

Gamma-hydroxybutarate (GHB): History and Modern-Day Use

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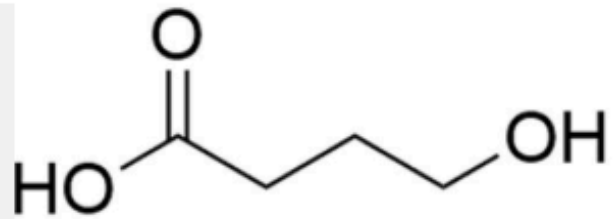
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Praveen Nandamuru, MD has no relevant financial relationships with ineligible companies to disclose.

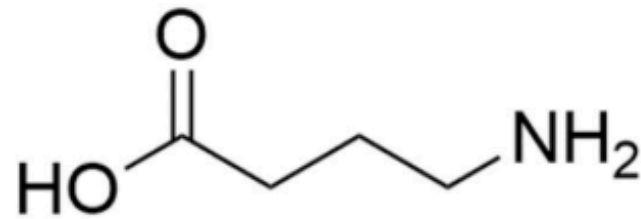
Objectives

- What is the history of Gamma-hydroxybutarate and how else is it used other than to treat hypersomnolence?
- What are the benefits and drawbacks of using it and sodium oxybate?
- What are the alternatives/competitors for sodium oxybate to treat hypersomnolence?

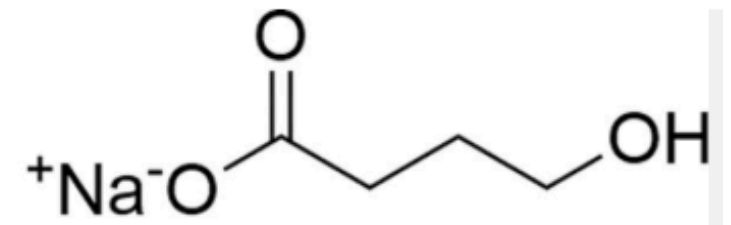
What is GHB?



