider nonsedating antiemetic medication	
	7c: nausea at wake	Give time for resolution	3.8, 4.0
		Titrate more slowly	
		Consume noncaffeinated beverage or crackers	
		Decrease second dose	
		Administer second dose earlier	
		If refractory, consider nonsedating antiemetic medication	
	7d: dizziness at bedtime	Counsel on safety and avoidance of rapid postural changes	3.4, 4.0
		Advise staying in bed after dose	
		Review concomitant medications and time of administration	
		Give time for resolution	
		Increase first dose (to shorten sleep onset time)	
		Decrease first dose (if falls asleep quickly)	
	7e: dizziness during night	Advise staying in bed	3.4, 4.0
		Counsel on safety and avoidance of rapid postural changes	
		Review concomitant medications and time of administration	
		Give time for resolution	
		Reduce duration between doses	
		Increase second dose (if prolonged return to sleep)	
		Increase first dose (if waking earlier than desired)	

Table 3 continued

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
	7f: dizziness upon awakening	Advise staying in bed until dizziness subsides	3.8, 4.0
		Counsel on safety and avoidance of rapid postural changes	
		Review concomitant medications and time of administration	
		Give time for resolution	
		Increase duration between second dose and waking	
		Decrease second dose	
	7g: decreased appetite/ weight loss	Give time for resolution	3.8, 4.0
		Monitor weight loss progression/significance	
		Evaluate other appetite-suppressing medications	
		Increase caloric intake	
		Consider nutritionist referral	
		Decrease total dose	
	7h: parasomnias	Counsel on safety	3.4, 4.0
		Review concomitant medications and time of administration	
		Titrate more slowly (if prior history of non-REM parasomnias)	
		Evaluate and align timing of natural sleep/wake schedule with LXB administration	
		Ensure adequate time for sleep (non-REM parasomnias)	
		Decrease first dose (non-REM parasomnias)	
		Increase total dose (REM parasomnias)	
		For idiopathic hypersomnia: consider change from once to twice nightly (non-REM parasomnias)	
	7i: diarrhea	Evaluate for underlying medical condition	3.8, 4.0
		Evaluate dietary factors	
		Titrate more slowly	
		Decrease total dose	
		Give time for resolution	
		Consider antidiarrheal medication	

Table 3 continued

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
	7j: hyperhidrosis	Evaluate for underlying medical condition	3.8, 4.0
		Give time for resolution	
		Optimize ambient temperature for sleep	
		Decrease total dose	
		Consider symptom medications	
	7k: anxiety	Evaluate psychological issues	3.4, 4.0
		Give time for resolution	
		Titrate more slowly	
		Decrease total dose	
		Consider nonsedating anxiolytic medication	
		Consider referral to psychologist/psychiatrist	
	7l: depression	For suicidality, discontinue and refer immediately for psychiatric evaluation	3.2, 4.0
		Evaluate psychological issues	
		Titrate more slowly	
		Decrease total dose	
		Consider antidepressant medication	
		Consider referral to psychologist/psychiatrist	
	7m: vomiting	Evaluate for underlying medical condition	3.8, 4.0
		Consume noncaffeinated beverage or crackers	
		Titrate more slowly	
		Give time for resolution	
		Decrease total dose	
		Consider nonsedating antiemetic medication	

Table 3 continued

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
	7n: enuresis	Urinate before bedtime and second dose	3.8, 4.0
		Restrict fluids before bedtime	
		Give time for resolution	
		Titrate more slowly	
		Decrease total dose based on timing of enuresis	
		For idiopathic hypersomnia: consider switching to twice nightly	

CBT-H cognitive behavioral therapy for hypersomnia, *CBT-I* cognitive behavioral therapy for insomnia, *LXB* low-sodium oxybate, *REM* rapid eye movement

[a]On a scale of 0–4

out before pursuing other strategies. Urgency of action is also dependent upon the level of severity; for mild and moderate headaches, granting time for resolution is more reasonable. If nausea occurs at bedtime, ensure that the patient is only using water (and not another type of beverage) as the diluent for LXB, and that the patient is not drinking anything else at the time of administration. For patients who have moderate or severe vomiting, a nonsedating antiemetic may be considered immediately. If the patient experiences dizziness after the first dose and has difficulty falling asleep right away, consider increasing the first dose to shorten the time to sleep onset. While increasing the dose may seem counterintuitive, helping the patient fall asleep faster may prevent dizziness from occurring. If the patient experiences dizziness but falls asleep quickly, consider lowering the first dose to reduce the adverse effect.

