Nature and Science of Sleep

Dovepress
open access to scientific and medical research

Open Access Full Text Article

REVIEW

Long-Term Treatment of Narcolepsy and Idiopathic Hypersomnia with Low-Sodium Oxybate

Logan D Schneider[1], Anne Marie Morse[2], Michael J Strunc[3], Joyce K Lee-Iannotti[4], Richard K Bogan[5]

[1]Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, Stanford, CA, USA; [2]Janet Weis Children's Hospital, Geisinger Medical Center, Danville, PA, USA; [3]The Center for Pediatric Sleep Medicine, Children's Hospital of The King's Daughters, Norfolk, VA, USA; [4]Department of Neurology, The University of Arizona College of Medicine, Phoenix, AZ, USA; [5]Department of Pulmonology, University of South Carolina School of Medicine, Columbia, SC, USA

Correspondence: Logan D Schneider, Department of Psychiatry and Behavioral Sciences, Stanford University School of Medicine, 450 Broadway St, Pavilion C 2nd Fl MC 5704, Redwood City, CA, 94063, USA, Tel +1 650 723-6601, Fax +1 650 721-3448, Email logands@gmail.com

Video abstract

Point your SmartPhone at the code above. If you have a QR code reader the video abstract will appear. Or use: https://youtu.be/7ZOAk26V35M

Abstract: Narcolepsy and idiopathic hypersomnia are chronic conditions that negatively affect alertness, mental and physical energy, functioning, and quality of life (QoL). Calcium, magnesium, potassium, and sodium oxybates (low-sodium oxybate; LXB) is an oxybate formulation with 92% less sodium than sodium oxybate (SXB; a treatment for narcolepsy) and the same active moiety. LXB is approved in the US for treatment of cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age or older with narcolepsy, and idiopathic hypersomnia in adults. In Phase 3 clinical trials, LXB exhibited a safety profile consistent with that of SXB in narcolepsy. Besides continued efficacy in treating symptoms, potential benefits of long-term LXB treatment include flexible optimization of dosing and regimen, improvement of QoL and functioning, weight loss, and (relative to SXB in narcolepsy) health benefits of reduced sodium content. Dosing of LXB is twice nightly (for narcolepsy) or once or twice nightly (for idiopathic hypersomnia) based on patient characteristics and response, and individualized titration can be leveraged over the long term as a patient's life circumstances change. Patients with narcolepsy transitioning from SXB initiate LXB at the same dose, and most patients require no further changes to achieve similar efficacy and tolerability. Improvements in functioning and QoL with LXB treatment could have cascading positive effects in multiple domains, particularly in younger patients. In clinical trials, LXB was associated with weight loss in both narcolepsy (in which obesity is a well-established comorbidity) and idiopathic hypersomnia, only occasionally leading participants to be underweight. As both narcolepsy and idiopathic hypersomnia are associated with increased risk of cardiometabolic and cardiovascular comorbidities, limiting medication-related sodium intake with LXB may have significant health benefits, although this has not yet been verified prospectively due to the prolonged follow-up required. LXB is a promising long-term treatment for narcolepsy and idiopathic hypersomnia.

Plain Language Summary: Narcolepsy and idiopathic hypersomnia are disorders that make people feel very sleepy. Low-sodium oxybate (LXB) is a medicine for these disorders. Doctors think LXB works on parts of the brain that keep people awake. LXB may quiet those brain parts down at night by reducing their electrical activity, which helps people sleep better. LXB wears off by the morning, so people can wake up normally and feel more alert the next day. LXB has less sodium (which is part of salt) than a medicine called sodium oxybate. Sodium oxybate has been used for narcolepsy for more than 20 years. LXB has several benefits. First, LXB may be healthier than medicines that contain a lot of sodium, such as a high-sodium oxybate. This is because sodium can increase blood pressure and risk of heart disease. Second, LXB can be taken twice each night for narcolepsy, or once or twice each night for idiopathic hypersomnia. This depends on a person's lifestyle, how well the medicine is working, and side effects. Third, people taking LXB are more able to work and do other activities and have better quality of life. Finally, people taking LXB may lose weight. This can help overweight or obese people.

Keywords: cardiovascular, dosing, LXB, hypersomnolence, quality of life, weight loss

Received: 16 March 2023
Accepted: 25 July 2023
Published: 19 August 2023

Introduction

Central disorders of hypersomnolence are a family of disorders characterized by excessive daytime sleepiness (EDS).[1] They include narcolepsy type 1 (NT1) and narcolepsy type 2 (NT2); idiopathic hypersomnia; Kleine-Levin syndrome; insufficient sleep syndrome; and hypersomnia due to a medical disorder, medication or substance, or psychiatric disorder.[1] Narcolepsy and idiopathic hypersomnia are chronic and potentially lifelong conditions[2,3] that negatively impact alertness, mental and physical energy, functioning, and quality of life (QoL).[4,5] Both are underrecognized and underdiagnosed.[6,7] Treatment options are generally limited and symptoms targeted due, in part, to incomplete understanding of their pathophysiology.[2]

Calcium, magnesium, potassium, and sodium oxybates (low-sodium oxybate; LXB; Xywav®) was developed to meet evolving health-care needs, with 8% of the sodium content of sodium oxybate (SXB), and approved by the US Food and Drug Administration (FDA) in 2020 for the treatment of cataplexy or EDS in patients 7 years of age or older with narcolepsy.[8–12] LXB is also effective in idiopathic hypersomnia, a therapeutic area with no other current FDA-approved treatments, and was approved by the US FDA in 2021 for the treatment of idiopathic hypersomnia in adults—the first medication to be indicated for the treatment of the entire disorder, rather than its individual symptoms (ie, EDS).[8,9]

The purpose of this paper is to discuss the impact and potential benefits of long-term LXB treatment in narcolepsy and idiopathic hypersomnia.

Narcolepsy and Idiopathic Hypersomnia: Presentation and Lifelong Burden

Narcolepsy is associated with a pentad of symptoms, including EDS, cataplexy, hypnagogic/hypnopompic hallucinations, sleep paralysis, and disrupted nighttime sleep (DNS).[13] EDS is a defining characteristic of both NT1 and NT2. Cataplexy is often present in NT1 but is always absent in NT2.[1] The onset of narcolepsy symptoms typically occurs during the teen years, with a potential second peak of onset in the mid-30s.[6,14] Symptoms evolve over a period of years; EDS is usually the first to appear, followed by cataplexy (in NT1), and then other symptoms.[1] NT1 is a stable, lifelong disorder, whereas NT2 may spontaneously remit.[1,15–19] The prevalence of narcolepsy in 2016 was estimated at 44.3 per 100,000 persons.[7] In association with the sleep/wake state instability and EDS of narcolepsy, the following are common: decreased functioning and ability to pursue activities,[4,20–22] decreased QoL,[4,5,23,24] increased usage of medical resources and associated health-care costs,[25] and reduced productivity and increased associated costs (eg, short-term disability incidents and days).[25]

Idiopathic hypersomnia is also characterized by EDS,[1] but in contrast to narcolepsy, patients emphasize virtually continuous cognitive aspects of EDS (eg, impaired alertness and difficulty sustaining attention; "brain fog") as being especially burdensome.[26] Cataplexy is absent.[1] Associated features include severe, prolonged sleep inertia (defined as "prolonged difficulty waking up with repeated returns to sleep, irritability, automatic behavior, and confusion") and long (>1 hr) unrefreshing naps.[1] Long sleep time (≥11 hr in a 24-hr period) may be present but is not necessary for diagnosis and may also be seen in narcolepsy.[27] Symptom onset is typically in the late teens or early 20s but may occur earlier.[1,15,28–30] Symptoms may be long-lasting or spontaneously remit.[16,17,19,28,30] The prevalence of idiopathic hypersomnia in 2016 was estimated at 10.3 per 100,000 persons.[7] Idiopathic hypersomnia is associated with decreased functioning, inability to pursue typical life activities, and poorer QoL.[4,5,31,32]

Diagnosis of Narcolepsy and Idiopathic Hypersomnia

Diagnosis of narcolepsy and idiopathic hypersomnia may be delayed by 10 years or more after symptom onset.[6,30,32,33] Diagnoses of other disorders, including psychiatric disorders, attention deficit/hyperactivity disorder (ADHD), other sleep disorders, and epilepsy,[34] are common and contribute to delays in receiving optimal care.