1, GHB



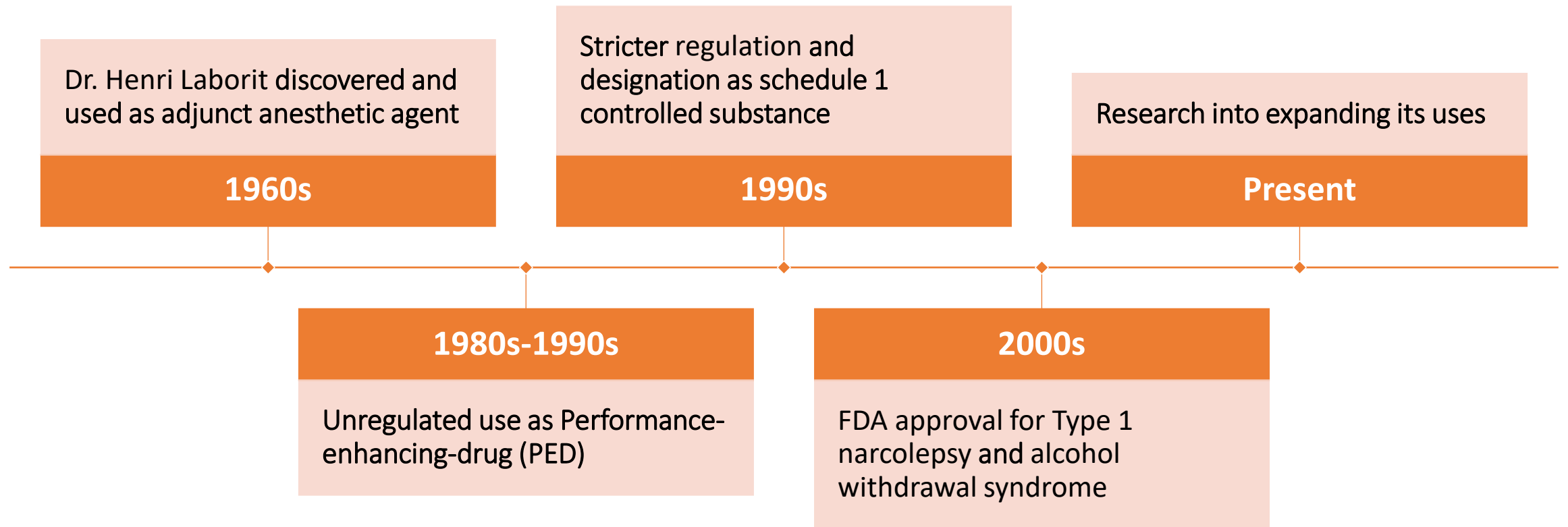
2, GABA



3, sodium oxybate

- Endogenous short-chain hydroxylated carboxylic acid
- CNS depressant action
 - Structurally like GABA

History



Toxicological Characterization of GHB as a Performance-Enhancing Drug

- Giorgetti A, Busardò FP and Giorgetti R (2022) Toxicological Characterization of GHB as a Performance-Enhancing Drug. *Front. Psychiatry* 13:846983. doi: 10.3389/fpsyt.2022.846983