Oxybate treatment has been associated with weight loss across multiple prior studies [56–59]. This may be desirable in cases where patients are overweight or obese and have other cardiometabolic disorders, as are common in narcolepsy and idiopathic hypersomnia [60–62]. However, where weight loss is undesired or patients become underweight, discontinuing oxybates, including LXB, should be considered.

The option to increase or decrease dose to address parasomnias may be counterintuitive. The approach taken differs on the basis of whether the patient is experiencing REM (increase dose) or non-REM (decrease dose) parasomnias. This relates to oxybate's effect on sleep architecture, where SXB has been found to decrease awakenings, dose-dependently increase slow-wave sleep, and dose-dependently decrease REM sleep (following a brief increase in REM sleep during treatment initiation) [63]. Further, effects on REM efficiency appear to be dependent on time of day, with an early study showing REM efficiency is increased following administration of GHB (single 2.25 g dose) prior to a nocturnal sleep episode but not a morning nap [64].

For patients whose anxiety or depression becomes severe to the point of interfering with their daily life and relationships, clinical judgment should be used regarding discontinuing oxybate treatment, including LXB, and further psychiatric care should be sought.

Transitioning from SXB to LXB

The recommendations for statement 8 are shown in Table 4.

Setting Expectations, Dose Adjustment, and Follow-up

There is limited information on the comparison of adverse events while taking SXB and after

Table 4 Transitioning from SXB to LXB

Topic	Statement number	Recommendation	Agreement rating[a] (initial, final)
Setting expectations, dose adjustment, and follow-up	8	When patients transition from SXB to LXB, they should expect a different taste but similar therapeutic response and side effects. Adjustment to dose and timing of doses may be required in some cases Initial patient contact should occur within 2–4 weeks after starting medication; if dose adjustment is required, follow-up contact should occur within 6 weeks. Following stabilization, regular follow-up visits should occur at least every 6 months	3.8, 4.0

LXB low-sodium oxybate, *SXB* sodium oxybate
[a]On a scale of 0–4

switching to LXB. The C_{max} of LXB is lower than that for SXB [18], which might be expected to result in some change in the frequency or severity of adverse events. In a real-world study of patients with narcolepsy transitioning from SXB to LXB over 8 weeks, participants experienced similar efficacy and safety with LXB as they had with SXB; most reported the transition process was easy and that they preferred LXB [65]. Similarly, in a real-world study of participants with narcolepsy assessed for 21 weeks after switching from SXB to LXB, participants experienced a maintenance of tolerability and efficacy and the majority preferred LXB to SXB at the end of the transition period [66, 67]. In particular, adverse events that may be related to a high sodium load, like hyperhidrosis and enuresis, decreased over time after participants switched from SXB to LXB.

Long-term data on the risk of cardiovascular diseases in patients taking LXB versus those taking SXB are not yet available. LXB may be associated with the development of fewer cardiovascular-related comorbidities (e.g., hypertension) due to the 92% reduction in sodium compared with SXB (which contains 1640 mg at the highest dose of 9 g). Patients with comorbid postural orthostatic tachycardia syndrome, for whom higher sodium intake (10–12 g of sodium daily) is recommended, in addition to other treatments, may benefit from taking SXB over LXB [68].

DISCUSSION

An expert panel of five practicing physicians with extensive expertise in treating patients with narcolepsy and/or idiopathic hypersomnia developed the recommendation statements. These panel members were well positioned to provide detailed guidance on issues pertaining to LXB dosing, transitioning, expectations, safety, and adverse events, and high agreement was obtained on all statements. As a result of the current lack of literature on LXB dosing optimization, these recommendations were derived using a modified Delphi process, with many of them being based on the extensive clinical experience of the panel members, rather than research studies.

CONCLUSION

This paper provides expert guidance on the optimization of LXB treatment for patients with narcolepsy or idiopathic hypersomnia. Healthcare professionals may use this resource to guide dosing decisions with their patients and to answer their patients' questions about the treatment.

ACKNOWLEDGEMENTS

Medical Writing and Editorial Assistance. The authors thank Phyllis C. Zee, MD, PhD for her participation in and contributions to the consensus panel. The authors thank Stephen D. Lande, PhD and Emily Barker, PhD (employees of Interactive Forums, Inc.) for their contributions to this manuscript. Under the direction of the authors, Emily Bruggeman, PhD and Sean Anderson, PhD (employees of Peloton Advantage, LLC, an OPEN Health company) provided medical writing and editorial support. Jazz Pharmaceuticals provided funding to Peloton Advantage for medical writing and editorial support, and funded the journal's Rapid Service Fee.

