

INPLASY

INPLASY2026100121

doi: 10.37766/inplasy2026.10.0121

Received: 28 October 2026

Published: 28 October 2026

Corresponding author:

Eric Nemec

nemece@sacredheart.edu

Author Affiliation:

Sacred Heart University.

Lower-sodium oxybate (calcium, magnesium, potassium, and sodium oxybates) for excessive daytime sleepiness in adults with central disorders of hypersomnolence: protocol for a systematic review with structured narrative synthesis

Blankenbaker, J; Tran J; Rose, SJ; Nemec, EC.

ADMINISTRATIVE INFORMATION

Support - No support.**Review Stage at time of this submission** - Formal screening of search results against eligibility criteria.**Conflicts of interest** - None declared.**INPLASY registration number:** INPLASY2026100121**Amendments** - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 28 October 2026 and was last updated on 28 October 2026.

INTRODUCTION

Review question / Objective In adults with central disorders of hypersomnolence (narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, or hypersomnia due to a medical condition), what are the effects of lower-sodium oxybate (LXB; Xywav; calcium, magnesium, potassium, and sodium oxybates) on subjective daytime sleepiness, disease-specific symptom severity, objective daytime sleepiness, and adverse events?

- Population: adults aged 18 years or older with a central disorder of hypersomnolence.
- Intervention: LXB at any dose or regimen.
- Comparators: placebo after randomized withdrawal; the participant's own pre-LXB baseline; prior high-sodium sodium oxybate (SXB) in transition studies.
- Outcomes: Epworth Sleepiness Scale (primary); Idiopathic Hypersomnia Severity Scale (idiopathic hypersomnia only), Maintenance of Wakefulness

Test, Multiple Sleep Latency Test and adverse events (secondary); nocturnal polysomnographic sleep-onset and REM latency (exploratory).

- Study designs: randomized controlled and randomized-withdrawal trials, open-label interventional studies and periods, and prospective or retrospective observational studies.

Rationale Narcolepsy and idiopathic hypersomnia are chronic, functionally disabling disorders in which excessive daytime sleepiness persists despite adequate nocturnal sleep. American Academy of Sleep Medicine guidance supports sodium oxybate for both conditions. However, the standard formulation delivers a substantial nightly sodium load, which raises concern about long-term cardiovascular risk. At equivalent doses, LXB contains 92% less sodium than sodium oxybate. It is FDA-approved for narcolepsy (2020) and for idiopathic hypersomnia in adults (2021).

The evidence for LXB comes from studies with different designs: randomized-withdrawal trials in participants already stabilized on LXB, single-arm open-label studies, and real-world transition

studies from sodium oxybate. These designs answer different questions (maintenance of effect, within-person change from baseline, and maintenance after switching). They also vary in diagnosis, dose, follow-up duration and outcome measure. We are not aware of a systematic review that organizes this evidence by diagnosis, evidence stream and time on treatment, or that appraises it with design-appropriate tools.

This review will synthesize the evidence on subjective and objective daytime sleepiness, idiopathic hypersomnia symptom severity, and adverse events. Each estimate will be interpreted against the prespecified clinical thresholds (items 18 and 19) and the certainty of evidence. The aim is to inform prescribing in adults with central disorders of hypersomnolence.

Condition being studied Central disorders of hypersomnolence are chronic neurological sleep disorders characterized by excessive daytime sleepiness despite adequate nocturnal sleep.

- Narcolepsy (ICSD-3): recurrent periods of an irrepressible need to sleep, or daytime lapses into sleep, occurring at least three times per week for at least three months. The diagnosis also requires cataplexy, cerebrospinal fluid hypocretin-1 deficiency (≤ 110 pg/mL or $\leq 1/3$ of control values), or characteristic findings on polysomnography and the Multiple Sleep Latency Test (mean sleep latency ≤ 8 minutes with ≥ 2 sleep-onset REM periods). Narcolepsy type 1 involves cataplexy and/or hypocretin deficiency; type 2 has neither.
- Idiopathic hypersomnia: daily excessive sleepiness for at least three months, often with prolonged non-restorative sleep and sleep inertia, where polysomnographic and MSLT findings do not meet narcolepsy criteria.
- Kleine-Levin syndrome and hypersomnia due to a medical condition: also central disorders of hypersomnolence, and eligible if identified. These disorders impair function and quality of life and usually require long-term pharmacotherapy.