Upon review of the *International Classification of Sleep Disorders*, 3rd Edition (ICSD-3) diagnostic criteria for narcolepsy (NT1 and NT2) and idiopathic hypersomnia, it is apparent that there is considerable overlap of diagnostic criteria, particularly between NT2 and idiopathic hypersomnia, for which findings on the multiple sleep latency test (MSLT) are the only clearly differentiating diagnostic criterion:[17] At least two sleep onset rapid eye movement periods (SOREMPs) are required for a diagnosis of NT2, and exclude an idiopathic hypersomnia diagnosis.[1] However, there are additional differences in associated characteristics, such as the frequent presence (idiopathic hypersomnia) vs typical absence (NT2) of sleep inertia, nonrestorative naps (idiopathic hypersomnia) vs restorative naps (NT2), and less

prevalent REM dissociative symptoms in idiopathic hypersomnia compared with NT2.[1] Similarities among the disorders represent a significant diagnostic challenge.

A defined protocol for diagnostic testing is lacking. Evaluation begins with clinical examination and history, aiming to narrow the list of possible diagnoses. Of the three disorders considered here, NT1 may be the easiest to identify if cataplexy is present, but other differential diagnoses need to be considered as well. Diagnostic testing (eg, polysomnography, actigraphy, and MSLT) is necessary to confirm a diagnosis according to the ICSD-3 criteria. Hypocretin levels in cerebrospinal fluid may be obtained (eg, for diagnosis of NT1 in the absence of cataplexy), but there is no official guidance regarding when and under what circumstances to measure these levels. The potential for misdiagnosis is considerable since several psychiatric comorbidities (eg, mood disorders) and other medical or behavioral conditions (eg, substance abuse) are associated with hypersomnolence.[1] In pediatric patients, presentation of EDS and cataplexy in narcolepsy or idiopathic hypersomnia can mimic symptoms of ADHD, epilepsy, or psychotic disorders,[15,34] and differentiation of excessive sleep due to idiopathic hypersomnia versus non-pathologic, age-appropriate long sleep duration can be difficult.[1] In response to these challenges, a new classification of sleep disorders, based on differently defined clinical characteristics and with less emphasis on MSLT results because of its limited sensitivity and specificity in this context, has been proposed.[35] This classification includes three diagnostic categories: narcolepsy, idiopathic hypersomnia, and idiopathic excessive sleepiness.[35]

Comorbidities associated with NT1, NT2, and idiopathic hypersomnia are wide-ranging, and many are overlapping. Obesity is a well-established comorbidity of narcolepsy,[21,36] estimated in the Burden of Narcolepsy Disease (BOND) study to be 2 to 3 times more likely in people with narcolepsy compared with non-narcolepsy controls (odds ratio [OR]: 2.3 [95% confidence interval, CI: 2.2 to 2.5]; $P<0.0001$).[37] The BOND study also identified an increased risk of cardiometabolic and cardiovascular (CV) conditions and events, including diabetes (OR [95% CI]: 1.8 [1.7, 1.8]; $P<0.0001$), stroke (2.5 [2.3, 2.7]; $P<0.0001$), myocardial infarction (1.6 [1.3, 1.8]; $P<0.0001$), cardiac arrest (1.6 [1.1, 2.3]; $P=0.0326$), and heart failure (2.6 [2.3, 2.9]; $P<0.0001$). These findings were verified more recently, in general, in the Cardiovascular Burden of Narcolepsy Disease (CV-BOND) study.[38] Finally, there is a significantly elevated prevalence of headache/migraine; psychiatric conditions, including anxiety disorders and mood disorders; and other sleep disorders, including periodic limb movement disorder (PLMD), sleep apnea, rapid eye movement (REM), sleep behavior disorder (RBD), and restless legs syndrome (RLS).[37] In a survey, many people with narcolepsy specified that they had comorbid psychiatric and sleep disorders (eg, depression [32.0–35.3%] and anxiety disorder [25.7–27.5%]) that had been correctly diagnosed, as opposed to having been misdiagnosed.[34] Idiopathic hypersomnia does not seem to be associated with obesity, but a retrospective claims analysis identified diabetes, hyperlipidemia, psychiatric disorders (mood, depressive, and anxiety disorders), and other sleep disorders (sleep apnea, PLMD, RLS, RBD) as common comorbidities.[39] CV conditions or events, including hypertension, major adverse cardiac event, atrial fibrillation, heart failure, and stroke, were also found to be common.[39] Finally, headache/migraine is common,[39] and autonomic dysfunction and cognitive symptoms relating to memory and attention have been reported.[40,41]

Treatment of Narcolepsy and Idiopathic Hypersomnia

Treatment of narcolepsy and idiopathic hypersomnia involves a whole-patient, multifactorial approach. Both nonpharmacologic and pharmacologic interventions should be incorporated, guided by the patient's individual circumstances, such as symptom profile and lifestyle (eg, parents of young children; women of childbearing potential). Nonpharmacologic interventions include lifestyle modifications and preventive therapy focusing on factors such as sleep hygiene (eg, discontinuation of electronics use well before bedtime), adjustment of work hours (eg, beginning work later in the day rather than early morning), regular exercise, and a healthy diet.[42–44] In addition, cognitive behavioral therapy for hypersomnia emphasizes education about the disease state, self-identity and self-image (including strategies for self-acceptance), structured daytime and nighttime activities, coping skills and emotional regulation, social support, and medical/legal/occupational issues (eg, potential accommodations).[45] As far as pharmacologic approaches, narcolepsy and idiopathic hypersomnia are often treated off-label, and treatment is generally symptomatic (eg, EDS and cataplexy) due to poor understanding of the pathophysiology of NT2 and idiopathic hypersomnia. The pathophysiology of NT1, as related to hypocretin deficiency, is clearer.[46] Approved pharmacologic agents commonly utilized in narcolepsy include oxybate (LXB [only indicated in the US], SXB, and recently

fixed-dose, high-sodium oxybate),[47,48] wake-promoting agents (eg, modafinil, armodafinil, solriamfetol, and pitolisant), and stimulants (eg, methylphenidate and dextroamphetamine). Antidepressants (eg, venlafaxine, clomipramine, and fluoxetine) are often used off-label. Currently, LXB is the only approved treatment for idiopathic hypersomnia in the US.[9] Modafinil was previously approved in the EU, but the approval was rescinded in 2011.[49] Off-label treatments for idiopathic hypersomnia include modafinil, stimulants (methylphenidate, amphetamines, and mazindol), clarithromycin, and pitolisant. Treatment guidelines provide recommendations for use of these agents.[50,51] Most of the pharmacologic therapies employed in central disorders of hypersomnolence have not undergone rigorous clinical trials or head-to-head studies. However, pivotal clinical trials of LXB have recently been conducted, supporting its use in both narcolepsy (NT1 and NT2)[52] and idiopathic hypersomnia.[53]

Development and Characterization of LXB

SXB is a standard of care, based on American Academy of Sleep Medicine and French consensus guidelines, for the treatment of EDS and cataplexy in narcolepsy.[50,51] However, at the recommended dosage range for adults (6–9 g/night), SXB contributes 1100 mg to 1640 mg to daily sodium intake.[52,54] The recommended upper limit of daily sodium intake in adults is 2000 mg/day to 2300 mg/day,[55–60] but for many people, dietary sodium intake exceeds this limit (mean for Americans aged 2–19 years in 2013–2014: 3033 mg/day).[61] Thus, treatment with SXB adds to sodium intake that may already be excessive. It is well established that excess sodium intake is associated with increased blood pressure and CV risk.[62–65]

LXB is a multiple-cation formulation of oxybate that contains 92% less sodium than SXB, with the same active moiety, at the same concentration, gram for gram.[8,9] In pharmacokinetic/pharmacodynamic (PK/PD) studies in healthy adults, LXB had lower maximum plasma drug concentration compared with SXB (C_{max}: arithmetic mean, 101.8 vs 135.7 µg/mL), delayed time to C_{max} ($T_{max:}$ median, 0.75 vs 0.50 h), and similar area under the plasma concentration–time curve ($AUC_{0\text{-}t}$: arithmetic mean, 235.4 vs 263.9 µg·h/mL; $AUC_{0\text{-}\infty}$: arithmetic mean, 236.5 vs 265.2 µg·h/mL) in the fasted state at equivalent oxybate doses.[66] Bioequivalence of LXB and SXB, under fasted conditions, was to be declared if the 90% CIs for the ratio of geometric least-squares means of log-transformed $AUC_{0\text{-}t}$, $AUC_{0\text{-}\infty}$, and C_{max} were all contained within 80% and 125%. As the criteria were met for AUC but not C_{max}, LXB and SXB were found to be not bioequivalent.[66] An additional finding was that C_{max} and AUC of LXB were lower under fed than fasted conditions.[66]

