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Effects of Oxybate on Sleep, Sleep Architecture, and Disrupted Nighttime Sleep

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Introduction

- Sleep disturbances are the third most common narcolepsy symptom, after excessive daytime sleepiness and cataplexy (type 1 only)[1]; sleep disturbances encompass and impact self-reported sleep quality, sleep architecture, and disrupted nighttime sleep (DNS)[2]
- DNS is characterized clinically by complaints of frequent awakenings from nighttime sleep and also by polysomnography-recorded awakenings or arousals (associated with frequent sleep-stage shifts) resulting in fragmented sleep[2,3]
- Sodium oxybate (SXB; Xyrem®) and low-sodium oxybate (LXB; Xywav®), both dosed twice nightly, and once-nightly sodium oxybate (ON-SXB; Lumryz™) are approved to treat excessive daytime sleepiness and cataplexy in patients with narcolepsy[4,5]
  - The effects of SXB and ON-SXB on sleep quality, sleep architecture, and DNS have been studied independently,[6-12] not in head-to-head trials
  - LXB contains the same active moiety as SXB, thus it is probable that it has similar effects on sleep. However, there are no data at present to support this assumption

Objectives

- Review the scientific literature regarding the impact of oxybate dose and regimen on sleep quality, sleep architecture, and DNS in patients with narcolepsy

Methods

- On May 3, 2023, PubMed was searched for articles on oxybate, narcolepsy, and DNS
  - Search string: *narcolepsy [tiab] AND 2020:2023 [dp] AND (DNS OR disrupted nighttime sleep OR disturbed nighttime sleep OR disrupted nocturnal sleep OR disturbed nocturnal sleep)*
  - Additional articles were identified in a prior literature review focused on those published in 2020 or earlier[2]
- Key data from 5 clinical studies of SXB and ON-SXB are presented

Conclusions

- A review of clinical data shows that oxybates, independent of their dosing regimen (once or twice nightly), are similarly effective in improving sleep quality, measures of sleep architecture, and DNS in participants with narcolepsy
- When choosing an oxybate treatment (whether SXB, LXB, or ON-SXB), clinicians should consider the unique profile of each therapy in order to optimize patient care
- Future studies that directly compare the impact of oxybate therapies on nighttime sleep are needed to better understand the relative effectiveness of each product

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Results

Table 1. Overview of Studies

Reference	Study Design	Timing of PSG Assessments
Study 1		
Black et al, 2010[6] Roth et al, 2017[7]	• Adult patients (>16 years of age) with NT1 (N=228; intent-to-treat) • 8 weeks, double-blind, placebo-controlled, parallel-group • 8 weeks of treatment (4 weeks dose titration, then 4 weeks stable dose) with: – SXB 4.5 g nightly – SXB 6 g nightly – SXB 9 g nightly – Placebo nightly	PSG was performed: • End of lead-in period (before withdrawal of cataplexy medications) • End of baseline period (after withdrawal of cataplexy medications and subsequent washout period) • After 4-week titration period • End of trial (after 8 weeks of treatment)
Study 2		
Black et al, 2009[8] Dauvilliers et al, 2017[12]	• Participants were adult patients (≥18 years of age) with narcolepsy treated with stable doses of modafinil (N=222; intent-to-treat) • 8 weeks, double-blind, placebo-controlled • 8 weeks of treatment (SXB 6 g nightly for first 4 weeks, then 9 g nightly for final 4 weeks) with: – Placebo SXB and placebo modafinil – SXB and placebo modafinil – Modafinil and placebo SXB – SXB and modafinil	PSG was performed: • Before end of baseline period • End of baseline period • After 4 weeks of treatment • After 8 weeks of treatment
Study 3		
Roth et al, 2022[11]	• Participants were adult patients (≥16 years of age) with NT1 or NT2 (N=190; modified intent-to-treat) • 17 weeks, double-blind, placebo-controlled, randomized, multicenter • After 3 weeks of screening, 13 weeks of treatment with ON-SXB (sequentially ascending doses) or placebo: – 4.5 g (1 week) – 6 g (2 weeks) – 7.5 g (5 weeks) – 9 g (5 weeks)	PSG was performed: • At baseline • At week 3 • At week 8 • At week 13
Study 4		
Mamelak et al, 2004[9]	• Participants were adult patients (≥18 years of age) with narcolepsy (N=25; enrolled) • 14 weeks, open-label pilot • After 2 weeks for withdrawal from antidepressants and sedative-hypnotic drugs and another 2 weeks for washout, 10 weeks of treatment with twice-nightly SXB: – Initiated at 4.5 g nightly (4 weeks) – 6 g nightly (2 weeks) – 7.5 g nightly (2 weeks) – 9 g nightly (2 weeks)	PSG was performed: • Before washout period • End of washout period • First night of treatment • After 4 weeks of treatment • End of each dosing period
Study 5		
Mignot et al, 2019[10]	• Participants were pediatric patients (7–17 years of age) with NT1 either SXB-treated or SXB-naive (N=106; enrolled) • Double-blind, placebo-controlled, randomized withdrawal – 3 weeks (patients already on SXB treatment) or 2 weeks (SXB-naive patients; titrated over 3–10 weeks) on stable-dose SXB treatment – 2 weeks, double-blind, placebo-controlled, randomized-withdrawal – 2 years, open-label	PSG was performed: • During screening • End of stable-dose period (SXB-naive only) • After 1 year of SXB treatment