Authorship. All authors have made substantial contributions to the conception or design of the work, or the acquisition, analysis, or interpretation of data, or the creation of new software used in the work; have drafted the work or revised it critically for important intellectual content; have approved the version to be published; and have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Author Contributions. Anne Marie Morse designed the study. Anne Marie Morse, Richard K. Bogan, Asim Roy, and Michael J. Thorpy contributed to data interpretation and to preparation, review, revision, and final approval of the manuscript.

Funding. The study and the journal's Rapid Service Fee were sponsored by Jazz Pharmaceuticals.

Data Availability. Data sharing is not applicable to this article, as no datasets were generated or analyzed during the current study.

Declarations

Conflict of Interest. Anne Marie Morse has received research/grant support and consultancy fees from Jazz Pharmaceuticals, Harmony Biosciences, Avadel Pharmaceuticals, Takeda Pharmaceuticals, Eisai, Alkermes, National Institutes of Health, and Geisinger Health Plan. She is the CEO and founder of DAMM Good Sleep, LLC. Richard K. Bogan is a shareholder of WaterMark Medical and Healthy Humming LLC. He serves on the board of directors for WaterMark Medical. He has served as a consultant to Jazz Pharmaceuticals, Harmony Biosciences, Takeda, Avadel, and Oventus. He has participated in industry-funded research for Avadel, BresoTec, Idorsia, Suven, Jazz Pharmaceuticals, Balance, Vanda, Merck, Eisai, Phillips, Fresca, Takeda, Liva Nova, Roche, Sommetrics, NLS, Sanofi, and Apinemed. He has taken part in speakers bureaus for Jazz Pharmaceuticals, Eisai, Harmony, and Idorsia. Asim Roy has received consultancy fees from Takeda, Avadel, and Inspire. He has participated in industry-sponsored research for Jazz Pharmaceuticals, Harmony, NLS, Eisai, Fisher Paykel, Inspire, Nyxoah, Signifier. Michael J. Thorpy has received fees for serving as a consultant or on advisory boards for Axsome, Balance Therapeutics, Flamel/Avadel, Harmony Biosciences, LLC, Jazz Pharmaceuticals, Suven Life Sciences Ltd., Takeda Pharmaceutical Co., Ltd, NLS Pharmaceuticals, XW Pharma, Idorsia Pharmaceuticals, and Eisai Pharmaceuticals.

Ethical Approval. This article is based on a modified Delphi approach in which all participants originally consented to participate and author the present manuscript. As acknowledged, Phyllis C. Zee, MD, PhD contributed to the consensus panel meetings and participated in the initial drafts of the manuscript. As a result of institutional regulations at a new position, she terminated her participation as an author prior to submission, but provided consent for publication and acknowledgement of her contributions. At the time of her participation, she had served on scientific advisory boards for Jazz Pharmaceuticals plc, Eisai, and Harmony

Biosciences; was a consultant for CVS Caremark; and owned stock in Teva.

REFERENCES

1. American Academy of Sleep Medicine. International classification of sleep disorders—third edition, text revision. Darien: American Academy of Sleep Medicine; 2023.

2. Scammell TE. Narcolepsy. N Engl J Med. 2015;373(27):2654–62.

3. Trotti LM, Ong JC, Plante DT, Friederich Murray C, King R, Bliwise DL. Disease symptomatology and response to treatment in people with idiopathic hypersomnia: initial data from the Hypersomnia Foundation Registry. Sleep Med. 2020;75:343–9.

4. Vernet C, Arnulf I. Idiopathic hypersomnia with and without long sleep time: a controlled series of 75 patients. Sleep. 2009;32(6):753–9.

5. Maski K, Trotti LM, Kotagal S, et al. Treatment of central disorders of hypersomnolence: an American Academy of Sleep Medicine clinical practice guideline. J Clin Sleep Med. 2021;17(9):1881–93.

6. Lopez R, Arnulf I, Drouot X, Lecendreux M, Dauvilliers Y. French consensus. Management of patients with hypersomnia: which strategy? Rev Neurol (Paris). 2017;173(1–2):8–18.

7. Bassetti CLA, Kallweit U, Vignatelli L, et al. European guideline and expert statements on the management of narcolepsy in adults and children. J Sleep Res. 2021;20:e13387.