METHODS

Search strategy A health sciences librarian developed the strategy. It combined LXB intervention terms with hypersomnolence condition terms and applied no publication-date restriction. We used an AI tool (Perplexity) to translate the PubMed strategy into each database's syntax, and the authors reviewed the translated strings.

PubMed

(Xywav[tiab] OR "JZP-258"[tiab] OR LXB[tiab] OR ((low[tiab] OR lower[tiab] OR reduced[tiab]) AND sodium[tiab] AND oxybate*[tiab]) OR (calcium[tiab]

AND magnesium[tiab] AND potassium[tiab] AND sodium[tiab] AND oxybate*[tiab]) OR (mixed[tiab] AND (cation*[tiab] OR salt*[tiab]) AND oxybate*[tiab])) AND ("Narcolepsy"[Mesh] OR narcolep*[tiab] OR "Idiopathic Hypersomnia"[Mesh] OR "idiopathic hypersomnia"[tiab] OR "Disorders of Excessive Somnolence"[Mesh] OR hypersomnolen*[tiab] OR hypersomnia*[tiab] OR "excessive daytime sleepiness"[tiab] OR cataplex*[tiab])

Scopus

TITLE-ABS-KEY(Xywav OR "JZP-258" OR LXB OR ((low OR lower OR reduced) AND sodium AND oxybate*) OR (calcium AND magnesium AND potassium AND sodium AND oxybate*) OR (mixed AND (cation* OR salt*) AND oxybate*)) AND TITLE-ABS-KEY(narcolep* OR "idiopathic hypersomnia" OR "disorders of excessive somnolence" OR hypersomnolen* OR hypersomnia* OR "excessive daytime sleepiness" OR cataplex*)

EBSCOhost (CINAHL Ultimate, Academic Search Premier, Cochrane Central Register of Controlled Trials)

(TI (xywav OR "JZP-258" OR LXB OR ((low OR lower OR reduced) AND sodium AND oxybate*) OR (calcium AND magnesium AND potassium AND sodium AND oxybate*) OR (mixed AND (cation* OR salt*) AND oxybate*)) OR AB (xywav OR "JZP-258" OR LXB OR ((low OR lower OR reduced) AND sodium AND oxybate*) OR (calcium AND magnesium AND potassium AND sodium AND oxybate*) OR (mixed AND (cation* OR salt*) AND oxybate*))) AND (TI (narcolep* OR "idiopathic hypersomnia" OR "disorders of excessive somnolence" OR hypersomnolen* OR hypersomnia* OR "excessive daytime sleepiness" OR cataplex*) OR AB (narcolep* OR "idiopathic hypersomnia" OR "disorders of excessive somnolence" OR hypersomnolen* OR hypersomnia* OR "excessive daytime sleepiness" OR cataplex*))

Searches were run between September 28 and October 4, 2026.

Participant or population • Included: adults aged 18 years or older with a central disorder of hypersomnolence, namely narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, Kleine-Levin syndrome, or hypersomnia due to a medical condition, as diagnosed in the primary study. • Excluded: pediatric participants; shift workers; insomnia disorders; sleep-related breathing disorders as the primary condition; and participants using sedatives, opioids, alcohol, illicit

substances or other CNS depressants when the effect of LXB cannot be separated from the effect of the concomitant substance. Narcolepsy type 1 and type 2 will be reported separately where data allow.

Intervention Lower-sodium oxybate (LXB; Xywav; JZP-258; calcium, magnesium, potassium, and sodium oxybates) oral solution at any dose, titration schedule or regimen (once or twice nightly). This includes open-label titration, stable-dose and extension periods, and LXB started after transition from sodium oxybate when LXB-specific outcomes are reported. Studies of high-sodium sodium oxybate (Xyrem/SXB) or once-nightly sodium oxybate alone are not eligible.