ON-SXB, once-nightly sodium oxybate; NT1, narcolepsy type 1; NT2, narcolepsy type 2; PSG, polysomnography; SXB, sodium oxybate.

- The study designs differed in several important parameters:
  - Dosage groups and titration schedule: In study 1, participants were randomized to dosing groups then titrated to their final dose; in study 2, the same groups received 6 g then 9 g; in study 3, parallel active-treatment and placebo arms underwent forced titration; in study 4, participants underwent forced titration and there was no placebo arm; in study 5, participants were titrated to individual optimal doses
  - Timing of PSG: Differed across studies; in study 5, PSG was not performed during the randomized withdrawal period

Table 2. Oxybate Effects on Sleep Architecture in Adult Participants

	Study 1[6]	Study 2[8]	Study 3[11]	Study 4[9]
Data Measure	*Median Change From Baseline to 8 Weeks*	*Median Change From Baseline to 4 Weeks (6 g) or 8 Weeks (9 g)*	*LSMD vs Placebo at Week 3 (6 g), Week 8 (7.5 g), or Week 13 (9 g)*	*Mean at 4 Weeks (4.5 g), 6 Weeks (6 g), 8 Weeks (7.5 g), or 10 Weeks (9 g)*
Total sleep time, min	**Increased** • Placebo: 0.3 • SXB 4.5 g: 0 • SXB 6 g: 13.0 • SXB 9 g: 18.0†	**No change** • Placebo: –5.5 • SXB 6 g: –5.0 • Placebo: –0.5 • SXB 9 g: –4.5	**Not assessed**	**No change (4.5 g decreased)** • Baseline: 383.4 • SXB 4.5 g: 364.8* • SXB 6 g: 363.0 • SXB 7.5 g: 374.1 • SXB 9 g: 380.8
Wake after sleep onset, min	**Decreased** • Placebo: 2.0 • SXB 4.5 g: –5.8 • SXB 6 g: –3.8 • SXB 9 g: –22.0†	**Not assessed**	**Not assessed**	**Not assessed**
Awakenings/arousals, n	**Awakenings decreased** • Placebo: –0.5 • SXB 4.5 g: –5.0 • SXB 6 g: –8.0†† • SXB 9 g: –12.0††	**Awakenings decreased** • Placebo: 0.5 • SXB 6 g: –1.0 • Placebo: –0.5 • SXB 9 g: –6††	**Arousals decreased** • ON-SXB 6 g: –6.4 • ON-SXB 7.5 g: –18.8†† • ON-SXB 9 g: –21.3†††	**Awakenings decreased** • Baseline: 50.2 • SXB 4.5 g: 50.0 • SXB 6 g: 45.1 • SXB 7.5 g: 37.3*** • SXB 9 g: 37.8**
N1 sleep time, min	**Decreased** • Placebo: –2.3 • SXB 4.5 g: –9.5 • SXB 6 g: –13.5††† • SXB 9 g: –22.5†††	**Decreased** • Placebo: 3.25 • SXB 6 g: –9.5 • Placebo: 1.5 • SXB 9 g: –16.0†††	**Decreased** • ON-SXB 6 g: –5.9† • ON-SXB 7.5 g: –11.0††† • ON-SXB 9 g: –13.4†††	**No change** • Baseline: 74.8 • SXB 4.5 g: 72.3 • SXB 6 g: 68.1 • SXB 7.5 g: 69.4 • SXB 9 g: 62.6
N2 sleep time, min	**No change** • Placebo: 3.5 • SXB 4.5 g: 9.5 • SXB 6 g: 13.0 • SXB 9 g: 31.5	**No change** • Placebo: –5.25 • SXB 6 g: 0.5 • Placebo: –8.25 • SXB 9 g: 3.5	**No change** • ON-SXB 6 g: –6.6 • ON-SXB 7.5 g: 3.6 • ON-SXB 9 g: –13.5	**No change** • Baseline: 217.8 • SXB 4.5 g: 216.9 • SXB 6 g: 216.9 • SXB 7.5 g: 224.1 • SXB 9 g: 238.0