Various Uses

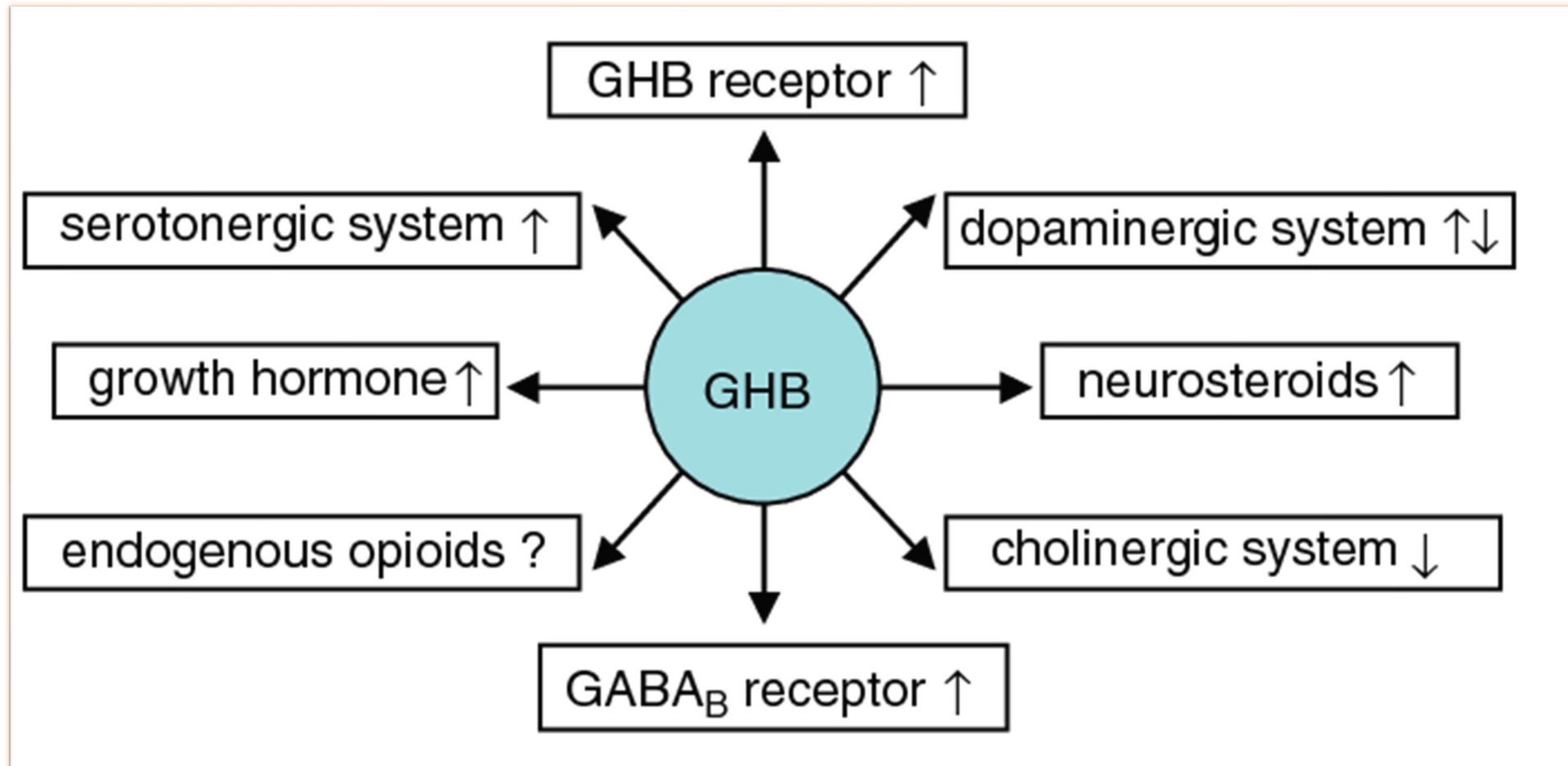
Narcolepsy-associated cataplexy

Alcohol dependence

Performance-enhancing

Club drug

Molecular Mechanisms of Potential Performance Enhancement



Studies showing use of GHB as PED

- 20% of women athletes using anabolic steroids were also using GHB
- 63% of withdrawal cases presenting to ED attributed to use of GHB for bodybuilding
- Group of patients in addiction center and prisoners used GHB to improve sleep or as a PED in conjunction with steroids

Improvement in Other Performance Aspects

Weight loss

Enhanced sexual
desire and
performance

Feeling stronger

Better
appearance

Toned muscles

**Increased
alertness**

Diminished acne

Improved social
bonding

Weight loss

- Early evidence: Rats treated with GHB
- Pediatric population
- Mechanism
 - Increased lipolysis and preferred fatty acid utilization
- Limitation: most evidence included obese patients or baseline altered metabolism



Psychoactive and other Performance Effects

Attention

- Conflicting studies on aiding vs. decreasing focus
- In narcolepsy patients --> improved attention
- Improvement in some aspects while impairing other aspects of alertness

Euphoria

- ↑ confidence, perception of strength

Self-control

Wellbeing

Improved sexual experience

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Reported medical benefits

Burn wounds treated with GHB epithelialized more rapidly

- Murphy et al., 2007
- Rousseau et al., 2014

Improvements in fatigue and pain in fibromyalgia patients

- Russell et al., 2011

Decrease peripheral insulin sensitivity, increasing lipolysis

- Donjacour et al., 2014

Burn wounds heal more rapidly?

Murphy et al, 2007

Rats with TBSA > 40%

Randomized

- Burn, no drug
- Burn + 100mg/kg GHB
- Burn + 200 mg/kg GHB
- Burn + 1000 mg/kg GHB
- Sham, no drug
- Sham + 100 mg/kg GHB

Analysis

- Dual energy x-ray absorptiometry
- Serum GH and IGF-1
- wound morphology by microscopy

Rousseau et al 2014

Humans with TBSA > 30%

Randomized 5 days after injury

- Evening bolus of 50 mg/kg(B)
- Continuous infusion at 10 mg/kg/hr(C)
- No GHB for 21 days(P)