8. Xyrem [summary of product characteristics]. Brussels: UCB Pharma; 2022.

9. Xyrem® (sodium oxybate) oral solution, CIII [prescribing information]. Palo Alto: Jazz Pharmaceuticals, Inc.; 2023.

10. Xywav® (calcium, magnesium, potassium, and sodium oxybates) oral solution, CIII [prescribing information]. Palo Alto: Jazz Pharmaceuticals, Inc.; 2023.

11. Dauvilliers Y, Bogan RK, Sonka K, Partinen M, Foldvary-Schaefer N, Thorpy MJ. Calcium, magnesium, potassium, and sodium oxybates oral solution: a lower-sodium alternative for cataplexy or excessive daytime sleepiness associated with narcolepsy. Nat Sci Sleep. 2022;14:531–43.

12. Szarfman A, Kuchenberg T, Soreth J, Lajmanovich S. Declaring the sodium content of drug products. N Engl J Med. 1995;333(19):1291.

13. US Food and Drug Administration. Quantitative labeling of sodium, potassium, and phosphorus for human over-the-counter and prescription drug products. Guidance for industry. US Food and Drug Administration; 2022.

14. US Food and Drug Administration. Clinical review for Binosto, NDA 202344. US Food and Drug Administration; 2012.

15. Junnarkar G, Allphin C, Profant J, et al. Development of a lower-sodium oxybate formulation for the treatment of patients with narcolepsy and idiopathic hypersomnia. Expert Opin Drug Discov. 2022;17(2):109–19.

16. Thorpy MJ, Bogan RK. Update on the pharmacologic management of narcolepsy: mechanisms of action and clinical implications. Sleep Med. 2020;68:97–109.

17. Felmlee MA, Morse BL, Morris ME. γ-Hydroxybutyric acid: pharmacokinetics, pharmacodynamics, and toxicology. AAPS J. 2021;23(1):22.

18. Chen C, Jenkins J, Zomorodi K, Skowronski R. Pharmacokinetics, bioavailability, and bioequivalence of lower-sodium oxybate in healthy participants in 2 open-label, randomized, crossover studies. Clin Transl Sci. 2021;14(6):2278–87.

19. Bogan RK, Thorpy MJ, Dauvilliers Y, et al. Efficacy and safety of calcium, magnesium, potassium, and sodium oxybates (lower-sodium oxybate [LXB]; JZP-

258) in a placebo-controlled, double-blind, randomized withdrawal study in adults with narcolepsy with cataplexy. Sleep. 2021;44(3):zsaa206.

20. Dauvilliers Y, Arnulf I, Foldvary-Schaefer N, et al. Safety and efficacy of lower-sodium oxybate in adults with idiopathic hypersomnia: a phase 3, placebo-controlled, double-blind, randomised withdrawal study. Lancet Neurol. 2022;21(1):53–65.

21. Horsnell M, Zhang E, Cook R, et al. Understanding the patient experience with sodium oxybate therapy for narcolepsy [poster]. In: Advances in sleep and circadian science; February 17–20, 2023; Clearwater Beach.

22. Bogan R, Thorpy MJ, Winkelman JW, Dubow J, Gudeman J, Seiden D. Randomized, crossover, open-label study of the relative bioavailability and safety of FT218, a once-nightly sodium oxybate formulation: phase 1 study in healthy volunteers. Sleep Med. 2022;100:442–7.

23. Lumryz™ (sodium oxybate) for extended-release oral solution, CIII [prescribing information]. Chesterfield: Avadel CNS Pharmaceuticals; 2023.

24. Roy A, Ito D, Morris S, Candler S, Profant J, Bae C. Individualized treatment patterns for patients with narcolepsy treated with oxybate: a clinical practice perspective. Nat Sci Sleep. 2023;15:767–78.

25. Broder MS, Gibbs SN, Yermilov I. An adaptation of the RAND/UCLA modified Delphi panel method in the time of COVID-19. J Healthc Leadersh. 2022;14:63–70.

26. Carter LP, Pardi D, Gorsline J, Griffiths RR. Illicit gamma-hydroxybutyrate (GHB) and pharmaceutical sodium oxybate (Xyrem): differences in characteristics and misuse. Drug Alcohol Depend. 2009;104(1–2):1–10.