The mechanism of action of oxybate (gamma-hydroxybutyrate; GHB) in the treatment of narcolepsy and idiopathic hypersomnia is unknown,[9] in part due to the incomplete understanding of the pathophysiology of these disorders.[1] Hypocretin deficiency is a key element of NT1, and NT2 may involve partial hypocretin/orexin deficiency severe enough to cause sleepiness but not cataplexy,[1] although this is controversial.[67] The pathophysiology of idiopathic hypersomnia remains unknown; no deficiency in hypocretin-1 has been observed.[1] Since GHB is an endogenous brain neurotransmitter that acts at GHB-specific receptors and gamma-aminobutyric acid B ($GABA_B$) receptors,[68] it is hypothesized that the therapeutic effects of oxybate on EDS and cataplexy are mediated through $GABA_B$ actions at dopaminergic and noradrenergic neurons, as well as at thalamocortical neurons, during sleep.[9]

Because bioequivalence criteria were not met in PK/PD studies,[66] a phase 3 clinical trial of LXB in narcolepsy (NCT03030599) was conducted in 2017–2019.[8,52] Overall, the results of this LXB study are broadly consistent with SXB in narcolepsy, with a similar efficacy and safety profile.[69–75] A study of LXB in idiopathic hypersomnia (NCT03533114) was conducted concurrently, in 2018–2020.[53]

The narcolepsy pivotal trial of LXB was a multicenter, double-blind, placebo-controlled, randomized withdrawal study in adults with narcolepsy with cataplexy.[52] Participants entered an open-label optimized treatment and titration period (OLOTTP; 12 weeks), followed by a stable-dose period (SDP; 2 weeks), and then a double-blind randomized withdrawal period (DBRWP; 2 weeks). An optional open-label extension (OLE) followed the DBRWP. The duration of the study was 16 weeks (main study) or 40 weeks (including the OLE). A total of 201 participants were enrolled and treated in the OLOTTP, and 149 participants entered the SDP (74.1% retention rate). The primary endpoint was met: There was a significant worsening in the weekly number of cataplexy attacks from the end of the SDP to the end of the DBRWP in the placebo group, compared with no change in the LXB group ($P<0.0001$). On the key secondary endpoint, scores on the Epworth Sleepiness Scale (ESS) significantly worsened from the end of the SDP to the end of the DBRWP in the placebo group and did not change in the LXB group ($P<0.0001$). On other secondary endpoints, LXB

demonstrated improvement compared with placebo on overall narcolepsy symptom severity, QoL, and self-assessed current health status. In post hoc analyses, LXB was found to reduce cataplexy frequency and increase cataplexy-free days per week during the OLOTTP and SDP.[76] Changes in cataplexy frequency observed during OLOTTP differed by cataplexy treatment at study entry, but cataplexy-free days were high in all groups at the end of the SDP.[76] Efficacy of LXB during the OLE was not measured in this trial. Improvements in DNS were not tested for LXB but were previously demonstrated for SXB, which were associated with beneficial effects on sleep architecture, including increases in non-rapid eye movement (NREM) sleep, stages 3 and 4 sleep, and delta power, and decreases in awakenings, REM sleep, stage 1 sleep, and stage shifts.[77–79]

Treatment-emergent adverse events (TEAEs) were common (reported by 76.1% while receiving LXB during the main study) and consistent with those seen in studies of SXB.[52,69,72,74] TEAEs resulting in LXB discontinuation during the main study (11.9% overall) were worsening cataplexy (3.5%), nausea (1.5%), and anxiety, depressed mood, depression, headache, and irritability (each 1.0%). Serious TEAEs were reported by 6 participants, and TEAEs considered related to study medication were reported by two participants (confusion and hallucinations in one participant after accidental deviation from usual interval between doses; muscle enzyme increased in one participant after intense activity). Similar to prior long-term safety results with SXB in narcolepsy,[71,80] the long-term safety and tolerability profiles of LXB during the OLE were generally consistent with those during the main study.[81] TEAEs were most prevalent early in the OLE and declined thereafter.[81]

The idiopathic hypersomnia pivotal trial of LXB was a multicenter, double-blind, placebo-controlled, randomized withdrawal study in adults with idiopathic hypersomnia.[53] Similar to the narcolepsy study, participants entered an initial open-label titration and optimization period (called OLT in this study; 10–14 weeks), followed by an SDP (2 weeks) and a DBRWP (2 weeks). A required OLE (24 weeks) followed the DBRWP. The duration of the study was 38 to 42 weeks. A total of 154 participants were enrolled and treated in the OLT, and 123 participants entered the SDP (79.9% retention rate). The primary endpoint was met: ESS scores worsened from the end of the SDP to the end of the DBRWP in the placebo group and remained stable in the LXB group ($P<0.0001$). In post hoc analyses, this effect was similar in subgroups of participants defined by sex, age, long sleep phenotype (ie, with or without long sleep), and baseline treatment (taking baseline idiopathic hypersomnia medication or treatment naive). On key secondary endpoints, Idiopathic Hypersomnia Severity Scale (IHSS) total scores increased (indicating worsening) from the end of the SDP to the end of the DBRWP in the placebo group and remained stable in the LXB group ($P<0.0001$), and the proportion of participants reporting worsening in symptoms on the Patient Global Impression of Change (PGIc) at the end of the DBRWP relative to the end of the SDP was greater with placebo compared with LXB ($P<0.0001$). On other secondary and exploratory endpoints, LXB demonstrated improvement compared with placebo on the Clinical Global Impression of Change, functional outcomes, sleep inertia, work productivity, and activity impairment. In post hoc analyses, scores on several of these measures improved during open-label LXB treatment in the OLT and SDP[82] and were maintained long term over the 24-week OLE.[83] TEAEs were reported by 80% of participants overall and were consistent with those seen in the LXB study in narcolepsy.[52,53] TEAEs leading to discontinuation occurred in 17% of participants while receiving LXB. Four participants experienced nine serious TEAEs; none were related to study drug.

The FDA approved LXB for the treatment of cataplexy or EDS in patients 7 years of age and older with narcolepsy in July 2020, and for the treatment of idiopathic hypersomnia in adults in August 2021.[9] The approval of LXB for the treatment of narcolepsy in pediatric patients is based on clinical trial data of SXB in pediatric participants 7 to 17 years of age with narcolepsy,[75] the similar treatment effects with LXB and SXB in clinical studies in adults with narcolepsy, PK data from studies of SXB in adult and pediatric participants, and PK data from studies of LXB in adults.[9] LXB is not approved outside of the US.

Benefits of Long-Term Treatment with LXB

There are no randomized controlled studies comparing LXB with other treatment options. LXB efficacy/tolerability is similar or superior to SXB for most patients with narcolepsy, although there are some patients who prefer SXB.[84] LXB is newly approved, and clinical trials of ~1 year in duration are available for narcolepsy and idiopathic hypersomnia;[52,53,76,82] for narcolepsy, there is also a well-established, 20-year history of SXB usage supporting certain benefits of oxybate treatment,

including individualized optimization of dosing and regimen, improvement of QoL and functioning, and association with weight loss. LXB also has the benefit of reduced sodium content.

Individualized Optimization of Dosing and Regimen

For narcolepsy, LXB dosing is twice nightly (symmetric or asymmetric), and titration is as needed (for those transitioning from SXB) or occurs in increments of up to 1.5 g/night/week.[9] Twice-nightly doses are separated by 2.5 to 4 hr.[9] A clear understanding of PK and PD will enhance dosing adjustments and improve drug efficacy and safety, particularly when administered with knowledge of circadian entrainment. For idiopathic hypersomnia, dosing is once or twice nightly, and titration occurs in increments of up to 1.5 g/night/week.[9] The recommended LXB dosing interval is based on its PK profile (peak exposure [C_{max}] within 1 hr and decay within 4 hr[66]). Once-nightly dosing or asymmetric twice-nightly dosing may be preferable based on individual patient circumstances (eg, single dosing in idiopathic hypersomnia if there is difficulty awakening during the night for a second dose, or asymmetric dosing in either disorder if there is awakening during the night after a single dose but difficulty waking up in the morning after an equal second dose).

