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SODIUM OXYBATE

Xyrem®

Drug Regimen Review Center

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Introduction

Narcolepsy is a neurologic disorder associated with (1) chronic daytime sleepiness (regardless of amount of nighttime sleep).¹ Other symptoms could follow such as brief episodes of (2) paralysis when falling asleep (sleep paralysis) or upon awakening (e.g. inability to move after awakening); occurs in 60-80% of patients, (3) cataplexy (brief episodes of partial or complete loss of voluntary muscle control whilst conscious during the day triggered by strong emotion commonly laughter (sometimes anger, surprise, or fear); occurs in 60% to 100% of patients), (4) vivid, dreamlike hallucinations while falling asleep (hypnagogic) or upon awakening (hypnopompic); occurs in 60-80% of patients, and interrupted/fragmented sleep patterns (e.g. waking up 4-5 times during the night for 10-20 minutes for no reason); occurs in 60% to 80% of patients.¹⁻³ It is reported that only about one third of patients will have all four symptoms.²

The prevalence of narcolepsy is approximately 1 in 2,000 and it usually begins between the ages of 10 and 20.^{1,2} People with narcolepsy can be categorized into two types; those with cataplexy and those without (the latter usually have less severe symptoms as well).¹ "People with narcolepsy and cataplexy experience periods of extreme daytime sleepiness and sudden loss of voluntary muscle tone in emotionally charged situations (cataplexy)."⁴ Narcolepsy with cataplexy is associated with a lack of hypocretins (also known as orexin).¹ These neurotransmitters are produced by the hypothalamus and functions to promote wakefulness and suppress rapid-eye-movement (REM) sleep.¹ Rapid eye movements, dreaming, and paralysis (to prevent actions and injury when dreaming) normally occurs only in REM sleep, but with the lack of hypocretins causing sleep at the wrong times, REM-associated cataplexy and dreamlike hallucinations could also occur at the wrong times because the normal distinct states of REM sleep, non-REM sleep, and wakefulness can mix together.¹ Most patients with cataplexy (95%) has certain human leukocyte antigen (HLA) subtypes, specifically, *DQB1*0602*.² It is thought that narcolepsy without cataplexy is caused by less severe injury to the hypocretin neurons or possibly a completely separate mechanism.^{1,2}

Risk factors for narcolepsy include anesthesia, head injury, history of meningitis or encephalitis, family history of narcolepsy (increases 20 to 40 times if a family member is affected), tumor, vascular malformations, stroke, and obesity.²

Diagnosis of narcolepsy is based on clinical history, a detailed family history and thorough examination (including a detailed neurologic examination); no diagnostic testing if there is a clear history of cataplexy with excessive daytime somnolence (Epworth Sleepiness Scale is very useful in determining the degree of excessive daytime sleepiness), or otherwise sleep laboratory testing or possibly laboratory testing (if symptoms not clear) e.g. HLA subtyping and CSF hypocretin/orexin levels (CSF hypocretin/orexin analysis is primarily a research tool).² "Nocturnal polysomnography followed by a multiple sleep latency test (MSLT) remains the gold standard for the diagnosis of narcolepsy."² It is also recommended to perform a drug screen to rule out pharmacologic modulations of sleep.²

Pharmacologic treatments for narcolepsy include central nervous system stimulants (e.g. amphetamines such as methylphenidate) for excessive sleepiness, antidepressants for cataplexy/sleep paralysis, and sodium oxybate; a central nervous system depressant derived from gamma aminobutyric acid (GABA).^{3,5,6}

Gamma-aminobutyric acid (GABA) is the primary inhibitory neurotransmitter in the brain.⁷ Most hypnotics including benzodiazepines (BZPs), non-BZP GABA_A receptor agonists (novel hypnotics and 'Z drugs'), gabapentin, pregabalin and sodium oxybate (SXB) work as GABA receptor modifiers.⁴ Also note that baclofen (muscle relaxant) is a GABA- β receptor agonist that increases GABA activity and reduces the production of glutamate and dopamine.⁸

Table 1. Comparison of hypnotics (adapted from information in Mason et al.^{4,6} and Micromedex⁵)

Hypnotics	Effect on GABA	Effect/Causes	Indications include
BZPs	Enhance the effects (GABA _A receptor involvement and not GABA-B receptors)	Hypnosis, anxiolysis, muscle relaxation, amnesia and anticonvulsant effects	Anxiety; behavioral disturbance or agitation/for sedation; panic disorders; to control and prevent seizure activity, to relieve chronic muscle spasm, in some sleep-related disorders including insomnia, alcohol withdrawal syndrome, and in conditions in which an increase in motor activity during sleep occurs.
Non-BZP GABA _A receptor agonists (novel hypnotics and 'Z drugs' including zolpidem, zaleplon, zopiclone and eszopiclone)	Bind to a different site on the GABA _A receptor complex than BZPs	Sedation (less noticeable muscle relaxation and anxiolysis than BZPs)	Treatment of sleep-onset insomnia and sleep-maintenance insomnia
Gabapentin	Increases the GABA content of neurons	Increase deep sleep and thereby improve the subjective quality of sleep. Exerts antinociceptive and anticonvulsant activity.	Partial seizures – Adjunct; Postherpetic neuralgia
Pregabalin	Effect on GABA transmission		Diabetic peripheral neuropathy - Neuropathic pain; Fibromyalgia; Neuropathic pain - Spinal cord injury; Partial seizure - Adjunct; Postherpetic neuralgia
Sodium oxybate	Mechanism of action is uncertain, but it has some affinity for gamma-aminobutyric acid B (GABA _B) receptors	Potent hypnotic (CNS depressant)	Narcolepsy with cataplexy