Slow-wave sleep time, min	**Increased** • Placebo: 0 • SXB 4.5 g: 3.0† • SXB 6 g: 21.0††† • SXB 9 g: 52.5†††	**Increased** • Placebo: 0 • SXB 6 g: 11† • Placebo: 0 • SXB 9 g: 43.5†††	**Increased** • ON-SXB 6 g: 22.1††† • ON-SXB 7.5 g: 26.8††† • ON-SXB 9 g: 38.4†††	**Increased** • Baseline: 3.0 (1st half), 0.6 (2nd half) • SXB 4.5 g: 3.5 (1st half), 0.7 (2nd half) • SXB 6 g: 5.5 (1st half), 4.5 (2nd half) • SXB 7.5 g: 9.8 (1st half), 4.5* (2nd half) • SXB 9 g: 14.2 (1st half), 12.6* (2nd half)
Rapid eye movement sleep time, min	**Decreased** • Placebo: –1.0 • SXB 4.5 g: –6.0 • SXB 6 g: –7.0 • SXB 9 g: –22.0†	**Decreased** • Placebo: 6.25 • SXB 6 g: –14.5†† • Placebo: 10 • SXB 9 g: –38.5†††	**Decreased** • ON-SXB 6 g: –16.7††† • ON-SXB 7.5 g: –27.2††† • ON-SXB 9 g: –24.5†††	**Decreased** • Baseline: 31.2 (1st half), 56.0 (2nd half) • SXB 4.5 g: 29.7 (1st half), 43.5* (2nd half) • SXB 6 g: 26.3 (1st half), 42.7*** (2nd half) • SXB 7.5 g: 31.3 (1st half), 34.9*** (2nd half) • SXB 9 g: 22.9 (1st half), 30.5*** 2nd half)
Delta power, $\mu V^2/Hz$	**Increased** • Placebo: –1103.0 • SXB 4.5 g: 7166.2†† • SXB 6 g: 14,736.3††† • SXB 9 g: 28,796.7†††	**Increased** • Placebo: –2326 • SXB 6 g: 10,474 • Placebo: –3221 • SXB 9 g: 18,443†††	**Increased (in NREM only)** • ON-SXB 6 g: 245.8†† • ON-SXB 7.5 g: 310.0† • ON-SXB 9 g: 573.6†††	**Increased** • Baseline: 69,709 • SXB 4.5 g: 74,480 • SXB 6 g: 82,308* • SXB 7.5 g: 91,917*** • SXB 9 g: 102,338***

LSMD, least squares mean difference; NREM, non–rapid eye movement; ON-SXB, once-nightly sodium oxybate; SXB, sodium oxybate.
$^{\dagger}P<0.05$ vs placebo. $^{\dagger\dagger}P<0.01$ vs placebo. $^{\dagger\dagger\dagger}P<0.001$ vs placebo. $^{*}P<0.05$ vs baseline. $^{**}P<0.01$ vs baseline. $^{***}P<0.005$ vs baseline.

- Although study design differences preclude direct comparisons, overall, oxybates consistently improved multiple sleep architecture measures, including lengthened slow-wave sleep and shortened REM sleep
  - For delta power, study 3 reported this variable in NREM only, unlike the other studies which included REM and NREM sleep
  - Data measures for studies 1 and 2 are reported as median change from baseline; for study 3, they are reported as LSMD vs placebo; for study 4, mean values are reported and statistically tested vs baseline due to lack of placebo comparator
- For many measures, greater improvements were seen with increasing doses of oxybate