For patients transitioning from SXB, LXB is initiated at the same dose and regimen.[9] In an interim analysis of a Phase 4, open-label study (SEGUE), 90.5% of participants with narcolepsy reported that the process of transitioning was easy. In the phase 3 study of LXB in narcolepsy, most (50/55; 90.9%) participants who entered taking SXB achieved a stable total nightly dose of LXB within 1 titration step (range: 0–8).[76] Sixteen (29.1%) required an increase in dose (maximum increase: 4.25 g/night), whereas 2 (3.6%) decreased their dose (by ≤1.5 g/night).[76] Hence, while most patients can transition from SXB to LXB with no change in dose, others require a change for similar efficacy.

Improvement of QoL and Functioning

A strength of LXB clinical studies is the use of multiple endpoints assessing not only symptoms but also consequences, such as impairment of QoL and/or functioning. LXB demonstrated efficacy on QoL and/or functioning (which in itself can be considered a measure of QoL) in both narcolepsy and idiopathic hypersomnia, as described earlier (measured using the SF-36 [narcolepsy] and FOSQ-10 and WPAI:SHP [idiopathic hypersomnia]).[52,53] Functioning was not assessed in clinical studies of LXB in narcolepsy. In idiopathic hypersomnia, few other agents have demonstrated benefits on functioning, limited mostly to improvement in driving ability.[85,86] Improvement in quality of wakefulness and functioning may have a broad impact on a person's life, including in the longer term as new opportunities arise that might not otherwise have been possible. For example, patients whose ability to work was limited as a result of idiopathic hypersomnia[32] and whose functioning improved with LXB treatment might experience an impact not only on their immediate employment prospects but also on their overall career trajectory. This could have cascading effects in other domains.

Weight Loss

In the LXB clinical trials, treatment during the open-label periods was associated with weight loss, similar to SXB.[87,88] In the study of LXB in narcolepsy,[89] 31.8% and 35.3% of participants were overweight or obese, respectively, at study entry, consistent with the well-established increased risk of obesity in narcolepsy.[21,36,37] At the end of the SDP, with a total of 14 weeks of LXB treatment, mean (SD) change in body weight in the overall population was −1.6 (3.5) kg.[89] Mean weight loss was numerically greater in oxybate-naive participants compared with participants who had been taking SXB at study entry; among oxybate-naive participants, mean weight loss was also numerically greater in participants who were overweight or obese compared with normal weight. Most (91%) normal weight participants remained normal weight, 15% of overweight participants became normal weight, and 8% of obese participants became overweight. A single TEAE of decreased weight was reported.

Results in the study of LXB in idiopathic hypersomnia were similar,[90] although, as noted earlier, idiopathic hypersomnia is not strongly associated with obesity.[39] At study entry, 33.8% and 24.7% of participants were overweight or obese, respectively. At the end of the SDP, mean (SD) change in body weight in the overall population was −2.5 (4.1) kg. Mean weight loss was numerically greater in overweight or obese versus normal weight participants. Weight loss was substantial (≥5%) in 28.7% of participants. Most (92.1%) of normal weight participants remained normal

weight, 16.7% of overweight participants became normal weight, and 12.1% of obese participants became overweight. TEAEs of decreased weight were reported by 5 (3.2%) participants.

The mechanism by which LXB leads to weight loss is unknown. For SXB, which is also associated with weight loss,[87,88] proposed mechanisms of weight loss include increased physical activity, normalization of hormone secretion (eg, growth hormone, leptin, and/or thyroid-stimulating hormone), and stimulation of metabolism and lipolysis.[87,91] In people previously treated with SXB, LXB might also be associated with reduced fluid retention as a result of its lower sodium content.

Reduced Sodium Intake

Sleep disorders and excess sodium intake are each associated with increased CV risk. Narcolepsy and idiopathic hypersomnia are associated with cardiometabolic and CV comorbidities and events,[37–39,92] and people with narcolepsy are more likely than healthy controls to demonstrate nocturnal non-dipping blood pressure,[93] which is itself a predictor of CV risk and mortality in the general population.[94–96] The mechanisms underlying the link between sleep disorders (and poor sleep or EDS in general[97,98]) and CV risk are poorly understood, but NT1 may be related to hypocretin deficiency and associated dysregulation of the sympathetic nervous system.[99]

The modest sodium load associated with LXB, compared with SXB, is likely to be beneficial for the health of people with narcolepsy or idiopathic hypersomnia, including young people. As these are chronic disorders that are often diagnosed in a period spanning adolescence to early adulthood,[6,30] providers should be cognizant of any long-term health consequences of the chosen treatment, even in patients who are young and appear otherwise healthy. Evidence indicates that presence of CV risk factors early in life may be predictive of poorer outcomes in adulthood. For example, a population-based longitudinal study in 38,589 participants found that hypertension and obesity in children were associated with a significantly increased risk of fatal or nonfatal CV events before the age of 60 years.[100]

Reduction in sodium intake is associated with decreased CV risk,[101–107] and high sodium-containing medications are associated with increased CV risk.[108–111] LXB has been recognized by the US FDA in the narcolepsy population for its significant reduction in chronic sodium burden compared with SXB, which "will be clinically meaningful in reducing cardiovascular morbidity in a substantial proportion of patients for whom the drug is indicated."[112] While this has not yet been verified prospectively due to the long-term follow-up required, the potential benefit of reduced sodium intake with LXB is inferred based on the literature on sodium intake, blood pressure, and CV health. However, it is notable that, in the LXB narcolepsy study, mean systolic blood pressure values and prevalence of CV/cardiometabolic comorbidities were higher in participants taking SXB at study entry, compared with participants who were not.[52,76] Concomitant use of stimulants and wake-promoting agents, which could also have been associated with higher blood pressure, was common in the same study whether or not participants were taking SXB at baseline (groups by treatment at study entry: SXB only, 67.3%; SXB + other anticataplectics, 60.9%; other anticataplectics, 77.8%; anticataplectic naive, 48.9%).[52,113] Finally, it is important to note that excessive sodium intake is only one element of larger cardiovascular, cardiometabolic, and cardiorenal management issues, and reduced sodium intake may not be positive for every patient (eg, in people with orthostatic hypotension, the higher sodium content in SXB may be beneficial). The American Heart Association has identified eight essential measures for improving and maintaining cardiovascular health, including diet as one component; others include monitoring and management of cardiovascular/cardiometabolic indicators (cholesterol, blood glucose, and blood pressure) and other lifestyle changes (exercise, cessation of nicotine use, weight management, and adequate sleep).[114]

Perspectives and Clinical Practice Considerations

Selection of the appropriate therapy for each patient is based on a number of considerations. Confidence in the diagnosis of narcolepsy or idiopathic hypersomnia is paramount, as LXB is not indicated for other sleep disorders. LXB may not be appropriate for all patients (eg, some parents of young children), and individual circumstances should be considered (eg, profession, wake time, history of psychiatric issues or substance abuse). Patients with long histories of depression or anxiety, with or without suicide attempts, may have worsening depression after initiating LXB and should be monitored.[9]

Conversely, however, improvement in depressive symptoms as measured with the Patient Health Questionnaire-9 was observed in the phase 3 study of LXB in narcolepsy.[52]

Misuse of illicitly produced and acquired GHB (the same active ingredient as in SXB and LXB) has been noted, potentially due to its anxiolytic, hypnotic, and euphoric effects.[68] In patients with a history of substance abuse, the potential for misuse or abuse of prescription oxybate therapy may be a barrier, but not necessarily always.[9] SXB has been available in the US through a long-running, restricted-distribution Risk Evaluation and Mitigation Strategy (REMS) program, which has also been applied to LXB since its approval.[115] The REMS program incorporates a number of safeguards to prevent abuse, misuse, and diversion, and historical data have demonstrated that controlled access to SXB was rigorously maintained.[115] Furthermore, LXB is not unique in having concerns of this type; other treatments with known potential for abuse and/or diversion (eg, methylphenidate[116]) are widely used in the treatment of hypersomnia.[50]

It is essential to ensure that patients with narcolepsy and idiopathic hypersomnia are treated optimally, focusing on addressing the debilitating and potentially hazardous symptoms of EDS and cataplexy in narcolepsy, and symptoms in idiopathic hypersomnia including (but not restricted to) EDS. Early, effective treatment may have significant benefits, as treatment of children and adolescents forms part of a continuum of care over the course of a potentially lifelong disease. Any effective treatment beginning during childhood/adolescence (a period of significant neuroplasticity) might actually alter the disease course, although this is speculative; in contrast, delayed treatment beginning during adulthood might be limited to management of symptoms after years of dysfunction. The potential cascading impact of treatment benefits on QoL and functioning, as described earlier, may be especially impactful in younger patients.