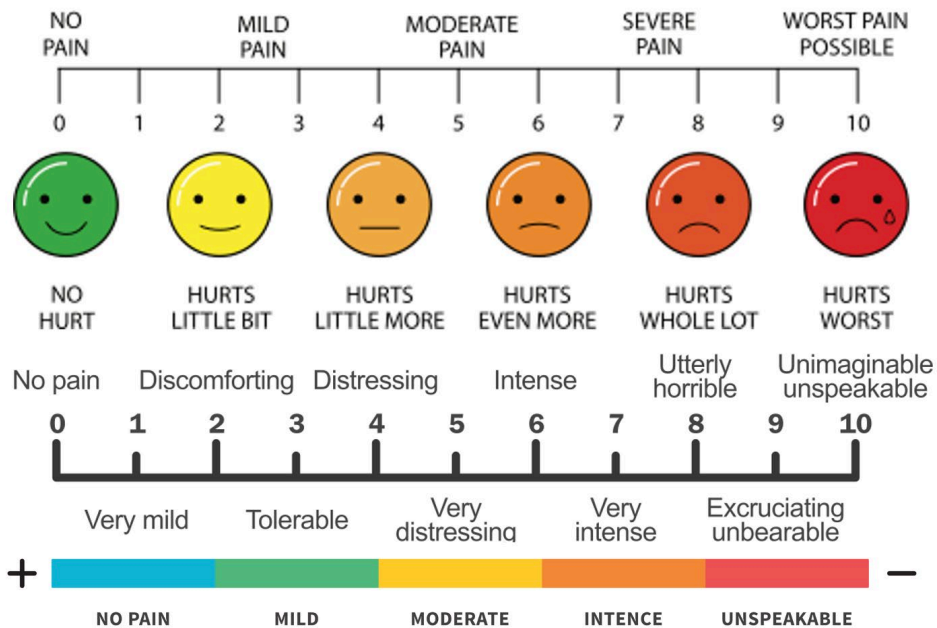
Analysis

- Skin biopsy, IGF1 levels

Results

- Group C > keratinocyte number and increase of IGF1 concentrations

Improvements in Fatigue and Pain in Fibromyalgia patients



Russell et al 2011

- RCT double-blind study
- 548 fibromyalgia patients
- Randomized
 - 4.5 g/day SXB
 - 6 g/day SXB
 - Placebo for 14 week
- Analysis
 - Fatigue and pain rating
 - Sleep assessment

Decreased Peripheral Insulin Sensitivity, Increasing Lipolysis

Concern for patients with diabetes?