27. Kamal RM, van Noorden MS, Franzek E, Dijkstra BA, Loonen AJ, De Jong CA. The neurobiological mechanisms of gamma-hydroxybutyrate dependence and withdrawal and their clinical relevance: a review. Neuropsychobiology. 2016;73(2):65–80.

28. Xywav and Xyrem REMS prescriber brochure: Jazz Pharmaceuticals; 2021. https://www.xywavxyremrems.com/. Accessed Feb 21, 2023.

29. Strunc MJ, Black J, Lillaney P, et al. The Xyrem® (sodium oxybate) Risk Evaluation and Mitigation Strategy (REMS) program in the USA: results from 2016 to 2017. Drugs Real World Outcomes. 2021;8(1):15–28.

30. George CF, Feldman N, Inhaber N, et al. A safety trial of sodium oxybate in patients with obstructive sleep apnea: acute effects on sleep-disordered breathing. Sleep Med. 2010;11(1):38–42.

31. Gottlieb DJ, Punjabi NM. Diagnosis and management of obstructive sleep apnea: a review. JAMA. 2020;323(14):1389–400.

32. Badr MS, Dingell JD, Javaheri S. Central sleep apnea: a brief review. Curr Pulmonol Rep. 2019;8(1):14–21.

33. US Xyrem Multicenter Study Group. A 12-month, open-label, multicenter extension trial of orally administered sodium oxybate for the treatment of narcolepsy. Sleep. 2003;26(1):31–5.

34. Morse AM, Dauvilliers Y, Arnulf I, et al. Long-term efficacy and safety of low-sodium oxybate in an open-label extension period of a placebo-controlled, double-blind, randomized withdrawal study in adults with idiopathic hypersomnia. J Clin Sleep Med. 2023;19(10):1811–22.

35. Ohayon MM. Narcolepsy is complicated by high medical and psychiatric comorbidities: a comparison with the general population. Sleep Med. 2013;14(6):488–92.

36. Cohen A, Mandrekar J, St Louis EK, Silber MH, Kotagal S. Comorbidities in a community sample of narcolepsy. Sleep Med. 2018;43:14–8.

37. Dauvilliers Y, Lopez R, Ohayon M, Bayard S. Hypersomnia and depressive symptoms: methodological and clinical aspects. BMC Med. 2013;11:78.

38. Vernet C, Leu-Semenescu S, Buzare MA, Arnulf I. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. J Sleep Res. 2010;19(4):525–34.

39. Ortega-Albás JJ, López-Bernabé R, García AL, Gómez JR. Suicidal ideation secondary to sodium oxybate. J Neuropsychiatry Clin Neurosci. 2010;22(3):352r.e26-e26.

40. Rossetti AO, Heinzer RC, Tafti M, Buclin T. Rapid occurrence of depression following addition of sodium oxybate to modafinil. Sleep Med. 2010;11(5):500–1.

41. Sarkanen T, Niemelä V, Landtblom AM, Partinen M. Psychosis in patients with narcolepsy as an adverse effect of sodium oxybate. Front Neurol. 2014;5:136.

42. Buckley PJ, Wolf CT. Psychosis in a 22-year-old woman with narcolepsy after restarting sodium oxybate. Psychosomatics. 2018;59(3):298–301.

43. Canellas-Dols F, Delgado C, Arango-Lopez C, Peraita-Adrados R. Narcolepsy-cataplexy and psychosis: a case study. Rev Neurol. 2017;65(2):70–4.

44. Chien J, Ostermann G, Turkel SB. Sodium oxybate-induced psychosis and suicide attempt in an 18-year-old girl. J Child Adolesc Psychopharmacol. 2013;23(4):300–1.

45. Sharpless BA, Barber JP. Lifetime prevalence rates of sleep paralysis: a systematic review. Sleep Med Rev. 2011;15(5):311–5.

46. Stallman HM, Kohler M. Prevalence of sleepwalking: a systematic review and meta-analysis. PLoS ONE. 2016;11(11): e0164769.

47. Fleetham JA, Fleming JA. Parasomnias. CMAJ. 2014;186(8):E273–80.

48. Stefani A, Högl B. Nightmare disorder and isolated sleep paralysis. Neurotherapeutics. 2021;18(1): 100–6.

49. Thorpy MJ, Arnulf I, Foldvary-Schaefer N, et al. Efficacy and safety of lower-sodium oxybate in an open-label titration period of a phase 3 clinical study in adults with idiopathic hypersomnia. Nat Sci Sleep. 2022;14:1901–17.