Strategies to improve treatment success include proactive and ongoing titration of LXB dosing and regimen to maximize efficacy and tolerability. A patient's optimal dose and regimen may change over time as the patient ages or individual circumstances evolve. Following that evolution with regular follow-up and monitoring with tools such as those used as endpoints in clinical trials may be helpful and complementary to discussions surrounding QoL.

Future Research

Future research should address knowledge gaps related to LXB and to the disorders of narcolepsy and idiopathic hypersomnia. Real-world evidence is presently sparse but should be available soon, as results from OLEs, phase 4 trials (including the SEGUE study mentioned earlier), and other studies are published. The mechanism of action of LXB, similar to SXB, is largely unknown;[9] improved understanding may emerge from preclinical studies. A better understanding of the sleep effects of LXB and correlation with outcomes in narcolepsy and idiopathic hypersomnia may contribute to improved understanding of the mechanism of action of LXB and open possibilities for its use in other sleep disorders. Finally, the potential impact of LXB treatment on future disease course and comorbid medical conditions should be explored in prospectively monitored, population-level/epidemiologic datasets, such as claims databases). Brain structural and functional changes have been demonstrated in narcolepsy and idiopathic hypersomnia,[117–120] as in obstructive sleep apnea,[121] and it would be of interest to explore possible neuroprotection with LXB treatment. A related issue is the impact of LXB, hypocretin deficiency, and other disease aspects in future risk of comorbidities.

Conclusion

LXB is a promising long-term treatment for narcolepsy and idiopathic hypersomnia, demonstrating efficacy on symptoms including EDS, cataplexy, and sleep inertia, with a safety profile consistent with that of SXB in narcolepsy. Individualized treatment involving titration of dosage/regimen can be leveraged over the long term to maximize efficacy and tolerability as a patient's life circumstances change. Improvements in functioning and QoL could have cascading positive effects in multiple domains, particularly in younger patients. Weight loss in people who are overweight or obese may have long-term health benefits, particularly as obesity is a well-established comorbidity of narcolepsy. Limiting medication-related sodium intake with LXB may have significant health benefits, especially in relation to decreased risk of cardiovascular morbidity.

Abbreviations

ADHD, attention deficit/hyperactivity disorder; AUC, area under the plasma concentration–time curve; BMI, body mass index; BOND, Burden of Narcolepsy Disease; CGIc, Clinical Global Impression of Change; CI, confidence interval; CV, cardiovascular; C_{max}, maximum plasma drug concentration; DNS, disrupted nighttime sleep; DBRWP, double-blind randomized withdrawal period; EDS, excessive daytime sleepiness; ESS, Epworth Sleepiness Scale; FDA, Food and Drug Administration; FOSQ-10, Functional Outcomes of Sleep Questionnaire, short version; $GABA_B$, gamma-aminobutyric acid B; GHB, gamma-hydroxybutyrate; ICSD-3, International Classification of Sleep Disorders, 3rd Edition; IH, idiopathic hypersomnia; IHSS, Idiopathic Hypersomnia Severity Scale; IQR, interquartile range; LSM, least squares mean; LXB, low-sodium oxybate; MCS, Mental Component Summary; MSLT, Multiple Sleep Latency Test; NT1, narcolepsy type 1; NT2, narcolepsy type 2; OLE, open-label extension; OLOTTP, open-label optimized treatment and titration period; OLT, open-label titration and optimization period; PCS, Physical Component Summary; PD, pharmacodynamic; PGIc, Patient Global Impression of Change; PK, pharmacokinetic; PLMD, periodic limb movement disorder; QoL, quality of life; RBD, REM sleep behavior disorder; REM, rapid eye movement; REMS, Risk Evaluation and Mitigation Strategy; RLS, restless legs syndrome; SD, standard deviation; SDP, stable-dose period; SE, standard error; SF-36, 36-item Short-Form Survey; SOREMP, sleep onset rapid eye movement period; SXB, high-sodium oxybate; TEAE, treatment-emergent adverse event; T_{max}, time to C_{max}; VAS, visual analog scale; VAS-SI, visual analog scale for sleep inertia; WPAI:SHP, Work Productivity and Activity Impairment Questionnaire: Specific Health Problem.

Acknowledgments

At the direction of the authors, Karyn Liu, PhD, and Michael J. Theisen, PhD, of Peloton Advantage, LLC, an OPEN Health company, provided medical writing and editorial support, which was funded by Jazz Pharmaceuticals.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

Support for the development of this article was funded by Jazz Pharmaceuticals.

Disclosure

Logan D. Schneider is a compensated member of advisory boards and speakers bureaus for Jazz Pharmaceuticals, Eisai, and Harmony Biosciences. Anne Marie Morse has received research/grant support and consultancy fees from Avadel, Geisinger Health Plan, ResMed Foundation, Harmony Biosciences, Jazz Pharmaceuticals, Takeda Pharmaceutical Co., Ltd, NLS Pharmaceuticals, Alkermes, UCB Pharmaceuticals, and NIH. She is also a paid expert consultant of Irish State Claims Agency; CEO of DAMM Good Sleep, LLC. Michael J. Strunc has participated in advisory boards for Jazz Pharmaceuticals. Joyce K. Lee-Iannotti has no conflicts of interest to disclose. Richard K. Bogan is a shareholder of Watermark Medical and Healthy Humming, LLC; serves on the board of directors for Watermark; is a medical consultant to Jazz Pharmaceuticals, Harmony Biosciences, Avadel Pharmaceuticals, Takeda, and Oventus; has conducted industry-funded research for Avadel, Axsome, Bresotec, Bayer, Idorsia, Suven, Jazz, Balance, NLS, Vanda, Merck, Eisai, Philips, Fresca, Takeda, LivaNova, Roche, Sanofi, Sommetrics, and Noctrix; and is on the speakers bureau for Jazz, Eisai, and Harmony.

References

1. American Academy of Sleep Medicine. *International Classification of Sleep Disorders – Third Edition,Text Revision (ICSD-3-TR)*. Darien, IL: American Academy of Sleep Medicine; 2023.
2. Barateau L, Lopez R, Dauvilliers Y. Treatment options for narcolepsy. *CNS Drugs*. 2016;30(5):369–379. doi:10.1007/s40263-016-0337-4
3. Billiard M, Sonka K. Idiopathic hypersomnia. *Sleep Med Rev*. 2016;29:23–33. doi:10.1016/j.smrv.2015.08.007