Table 3. Oxybate Effects on Sleep Architecture in Pediatric Participants

	Study 5[10]
Data Measure	*Median Change From Baseline (Individual Doses)*
Total sleep time, min	**Not assessed**
Wake after sleep onset, min	**Not assessed**
Awakenings/arousals, n	**Arousals decreased** • SXB-naive: –43.0 arousals, –4.0 awakenings • Taking SXB at study entry: –1.0 arousals, 1.5 awakenings
N1 sleep time, %	**Decreased** • SXB-naive: –4.6% • Taking SXB at study entry: –0.6%
N2 sleep time, %	**No change[a]**
Slow-wave sleep time, %	**Increased** • SXB-naive: 12.6% • Taking SXB at study entry: –1.0%
Rapid eye movement sleep time, %	**Decreased** • SXB-naive: –6.0% • Taking SXB at study entry: not assessed
Delta power, $\mu V^2/Hz$	**Not assessed**

SXB, sodium oxybate.
[a]Values not reported.

- In the single study assessing pediatric participants with narcolepsy, SXB decreased arousals, decreased percent time in N1 and REM sleep, and increased percent time in slow-wave sleep in participants naive to oxybate therapy at study entry

Table 4. Oxybate Effects on DNS and Sleep Quality in Adult Participants

	Study 1[7]	Study 2[12]	Study 3[11]	Study 4[9]
Data Measure	*LSM Change From Baseline to Week 8 (per Hour)[a]*	*LSM Change From Baseline (Total)*	*LSMD Change From Baseline (Total)*	*Participants, %*
Shifts from N2/N3/REM to N1/wake	**Decreased** • Placebo: –0.8 • SXB 4.5 g: –1.7 • SXB 6 g: –2.7† • SXB 9 g: –4.4†††	**Decreased** • Placebo: –0.6 • SXB 9 g: –16.5†††	**Decreased[b]** • ON-SXB 6 g: –9.0†† • ON-SXB 7.5 g: –16.2††† • ON-SXB 9 g: –21.1†††	**Not assessed**
Shifts from N2/N3 to N1/wake	**Decreased** • Placebo: –0.3 • SXB 4.5 g: –0.9 • SXB 6 g: –1.7† • SXB 9 g: –3.1†††	**Not assessed**		**Not assessed**
Shifts from REM to N1/wake	**Decreased** • Placebo: –1.9 • SXB 4.5 g: –3.8 • SXB 6 g: –5.0 • SXB 9 g: –7.6†	**Decreased** • Placebo: –0.6 • SXB 9 g: –6.0†††		**Not assessed**
Participant-reported sleep quality	**Improved (4-point Likert scale)[c]** • Placebo: –0.10 • SXB 4.5 g: –0.41† • SXB 6 g: –0.31† • SXB 9 g: –0.46†††	**Improved (Question 6 of the PSQI)** • Placebo: –0.07 • SXB 9 g: –0.52†††	**Improved (Visual analog scale from 0–100)[d]** • ON-SXB 6 g: 5.4†† • ON-SXB 7.5 g: 7.4†† • ON-SXB 9 g: 6.5†	**Improved (Self-reported degree of change)** • Baseline: 0% (much), 14% (somewhat) • SXB 4.5 g: 19% (much), 57% (somewhat) • SXB 6 g: 24% (much), 67% (somewhat) • SXB 7.5 g: 24% (much), 62% (somewhat) • SXB 9 g: 24% (much), 57% (somewhat)

LSM, least squares mean; LSMD, least squares mean difference; ON-SXB, once-nightly sodium oxybate; PSQI, Pittsburgh Sleep Quality Index; REM, rapid eye movement; SXB, sodium oxybate.
[a]Per hour values at 9 g translate to reductions of approximately 30.8 (N2/3/REM to N1/wake), 21.7 (N2/3 to N1/wake), and 53.2 (REM sleep to N1/wake) total shifts per night, assuming a total sleep time of 7 hours but not accounting for time spent in individual sleep stages.
[b]Assessed as total number of transitions from sleep to wake or N1 from N1, N2, N3, and REM.
[c]Assessed with 4-point Likert-type scale (0, excellent; 1, good; 2, fair; 3, poor).
[d]Baseline scores were 53.8 and 55.9 in ON-SXB and placebo groups, respectively.
$^{\dagger}P<0.05$ vs placebo. $^{\dagger\dagger}P<0.01$ vs placebo. $^{\dagger\dagger\dagger}P<0.001$ vs placebo.

- Reductions in sleep-stage shifts and improvements in participant-reported sleep quality were observed in all trials in which these variables were measured
- Study 1 reported shifts per hour, while studies 2 and 3 reported total shifts per night

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