50. Bogan RK, Roth T, Schwartz J, Miloslavsky M. Time to response with sodium oxybate for the treatment of excessive daytime sleepiness and cataplexy in patients with narcolepsy. J Clin Sleep Med. 2015;11(4):427–32.

51. Rassu AL, Evangelista E, Barateau L, et al. Idiopathic Hypersomnia Severity Scale to better quantify symptoms severity and their consequences in idiopathic hypersomnia. J Clin Sleep Med. 2022;18(2): 617–29.

52. Pigeon WR. Treatment of adult insomnia with cognitive-behavioral therapy. J Clin Psychol. 2010;66(11):1148–60.

53. Ong JC, Dawson SC, Mundt JM, Moore C. Developing a cognitive behavioral therapy for hypersomnia using telehealth: a feasibility study. J Clin Sleep Med. 2020;16(12):2047–62.

54. Bogan RK, Foldvary-Schaefer N, Skowronski R, Chen A, Thorpy MJ. Long-term safety and tolerability during a clinical trial and open-label extension of lower-sodium oxybate in participants with narcolepsy with cataplexy. CNS Drugs. 2023;37(4): 323–35.

55. Goksan B, Gunduz A, Karadeniz D, et al. Morning headache in sleep apnoea: clinical and polysomnographic evaluation and response to nasal continuous positive airway pressure. Cephalalgia. 2009;29(6):635–41.

56. Plazzi G, Ruoff C, Lecendreux M, et al. Treatment of paediatric narcolepsy with sodium oxybate: a double-blind, placebo-controlled, randomised-withdrawal multicentre study and open-label investigation. Lancet Child Adolesc Health. 2018;2(7):483–94.

57. Schinkelshoek MS, Smolders IM, Donjacour CE, et al. Decreased body mass index during treatment with sodium oxybate in narcolepsy type 1. J Sleep Res. 2019;28(3):e12684.

58. Husain AM, Ristanovic RK, Bogan RK. Weight loss in narcolepsy patients treated with sodium oxybate. Sleep Med. 2009;10(6):661–3.

59. Ponziani V, Pizza F, Zenesini C, Vignatelli L, Pession A, Plazzi G. BMI changes in pediatric type 1 narcolepsy under sodium oxybate treatment. Sleep. 2021;44(7):1–7.

60. Black J, Reaven NL, Funk SE, et al. Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study. Sleep Med. 2017;33:13–8.

61. Saad R, Ben-Joseph RH, Prince P, Stack C, Bujanover S, Taylor B. Clinical presentation prior to idiopathic hypersomnia diagnosis among US adults: a retrospective, real-world claims analysis [poster 497]. Annual Meeting of the Associated Professional Sleep Societies; June 10–13, 2021.

62. Saad R, Prince P, Taylor B, Ben-Joseph RH. Characteristics of adults newly diagnosed with idiopathic hypersomnia in the United States. Sleep Epidemiol. 2023. https://doi.org/10.1016/j.sleepe.2023.100059.

63. Mamelak M, Black J, Montplaisir J, Ristanovic R. A pilot study on the effects of sodium oxybate on sleep architecture and daytime alertness in narcolepsy. Sleep. 2004;27(7):1327–34.

64. Lapierre O, Montplaisir J, Lamarre M, Bedard MA. The effect of gamma-hydroxybutyrate on nocturnal and diurnal sleep of normal subjects: further considerations on REM sleep-triggering mechanisms. Sleep. 1990;13(1):24–30.

65. Leary EB, Kirby MT, Skowronski R, Xu K, Pfister C, Macfadden W. Effectiveness and treatment optimization among participants with narcolepsy switching from sodium oxybate to lower-sodium oxybate: interim data from the SEGUE study [poster 138]. Annual Meeting of the Associated Professional Sleep Societies; June 4–8, 2022; Charlotte, NC.

66. Bae CJ, Zee PC, Leary EB, et al. Effectiveness and tolerability in people with narcolepsy transitioning from high-sodium oxybate to low-sodium oxybate: data from the real-world TENOR study. Sleep Med. 2023;109:65–74.

67. Husain AM, Zee PC, Leary EB, et al. Dosing and transition characteristics in people with narcolepsy transitioning from sodium oxybate to low-sodium oxybate: data from the real-world TENOR study. Sleep Med. 2024;113:328–37.

68. Miller AJ, Raj SR. Pharmacotherapy for postural tachycardia syndrome. Auton Neurosci. 2018;215:28–36.