4. Wasling HB, Bornstein A, Wasling P. Quality of life and procrastination in post-H1N1 narcolepsy, sporadic narcolepsy and idiopathic hypersomnia, a Swedish cross-sectional study. *Sleep Med*. 2020;76:104–112. doi:10.1016/j.sleep.2020.10.014
5. Ozaki A, Inoue Y, Nakajima T, et al. Health-related quality of life among drug-naive patients with narcolepsy with cataplexy, narcolepsy without cataplexy, and idiopathic hypersomnia without long sleep time. *J Clin Sleep Med*. 2008;4(6):572–578. doi:10.5664/jcsm.27352
6. Thorpy MJ, Krieger AC. Delayed diagnosis of narcolepsy: characterization and impact. *Sleep Med*. 2014;15(5):502–507. doi:10.1016/j.sleep.2014.01.015
7. Acquavella J, Mehra R, Bron M, Suomi JMH, Hess GP. Prevalence of narcolepsy, other sleep disorders, and diagnostic tests from 2013–2016: insured patients actively seeking care. *J Clin Sleep Med*. 2020;16(8):1255–1263. doi:10.5664/jcsm.8482
8. 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):109–119. doi:10.1080/17460441.2022.1999226
9. *Xywav®. (Calcium, Magnesium, Potassium, and Sodium Oxybates) Oral Solution, CIII [Prescribing Information]*. Palo Alto, CA: Jazz Pharmaceuticals, Inc; 2023.
10. US Food and Drug Administration. Quantitative labeling of sodium, potassium, and phosphorus for human over-the-counter and prescription drug products. Guidance for industry; 2022. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/quantitative-labeling-sodium-potassium-and-phosphorus-human-over-counter-and-prescription-drug. Accessed October 11, 2022.
11. US Food and Drug Administration. Clinical review for Binosto, NDA 202344; 2012. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202344Orig1s000MedR.pdf. Accessed February 28, 2023.
12. Szarfman A, Kuchenberg T, Soreth J, Lajmanovich S. Declaring the sodium content of drug products. *N Engl J Med*. 1995;333(19):1291. doi:10.1056/NEJM199511093331917
13. Overeem S, Reading P, Bassetti CL. Narcolepsy. *Sleep Med Clin*. 2012;7:263–281. doi:10.1016/j.jsmc.2012.03.013
14. Dauvilliers Y, Montplaisir J, Molinari N, et al. Age at onset of narcolepsy in two large populations of patients in France and Quebec. *Neurology*. 2001;57(11):2029–2033. doi:10.1212/WNL.57.11.2029
15. American Academy of Sleep Medicine. *International Classification of Sleep Disorders*. 3rd ed. Darien, IL: American Academy of Sleep Medicine; 2014.
16. Lopez R, Doukkali A, Barateau L, et al. Test-retest reliability of the multiple sleep latency test in central disorders of hypersomnolence. *Sleep*. 2017;40(12). doi:10.1093/sleep/zsx164
17. Trotti LM, Staab BA, Rye DB. Test-retest reliability of the multiple sleep latency test in narcolepsy without cataplexy and idiopathic hypersomnia. *J Clin Sleep Med*. 2013;9(8):789–795. doi:10.5664/jcsm.2922
18. Ruoff C, Pizza F, Trotti LM, et al. The MSLT is repeatable in narcolepsy type 1 but not narcolepsy type 2: a retrospective patient study. *J Clin Sleep Med*. 2018;14(1):65–74. doi:10.5664/jcsm.6882
19. Kim T, Lee JH, Lee CS, Yoon IY. Different fates of excessive daytime sleepiness: survival analysis for remission. *Acta Neurol Scand*. 2016;134(1):35–41. doi:10.1111/ane.12504
20. Beusterien KM, Rogers AE, Walsleben JA, et al. Health-related quality of life effects of modafinil for treatment of narcolepsy. *Sleep*. 1999;22(6):757–765. doi:10.1093/sleep/22.6.757
21. Mutti C, Brunetti V, Figorilli M, et al. Clinical characteristics of a large cohort of patients with narcolepsy candidate for pitolisant: a cross-sectional study from the Italian PASS Wakix® Cohort. *Neurol Sci*. 2022;43(9):5563–5574. doi:10.1007/s10072-022-06210-9
22. Davidson RD, Biddle K, Nassan M, Scammell TE, Zhou ES. The impact of narcolepsy on social relationships in young adults. *J Clin Sleep Med*. 2022;18(12):2751–2761. doi:10.5664/jcsm.10212
23. Vignatelli L, D'Alessandro R, Mosconi P, et al. Health-related quality of life in Italian patients with narcolepsy: the SF-36 health survey. *Sleep Med*. 2004;5(5):467–475. doi:10.1016/j.sleep.2004.04.003
24. Rovere H, Rossini S, Reimao R. Quality of life in patients with narcolepsy: a WHOQOL-bref study. *Arq Neuropsiquiatr*. 2008;66(2a):163–167. doi:10.1590/S0004-282X2008000200004
25. Black J, Reaven NL, Funk SE, et al. The Burden of Narcolepsy Disease (BOND) study: health-care utilization and cost findings. *Sleep Med*. 2014;15(5):522–529. doi:10.1016/j.sleep.2014.02.001
26. Fronczek R, Arnulf I, Baumann CR, Maski K, Pizza F, Trotti LM. To split or to lump? Classifying the central disorders of hypersomnolence. *Sleep*. 2020;43(8). doi:10.1093/sleep/zsaa044
27. Vernet C, Arnulf I. Narcolepsy with long sleep time: a specific entity? *Sleep*. 2009;32(9):1229–1235. doi:10.1093/sleep/32.9.1229
28. Bruck D, Parkes JD. A comparison of idiopathic hypersomnia and narcolepsy-cataplexy using self report measures and sleep diary data. *J Neurol Neurosurg Psychiatry*. 1996;60(5):576–578. doi:10.1136/jnnp.60.5.576
29. Bassetti C, Aldrich MS. Idiopathic hypersomnia. A series of 42 patients. *Brain*. 1997;120(8):1423–1435. doi:10.1093/brain/120.8.1423
30. Anderson KN, Pilsworth S, Sharples LD, Smith IE, Shneerson JM. Idiopathic hypersomnia: a study of 77 cases. *Sleep*. 2007;30(10):1274–1281. doi:10.1093/sleep/30.10.1274
31. Stevens J, Schneider LD, Husain AM, et al. Impairment in functioning and quality of life in patients with idiopathic hypersomnia: the real world idiopathic hypersomnia outcomes study (ARISE). *Nat Sci Sleep*. 2023;15:593–606. doi:10.2147/NSS.S396641
32. Whalen M, Roy B, Steininger T, Dronamraju N, Enson D. Patient perspective on idiopathic hypersomnia: impact on quality of life and satisfaction with the diagnostic process and management [poster 157]. Presented at: Annual Meeting of the Associated Professional Sleep Societies; Charlotte, NC; 2022.
33. Whalen M, Roy B, Steininger T, Dronamraju N, Enson D. Physician perspective on idiopathic hypersomnia: awareness, diagnosis, and impact on patients [poster 156]. Presented at: Annual Meeting of the Associated Professional Sleep Societies; Charlotte, NC; 2022.
34. Ohayon MM, Thorpy MJ, Carls G, et al. The Nexus Narcolepsy Registry: methodology, study population characteristics, and patterns and predictors of narcolepsy diagnosis. *Sleep Med*. 2021;84:405–414. doi:10.1016/j.sleep.2021.06.008
35. Lammers GJ, Bassetti CLA, Dolenc-Groselj L, et al. Diagnosis of central disorders of hypersomnolence: a reappraisal by European experts. *Sleep Med Rev*. 2020;52:101306. doi:10.1016/j.smrv.2020.101306
36. Poli F, Pizza F, Mignot E, et al. High prevalence of precocious puberty and obesity in childhood narcolepsy with cataplexy. *Sleep*. 2013;36(2):175–181. doi:10.5665/sleep.2366