Comparator Three comparison types will be analyzed separately and never combined:• (A) placebo, after randomized withdrawal from stabilized LXB treatment;• (B) the participant's own pre-LXB baseline, off oxybate or oxybate-naïve;• (C) prior sodium oxybate treatment, in studies of transition from SXB to LXB.

Study designs to be included RCTs, including randomized-withdrawal trials; nonrandomized interventional studies, including single-arm open-label studies; open-label titration, stable-dose and extension periods of eligible trials; and prospective or retrospective observational studies. Excluded: case reports, narrative reviews, editorials and animal studies.

Eligibility criteria Inclusion: reports must provide extractable, LXB-specific data for at least one prespecified outcome. Exclusion: grey literature (conference abstracts, dissertations and unpublished data), and non-English publications without an available translation. Multiple reports: reports from the same study are linked and treated as one study. Each cohort contributes no more than one estimate per outcome, evidence stream and time window. The primary report for each cohort, outcome and time point is chosen in this order: 1. the report presenting the prespecified analysis in the randomized or full analysis population; 2. otherwise, the report with the largest analyzed sample; 3. otherwise, the most recent peer-reviewed full report. Secondary reports supply only missing information (for example, standard deviations, subgroup values or interim visits) and do not add data points. Open-label extension data are treated as later time points of the parent cohort, not as new populations.

Information sources PubMed (MEDLINE), Scopus, and EBSCOhost (CINAHL Ultimate,

Academic Search Premier, and the Cochrane Central Register of Controlled Trials). Each database was searched from inception, without date limits, between September 28 and October 4, 2026. Grey literature was not searched. Reports from the same study, including companion, post hoc, and extension publications identified in the search, were linked to their parent study.

Main outcome(s) Subjective daytime sleepiness, measured by Epworth Sleepiness Scale (ESS) total score (range 0–24; higher scores mean greater sleepiness).

- Randomized-withdrawal comparisons: between-group mean difference in change from the end of the stable-dose period, with 95% CI. Reported adjusted (least-squares or ANCOVA) estimates are used when available; otherwise the difference is calculated from arm-level data and labeled as derived. Reported nonparametric estimates are presented alongside.
- Within-person and transition comparisons: mean change from baseline with 95% CI (least-squares mean $\pm 1.96 \times \text{SE}$). When only time-point means are reported, the raw difference is presented without a CI.

Interpretation

A 2-point decrease is the prespecified threshold for a clinically important change. A score of 10 or less is classed as within the normal range.

Timing

Outcomes are classified by cumulative weeks of LXB exposure from the first dose: short-term ≤ 16 weeks; intermediate >16 to ≤ 26 weeks; long-term >26 weeks. Randomized-withdrawal comparisons are reported separately from these windows.

Additional outcome(s) Secondary outcomes

- IHSS (idiopathic hypersomnia only): Idiopathic Hypersomnia Severity Scale total score (0–50). Threshold: 4-point decrease; a score below 22 corresponds to the range of healthy controls.
- MWT: Maintenance of Wakefulness Test mean sleep latency (minutes). Threshold: 2-minute increase.
- MSLT: Multiple Sleep Latency Test mean sleep latency (minutes). Threshold: 1-minute increase.
- Adverse events: participants with at least one treatment-emergent adverse event (TEAE), serious TEAEs, and discontinuation due to TEAEs with reasons. Named TEAEs are reported if they occur in at least 5% of participants in at least two cohorts, or are reported as a reason for stopping LXB. Proportions use period-specific safety

population denominators, by arm in randomized-withdrawal periods.

Exploratory outcome

Nocturnal polysomnographic sleep-onset latency and REM latency (minutes).

Data management Records were imported into Covidence for deduplication and two-stage screening. Two reviewers independently screened titles and abstracts and then full texts, recording reasons for exclusion at full text. Conflicts were resolved by discussion, with a third reviewer deciding if consensus was not reached.

Data were extracted independently by two reviewers into a standardized spreadsheet. The spreadsheet records:

- study and cohort linkage
- diagnosis
- evidence stream
- study period
- weeks since LXB initiation
- time window
- the number analyzed and the proportion of the parent cohort retained
- effect estimates with their dispersion type (SD or SE)
- adverse-event denominators

Discrepancies between reports of the same cohort were recorded. Full-analysis and completer results were both extracted when available, with full-analysis results as primary.