Donjacour et. Al 2014

Case report 2 yo with T1DM and narcolepsy

High fasting glucose with ketones in urine

Increased supplemental insulin with increasing doses of sodium oxybate

Desired effects

Euphoria

Sensation of increased energy

Weight loss

Improved communication

Improved sexual performance

Pleasant mood

Relaxation

Mitigation of daily worries

Self-confidence

Improving dance performance

Adverse effects

Urticaria

Headache

Weakness

Fatigue

Irritability

Short-term memory loss

N/V

Weight loss

Diarrhea/incontinence

Dizziness

Confusion

Hallucinations

Incoordination

Peripheral vision loss

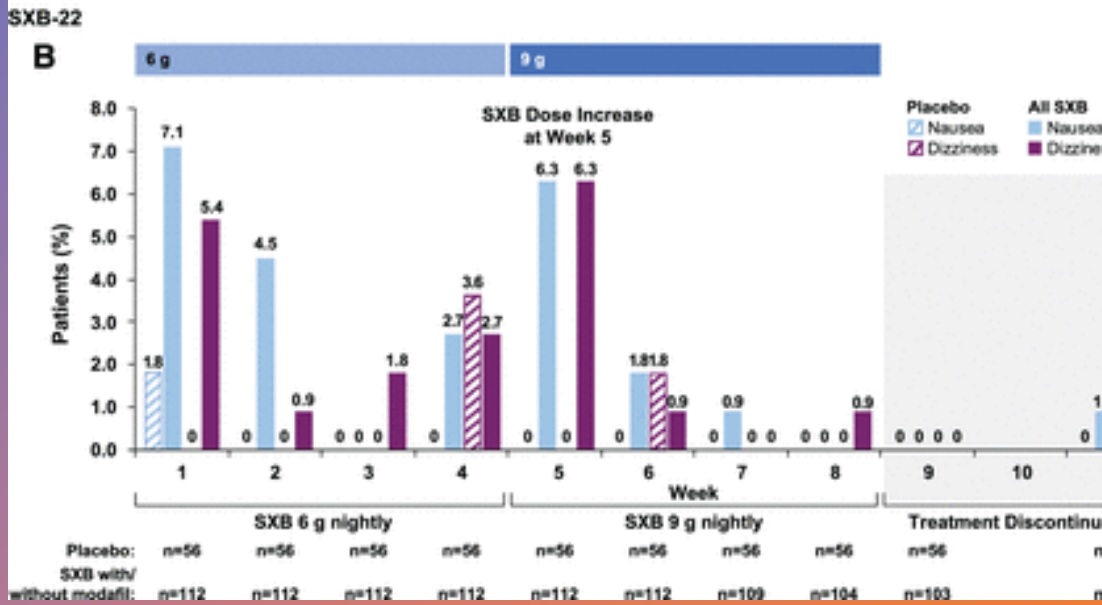
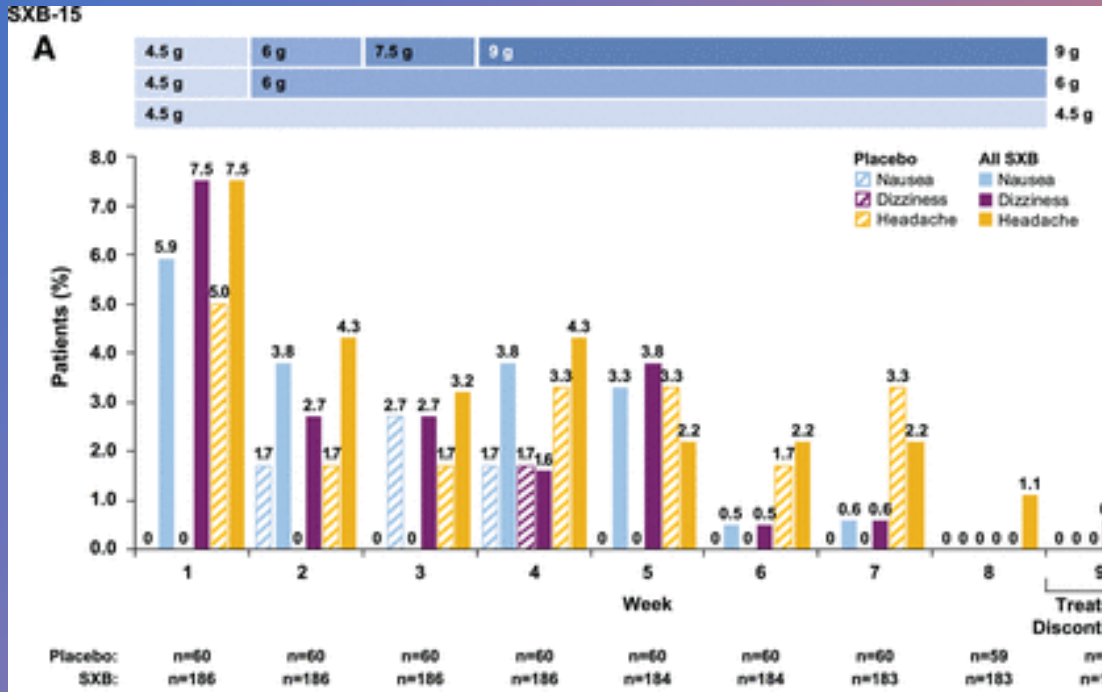
Unconsciousness

Death

Health Risks/Adverse effects

- Considered mild in therapeutic setting
- Users in high doses
 - CNS depression with apnea, LOC, Coma, Death
 - Galloway et. Al 1997
- Difficulty quantifying as dietary supplement
- Withdrawal symptoms

Treatment-emergent adverse effects



- Aatif M. Husain, MD, et. Al 2020
- Dizziness lasted the longest
- Nausea and headache abated more quickly

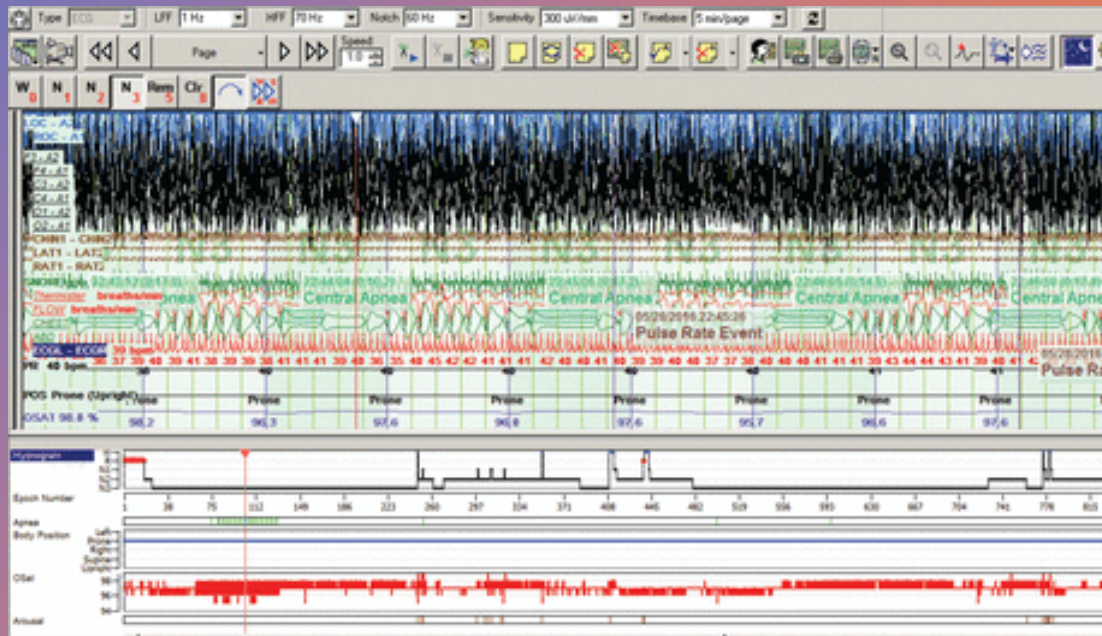
PSG While on Sodium Oxybate Follow-Up PSG off of S