37. Black J, Reaven NL, Funk SE, et al. Medical comorbidity in narcolepsy: findings from the Burden of Narcolepsy Disease (BOND) study. *Sleep Med*. 2017;33:13–18. doi:10.1016/j.sleep.2016.04.004
38. Ben-Joseph RH, Saad R, Black J, et al. Cardiovascular Burden of Narcolepsy Disease (CV-BOND): a real-world evidence study. *Sleep*. 2023. doi:10.1093/sleep/zsad161
39. Saad R, Prince P, Taylor B, Ben-Joseph RH. Characteristics of adults newly diagnosed with idiopathic hypersomnia in the United States. *Sleep Epidemiol*. 2023. 18 July Online Ahead of Print. doi:10.1016/j.sleepe.2023.100059
40. Miglis MG, Schneider L, Kim P, Cheung J, Trotti LM. Frequency and severity of autonomic symptoms in idiopathic hypersomnia. *J Clin Sleep Med*. 2020;16(5):749–756. doi:10.5664/jcsm.8344
41. Vernet C, Leu-Semenescu S, Buzare MA, Arnulf I. Subjective symptoms in idiopathic hypersomnia: beyond excessive sleepiness. *J Sleep Res*. 2010;19(4):525–534. doi:10.1111/j.1365-2869.2010.00824.x
42. Arnulf I, Leu-Semenescu S, Dodet P. Precision medicine for idiopathic hypersomnia. *Sleep Med Clin*. 2019;14(3):333–350. doi:10.1016/j.jsmc.2019.05.007
43. Maski K, Mignot E, Plazzi G, Dauvilliers Y. Disrupted nighttime sleep and sleep instability in narcolepsy. *J Clin Sleep Med*. 2022;18(1):289–304. doi:10.5664/jcsm.9638
44. Schneider LD, Stevens J, Husain AM, et al. Symptom severity and treatment satisfaction in patients with idiopathic hypersomnia: the real world idiopathic hypersomnia outcomes study (ARISE). *Nat Sci Sleep*. 2023;15:89–101. doi:10.2147/NSS.S386021
45. 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):2047–2062. doi:10.5664/jcsm.8750
46. Kornum BR, Knudsen S, Ollila HM, et al. Narcolepsy. *Nat Rev Dis Primers*. 2017;3:16100. doi:10.1038/nrdp.2016.100
47. Avadel pharmaceuticals announces final FDA approval of LUMRYZ™ (sodium oxybate) for extended-release oral suspension as the first and only once-at-bedtime oxybate for cataplexy or excessive daytime sleepiness in adults with narcolepsy [press release]; 2023. Available from: https://investors.avadel.com/news-releases/news-release-details/avadel-pharmaceuticals-announces-final-fda-approval-lumryztm. Accessed May 1, 2023.
48. *Lumryz™ (Sodium Oxybate) for Extended-Release Oral Solution, CIII [Prescribing Information]*. Chesterfield, MO: Avadel CNS Pharmaceuticals; 2023.
49. European Medicines Agency. Modafinil; 2011. Available from: https://www.ema.europa.eu/en/medicines/human/referrals/modafinil#:~:text=Looking. Accessed February 2, 2022.
50. 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):1881–1893. doi:10.5664/jcsm.9328
51. Lopez R, Arnulf I, Drouot X, Lecendreux M, Dauvilliers Y. French consensus. Management of patients with hypersomnia: which strategy? *Rev Neurol*. 2017;173(1–2):8–18. doi:10.1016/j.neurol.2016.09.018
52. 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. doi:10.1093/sleep/zsaa206
53. 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. doi:10.1016/S1474-4422(21)00368-9
54. *Xyrem® (Sodium Oxybate) Oral Solution, CIII [Prescribing Information]*. Palo Alto, CA: Jazz Pharmaceuticals, Inc.; 2023.
55. World Health Organization. *Guideline: Sodium Intake for Adults and Children*. Geneva, Switzerland: World Health Organization; 2012.
56. Institute of Medicine. *Sodium Intake in Populations: Assessment of Evidence*. Washington, DC: National Academies Press; 2013.
57. U.S. Department of Health and Human Services, U.S. Department of Agriculture. *2015–2020 Dietary Guidelines for Americans*. 8th ed. Washington, DC: United States Department of Agriculture; 2015.
58. US Food and Drug Administration. Voluntary sodium reduction goals: target mean and upper bound concentrations for sodium in commercially processed, packaged, and prepared foods: guidance for industry. 2021. Available from: https://www.fda.gov/media/98264/download. Accessed December 8, 2021.
59. National Academies of Sciences Engineering and Medicine. *Dietary Reference Intakes for Sodium and Potassium*. Washington, DC: National Academies Press; 2019.
60. United States Department of Agriculture. Scientific report of the 2015 dietary guidelines advisory committee. Washington, DC: United States Department of Health and Human Services; United States Department of Agriculture; 2015.
61. Quader ZS, Zhao L, Gillespie C, et al. Sodium intake among persons aged ≥2 years - United States, 2013–2014. *MMWR Morb Mortal Wkly Rep*. 2017;66(12):238–324. doi:10.15585/mmwr.mm6612a3
62. Strazzullo P, D'Elia L, Kandala NB, Cappuccio FP. Salt intake, stroke, and cardiovascular disease: meta-analysis of prospective studies. *BMJ*. 2009;339:b4567. doi:10.1136/bmj.b4567
63. Ma Y, He FJ, Sun Q, et al. 24-Hour urinary sodium and potassium excretion and cardiovascular risk. *N Engl J Med*. 2022;386(3):252–263. doi:10.1056/NEJMoa2109794
64. Gardener H, Rundek T, Wright CB, Elkind MS, Sacco RL. Dietary sodium and risk of stroke in the Northern Manhattan study. *Stroke*. 2012;43(5):1200–1205. doi:10.1161/STROKEAHA.111.641043
65. Mozaffarian D, Fahimi S, Singh GM, et al. Global sodium consumption and death from cardiovascular causes. *N Engl J Med*. 2014;371(7):624–634. doi:10.1056/NEJMoa1304127
66. 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):2278–2287. doi:10.1111/cts.13087
67. Thannickal TC, Nienhuis R, Siegel JM. Localized loss of hypocretin (orexin) cells in narcolepsy without cataplexy. *Sleep*. 2009;32(8):993–998. doi:10.1093/sleep/32.8.993
68. 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. doi:10.1159/000443173
69. U.S. Xyrem Multicenter Study Group. A randomized, double blind, placebo-controlled multicenter trial comparing the effects of three doses of orally administered sodium oxybate with placebo for the treatment of narcolepsy. *Sleep*. 2002;25(1):42–49.

70. U.S. Xyrem Multicenter Study Group. Sodium oxybate demonstrates long-term efficacy for the treatment of cataplexy in patients with narcolepsy. *Sleep Med*. 2004;5(2):119–123. doi:10.1016/j.sleep.2003.11.002
71. U.S. 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):31–35.
72. Xyrem International Study Group. A double-blind, placebo-controlled study demonstrates sodium oxybate is effective for the treatment of excessive daytime sleepiness in narcolepsy. *J Clin Sleep Med*. 2005;1(4):391–397. doi:10.5664/jcsm.26368
73. Xyrem International Study Group. Further evidence supporting the use of sodium oxybate for the treatment of cataplexy: a double-blind, placebo-controlled study in 228 patients. *Sleep Med*. 2005;6(5):415–421. doi:10.1016/j.sleep.2005.03.010
74. Black J, Houghton WC. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 2006;29(7):939–946. doi:10.1093/sleep/29.7.939
75. 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):483–494. doi:10.1016/S2352-4642(18)30133-0
76. Dauvilliers Y, Šonka K, Bogan RK, et al. Changes in cataplexy frequency in a clinical trial of lower-sodium oxybate with taper and discontinuation of other anticataplectic medications. *CNS Drugs*. 2022;36:633–647. doi:10.1007/s40263-022-00926-0
77. Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly administration of sodium oxybate results in significant reduction in the nocturnal sleep disruption of patients with narcolepsy. *Sleep Med*. 2009;10(8):829–835. doi:10.1016/j.sleep.2009.05.004
78. Dauvilliers Y, Roth T, Guinta D, Alvarez-Horine S, Dynin E, Black J. Effect of sodium oxybate, modafinil, and their combination on disrupted nighttime sleep in narcolepsy. *Sleep Med*. 2017;40:53–57. doi:10.1016/j.sleep.2017.07.030
79. Black J, Pardi D, Hornfeldt CS, Inhaber N. The nightly use of sodium oxybate is associated with a reduction in nocturnal sleep disruption: a double-blind, placebo-controlled study in patients with narcolepsy. *J Clin Sleep Med*. 2010;6(6):596–602. doi:10.5664/jcsm.27994
80. Husain AM, Bujanover S, Ryan R, Scheckner B, Black J, Profant J. Incidence and duration of common, early-onset adverse events occurring during 2 randomized, placebo-controlled, phase 3 studies of sodium oxybate in participants with narcolepsy. *J Clin Sleep Med*. 2020;16(9):1469–1474. doi:10.5664/jcsm.8530
81. 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):323–335. doi:10.1007/s40263-023-00992-y
82. 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;14:1901–1917. doi:10.2147/NSS.S369122
83. Morse AM, Dauvilliers Y, Arnulf I, et al. Long-term efficacy and safety of lower-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. July 6 Online Ahead of Print. doi:10.5664/jcsm.10698
84. Leary EB, Pfister C, Fuller DS, Macfadden W. Effectiveness and optimization of low-sodium oxybate in participants with narcolepsy switching from sodium oxybate (SEGUE) [poster 324]. Presented at: Annual Meeting of the Associated Professional Sleep Societies; Indianapolis, IN; 2023.
85. Philip P, Chaufton C, Taillard J, et al. Modafinil improves real driving performance in patients with hypersomnia: a randomized double-blind placebo-controlled crossover clinical trial. *Sleep*. 2014;37(3):483–487. doi:10.5665/sleep.3480
86. Sagaspe P, Micoulaud-Franchi JA, Coste O, et al. Maintenance of Wakefulness Test, real and simulated driving in patients with narcolepsy/hypersomnia. *Sleep Med*. 2019;55:1–5. doi:10.1016/j.sleep.2018.02.009
87. Husain AM, Ristanovic RK, Bogan RK. Weight loss in narcolepsy patients treated with sodium oxybate. *Sleep Med*. 2009;10(6):661–663. doi:10.1016/j.sleep.2008.05.012
88. 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. doi:10.1111/jsr.12684
89. Foldvary-Schaefer N, Skowronski R, Hickey L, Chen A, Measey TJ, Dauvilliers Y. Weight changes during treatment with lower-sodium oxybate in a phase 3 clinical study in patients with narcolepsy [poster 136]. Presented at: Annual Meeting of the Associated Professional Sleep Societies; Charlotte, NC; 2022.
90. Dauvilliers Y, Chandler P, Hickey L, Chen A, Steininger T, Foldvary-Schaefer N. Weight changes during treatment with lower-sodium oxybate in a phase 3 clinical study in patients with idiopathic hypersomnia [poster 132]. Presented at: Annual Meeting of the Associated Professional Sleep Societies; Charlotte, NC; 2022.
91. Donjacour CE, Aziz NA, Overeem S, Kalsbeek A, Pijl H, Lammers GJ. Glucose and fat metabolism in narcolepsy and the effect of sodium oxybate: a hyperinsulinemic-euglycemic clamp study. *Sleep*. 2014;37(4):795–801. doi:10.5665/sleep.3592
92. Cohen A, Mandrekar J, St Louis EK, Silber MH, Kotagal S. Comorbidities in a community sample of narcolepsy. *Sleep Med*. 2018;43:14–18. doi:10.1016/j.sleep.2017.11.1125
93. Dauvilliers Y, Jaussent I, Krams B, et al. Non-dipping blood pressure profile in narcolepsy with cataplexy. *PLoS One*. 2012;7(6):e38977. doi:10.1371/journal.pone.0038977
94. Hermida RC, Crespo JJ, Otero A, et al. Asleep blood pressure: significant prognostic marker of vascular risk and therapeutic target for prevention. *Eur Heart J*. 2018;39(47):4159–4171. doi:10.1093/eurheartj/ehy475
95. Hozawa A, Inoue R, Ohkubo T, et al. Predictive value of ambulatory heart rate in the Japanese general population: the Ohasama study. *J Hypertens*. 2008;26(8):1571–1576. doi:10.1097/HJH.0b013e3283041172
96. Ohkubo T, Hozawa A, Yamaguchi J, et al. Prognostic significance of the nocturnal decline in blood pressure in individuals with and without high 24-h blood pressure: the Ohasama study. *J Hypertens*. 2002;20(11):2183–2189. doi:10.1097/00004872-200211000-00017
97. Grandner MA, Jackson NJ, Pak VM, Gehrman PR. Sleep disturbance is associated with cardiovascular and metabolic disorders. *J Sleep Res*. 2012;21(4):427–433. doi:10.1111/j.1365-2869.2011.00990.x
98. Bock J, Covassin N, Somers V. Excessive daytime sleepiness: an emerging marker of cardiovascular risk. *Heart*. 2022;108(22):1761–1766. doi:10.1136/heartjnl-2021-319596