Quality assessment / Risk of bias analysis Two reviewers independently assessed risk of bias for each cohort, outcome, and study period, and a third reviewer resolved disagreements.

- Randomized-withdrawal comparisons: assessed with the Cochrane Risk of Bias 2 (RoB 2) tool.
- Open-label periods, single-arm studies and observational transition studies: assessed with the ROBINS-I version 2 for Before-After (Pre-Post) Studies With No Control Group.
- Attrition and enrichment: assessed within these tools. This includes selective retention, into extension and randomized-withdrawal periods, of participants who tolerated and responded to titration.

Certainty of evidence will be rated for each outcome using the GRADE approach, across risk of bias, inconsistency, indirectness, imprecision (judged against the clinical thresholds) and publication bias. Findings will be presented in a Summary of Findings table.

Strategy of data synthesis No meta-analysis will be performed, because study designs, comparators and time points differ. Findings will be

synthesized narratively following the Synthesis Without Meta-analysis (SWiM) guideline and Cochrane Handbook Chapter 12.

Grouping. Results are grouped first by diagnosis: narcolepsy (type 1 and type 2 separately where possible), idiopathic hypersomnia, and other central disorders of hypersomnolence if identified. Within each diagnosis, results are grouped by evidence stream, then by time window and outcome. The three evidence streams are never combined:

- (A) randomized withdrawal, LXB continuation versus placebo, interpreted as maintenance of effect in stabilized participants;
- (B) within-person change from a pre-LXB baseline. Cohorts whose baseline mixes treated and untreated participants are labeled "B-mixed" when stratified data are unavailable;
- (C) transition from SXB to LXB, interpreted as maintenance of response after switching.

Reporting. Each cohort's effect estimate and 95% CI are reported and interpreted against the thresholds above. Where two or more cohorts share a diagnosis-stream-window-outcome cell, the range of estimates and the consistency of effect direction are described. Vote counting based on statistical significance is not used.

Presentation. Results are presented in a study characteristics table, a cohort-by-time-window results matrix with effect-direction indicators, forest-style plots without pooled estimates, and longitudinal plots for cohorts with repeated measurements.

Interpretation. Causal inference relies mainly on Stream A. Streams B and C describe magnitude, trajectory, and durability. Their interpretation explicitly considers open-label assessment of self-reported outcomes, regression to the mean, and selective retention into extension periods.

Subgroup analysis No statistical subgroup analyses are planned. Results will be stratified descriptively by:

- diagnosis (narcolepsy type 1, narcolepsy type 2, idiopathic hypersomnia, other central disorders of hypersomnolence)
- evidence stream
- time window

Where reported, results will also be described by oxybate status at study entry (oxybate-naïve versus washed out from prior oxybate).

Sensitivity analysis No statistical sensitivity analyses are planned, because no pooled estimates will be calculated. Descriptive comparisons will include:

- full-analysis versus completer results, where both are reported;
- reported versus derived effect estimates, including parametric versus nonparametric between-group estimates in randomized-withdrawal comparisons;
- "B-mixed" cohorts versus cohorts with untreated baselines;
- interpretation of findings with and without studies judged at high risk of bias.

Language restriction English only, unless a translation of a non-English publication was available.

Country(ies) involved United States.

Other relevant information An AI tool (Perplexity) was used to translate the search strategy into database-specific syntax and to help prepare figures. AI was not used for study selection, data extraction or risk-of-bias judgments.

Keywords lower-sodium oxybate; Xywav; narcolepsy; idiopathic hypersomnia; excessive daytime sleepiness; Epworth Sleepiness Scale; systematic review.

Dissemination plans Results will be submitted for publication in a peer-reviewed journal and presented at a professional conference. The INPLASY record will be updated with the citation and DOI on publication.

Contributions of each author

Author 1 - Julia Blankenbaker
 Email: blankenbakerj@mail.sacredheart.edu
 Author 2 - Jessica Tran
 Email: tranj4@mail.sacredheart.edu
 Author 3 - Suzanne Rose
 Email: srose@stamhealth.org
 Author 4 - Eric Nemec
 Email: nemece@sacredheart.edu