Medications	venlafaxine, sodium oxybate	venlafaxine, methy
Body mass index (percentile)	37.0	69.0
Weight (percentile)	50.0	75.0
Height (percentile)	69.0	72.0
Apnea-hypopnea index (events/h)	4.2	2.5
Central apnea index (events/h)	4.2	1.2
Oxygen saturation 92–100% (percent time)	100.0	100.0
End-tidal CO ₂ 0–45% (percent time)	Not available	99.4
Wake (percent)	3.0	4.9
Stage N1 sleep (percent)	1.1	5.0
Stage N2 sleep (percent)	37.7	58.3
Stage N3 sleep (percent)	59.1	31.7
REM sleep (percent)	2.0	4.9
Sleep latency (minutes)	0.0	1.6
REM sleep latency (minutes)	0.0	133.0

PSG = polysomnography, REM = rapid eye movement.

Central Sleep Apnea with Sodium Oxybate(SO) in a Pediatric Patient

- Arezou Heshmati, MD
- AHI of 4.3 per hour, all central apneas
- No central apneas on previous polysomnogram
- 2 months later, repeat PSG off SO showed AHI of 2.5 per hour, CAI of 1.2 per hour



Misdirection/ Accessibility

Changing name of
products decreases
awareness

Easily home-
produced

"natural and safe
alternative"

- Endogenous

"amino acid?"

Addictive

- Mechanism
 - High concentration--->dopamine inhibition
 - Low concentration-->dopamine release
- "high" sensation
- Escalating self-administered doses
- Short half life-->higher frequency of use-->↑risk of coma

Combination with other Drugs

↓ adverse effects of
methamphetamines?

Anxiolytic effect
when taken with LSD

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Clinically used forms of GHB

Xyrem (Sodium Oxybate)

Xywav (Ca, Mg, K, Na oxybate)

Lumryz (Sodium oxybate)

- One time dosing, extended-release

Sodium
oxybate
versus Lower
Sodium
Oxybate for
Narcolepsy

Patient-Reported Sleep Quality in People With Narcolepsy Transitioning From Sodium Oxybate to Lower-Sodium Oxybate, *Sleep*, Volume 46, Issue Supplement_1, May 2023, Page A262, <https://doi.org/10.1093/sleep/zsad077.0598>

- More refreshed with lower sodium oxybate

Asymmetric/Atypical dosing

Typical dosing

- 2 equal doses
 - 1st at bedtime, second 2.5-4 hours after
 - Normal doses: 2.25, 3, 3.75, or 4.5 grams for each administration

Case report

- One physician-57 narcolepsy patients treated with sodium oxybate
- 18 had atypical prescriptions
 - 11 with asymmetric dosing
 - 10 larger 1st dose
 - 1 larger second dose

Discussion

Interesting cases involving sodium oxybate?

Positive effects other than related to sleep that any patients have mentioned?

Any recollection of gamma-hydroxybutyrate use prior to approval of sodium oxybate?

Experiences with any comorbidities that made it challenging to use sodium oxybate?

Any experience using one-time dosing or asymmetric dosing?



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