99. Bigalke JA, Shan Z, Carter JR. Orexin, sleep, sympathetic neural activity, and cardiovascular function. *Hypertension*. 2022;79(12):2643–2655. doi:10.1161/HYPERTENSIONAHA.122.19796
100. Jacobs DR Jr, Woo JG, Sinaiko AR, et al. Childhood cardiovascular risk factors and adult cardiovascular events. *N Engl J Med*. 2022;386 (20):1877–1888. doi:10.1056/NEJMoa2109191
101. Aburto NJ, Ziolkovska A, Hooper L, Elliott P, Cappuccio FP, Meerpohl JJ. Effect of lower sodium intake on health: systematic review and meta-analyses. *BMJ*. 2013;346:f1326. doi:10.1136/bmj.f1326
102. Bibbins-Domingo K, Chertow GM, Coxson PG, et al. Projected effect of dietary salt reductions on future cardiovascular disease. *N Engl J Med*. 2010;362(7):590–599. doi:10.1056/NEJMoa0907355
103. Cook NR, Cutler JA, Obarzanek E, et al. Long term effects of dietary sodium reduction on cardiovascular disease outcomes: observational follow-up of the trials of hypertension prevention (TOHP). *BMJ*. 2007;334(7599):885–888. doi:10.1136/bmj.39147.604896.55
104. Whelton PK, Appel L, Charleston J, et al. The effects of nonpharmacologic interventions on blood pressure of persons with high normal levels. results of the trials of hypertension prevention, phase I. *JAMA*. 1992;267(9):1213–1220. doi:10.1001/jama.1992.03480090061028
105. Whelton PK, Appel L, Charleston J, et al. Effects of weight loss and sodium reduction intervention on blood pressure and hypertension incidence in overweight people with high-normal blood pressure. *Arch Intern Med*. 1997;157(6):657–667.
106. Sacks FM, Svetkey LP, Vollmer WM, et al. Effects on blood pressure of reduced dietary sodium and the Dietary Approaches to Stop Hypertension (DASH) diet. DASH-Sodium Collaborative Research Group. *N Engl J Med*. 2001;344(1):3–10. doi:10.1056/NEJM200101043440101
107. Neal B, Wu Y, Feng X, et al. Effect of salt substitution on cardiovascular events and death. *N Engl J Med*. 2021;385(12):1067–1077. doi:10.1056/NEJMoa2105675
108. Zeng C, Rosenberg L, Li X, et al. Sodium-containing Acetaminophen and cardiovascular outcomes in individuals with and without hypertension. *Eur Heart J*. 2022;43(18):1743–1755. doi:10.1093/eurheartj/ehac059
109. George J, Majeed W, Mackenzie IS, Macdonald TM, Wei L. Association between cardiovascular events and sodium-containing effervescent, dispersible, and soluble drugs: nested case-control study. *BMJ*. 2013;347:f6954. doi:10.1136/bmj.f6954
110. Benitez-Camps M, Morros Padros R, Pera-Pujadas H, et al. Effect of effervescent paracetamol on blood pressure: a crossover randomized clinical trial. *J Hypertens*. 2018;36(8):1656–1662. doi:10.1097/HJH.0000000000001733
111. Ubeda A, Llopico J, Sanchez MT. Blood pressure reduction in hypertensive patients after withdrawal of effervescent medication. *Pharmacoepidemiol Drug Saf*. 2009;18(5):417–419. doi:10.1002/pds.1701
112. Clinical superiority findings; 2021. Available from: https://www.fda.gov/industry/designating-orphan-product-drugs-and-biological-products/clinical-superiority-findings. Accessed July 9, 2021.
113. Bosco A, Lopez R, Barateau L, et al. Effect of psychostimulants on blood pressure profile and endothelial function in narcolepsy. *Neurology*. 2018;90(6):e479–e491. doi:10.1212/WNL.0000000000004911
114. Life's Essential 8; 2022. Available from: https://www.heart.org/en/healthy-living/healthy-lifestyle/lifes-essential-8. Accessed January 16, 2023.
115. 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. doi:10.1007/s40801-020-00223-6
116. Molina BSG, Kipp HL, Joseph HM, et al. Stimulant diversion risk among college students treated for ADHD: primary care provider prevention training. *Acad Pediatr*. 2020;20(1):119–127. doi:10.1016/j.acap.2019.06.002
117. Boucetta S, Montplaisir J, Zadra A, et al. Altered regional cerebral blood flow in idiopathic hypersomnia. *Sleep*. 2017;40(10). doi:10.1093/sleep/zsx140
118. Pomares FB, Boucetta S, Lachapelle F, et al. Beyond sleepy: structural and functional changes of the default-mode network in idiopathic hypersomnia. *Sleep*. 2019;42(11). doi:10.1093/sleep/zsz156
119. Dauvilliers Y, Evangelista E, de Verbizier D, Barateau L, Peigneux P. [18F]Fludeoxyglucose-positron emission tomography evidence for cerebral hypermetabolism in the awake state in narcolepsy and idiopathic hypersomnia. *Front Neurol*. 2017;8:350. doi:10.3389/fneur.2017.00350
120. Scherfler C, Frauscher B, Schocke M, et al. White and gray matter abnormalities in narcolepsy with cataplexy. *Sleep*. 2012;35(3):345–351. doi:10.5665/sleep.1692
121. Huang X, Tang S, Lyu X, Yang C, Chen X. Structural and functional brain alterations in obstructive sleep apnea: a multimodal meta-analysis. *Sleep Med*. 2019;54:195–204. doi:10.1016/j.sleep.2018.09.025