“Gamma-hydroxybutyrate (GHB) is a short chain fatty acid endogenously produced within the central nervous system (CNS) and acts as a precursor and metabolite of the inhibitory neurotransmitter γ -aminobutyric acid (GABA).”⁹ Sodium oxybate is the sodium salt of GHB.^{6,7} GHB is a known substance of abuse and is a Schedule I controlled substance, whereas the brand Xyrem (sodium oxybate) is a Schedule III controlled substance.⁶ It has a high potential for abuse/diversion.¹⁰ GHB is abused for its euphoric, stimulant, sedative, and sexual effects.¹¹ Street names of GHB include “Liquid Ecstasy, Liquid X, Liquid E, Georgia Home Boy, Grievous Bodily Harm, G-Riffick, Soap, Scoop, Salty Water, Somatomax, and Organic Quaalude.”⁶ GHB also has 2 precursors/analogues: gamma butyrolactone (GBL) and 1,4 butanediol (BD) that are rapidly metabolized to GHB when ingested.¹¹ GHB is one of the drugs categorized as “club drugs” by the National Institute on Drug Abuse (NIDA) because of their association with use in party situations.¹² The others are rohypnol (slang: “roofies”), MDMA (3-4 methylenedioxymethamphetamine; slang terms: “ecstasy”, “XTC”, “e”, “x”, and “adam”), ketamine (slang: “special K”), and methamphetamine.¹² GHB and rohypnol has been referred to as “date-rape drugs”.¹² Both enhance GABA causing inhibition in neurotransmission with resultant CNS depressant effects such as drowsiness, confusion, memory loss, coma etc. and possibly death.¹² Kapoor et al. report that “GHB is abused by three main groups of users: Body builders who use the substance believing that it stimulated the release of growth hormone; sexual predators who covertly administer the drug for its sedative and amnesic effects and club-goers (rave parties) who take the drug for its euphoric effects.”¹³ Albertson et al. also include gamma-hydroxybutyrate in their recent review entitled “The Changing Drug Culture: Use and Misuse of Appearance- and Performance-Enhancing Drugs.”¹⁴ Use amongst certain sub groups are also reported (e.g. homosexual men).¹⁵⁻¹⁸ Other reported illicit uses include the treatment of insomnia, generalized and social anxiety, and alcohol dependence.¹¹

Sodium oxybate is only available through the Xyrem REMS program, all patients and prescribers must be enrolled, and it may only be dispensed to the patient by a specially certified pharmacy. The program also

involves educational materials to be reviewed by the prescriber with the patient and postmarketing evaluations/surveillance. The first prescription is limited to a one month supply and thereafter may be written for 3 months maximum (patients are required to be seen every 3 months by their provider).^{5,6,10} At maximum FDA-approved dosing of Xyrem, it would cost approximately \$160,000 for a year's treatment (500 mg/mL (180 mL): \$4455.60 x 3 bottles x 12 months), although the price to Medicaid would be different with contracting and rebates.⁶

Methodology

A Cochrane Library literature search for systematic reviews was conducted. Medline (PubMed), Up to Date¹¹, the Agency for Healthcare Research and Quality (AHRQ), the FDA website (including product labeled information), ClinicalKey¹⁹, Micromedex⁵ and Lexicomp⁶ were searched for safety information, systematic reviews, clinical trials, and guidelines. As per the hierarchy of evidence, high quality systematic reviews and evidence based guidelines were searched for first.

Indication(s) of Xyrem (sodium oxybate)

Sodium oxybate (Xyrem) is FDA-approved for the treatment of cataplexy in narcolepsy or the treatment of excessive daytime sleepiness (EDS) in narcolepsy.¹⁰ "In Europe, GHB is available as Xyrem®, as Alcover®, which has been studied for treatment of alcohol and drug dependence, and as Somsanit®, which has been approved as an anaesthetic."¹¹

Non-FDA approved uses include⁵:

- Alcoholism
- Alcohol withdrawal syndrome
- Breathing-related sleep disorder
- Fibromyalgia
- General anesthesia
- Opioid withdrawal
- Sedation during cardiac catheterization in children

Treatment options for narcolepsy

According to *Ferri's Clinical Advisor 2016**, nonpharmacologic therapy include "avoidance of over-the-counter drugs and illicit drugs, optimal sleep hygiene and scheduled daily naps, and psychosocial support can be used for symptoms of excessive daytime somnolence. However, nonpharmacologic therapy is typically not sufficient for treatment of narcolepsy alone but is often used as adjunct therapy with medications."²

Pharmacologic treatment options depend on whether treatment is aimed at excessive daytime somnolence and/or cataplexy.

Table 2. Pharmacological treatment options for narcolepsy^{2,5,20}

Excessive daytime somnolence	Cataplexy
Sodium oxybate (refer to appendix 1)	Sodium oxybate (refer to appendix 1)
Modafinil 200 mg ORALLY once daily in the morning; doses up to 400 mg have been used	Note the American Academy of Sleep Medicine practice parameters ²¹ include TCAs, SSRIs and venlafaxine as potentially effective treatment options.
Armodafinil 150 mg to 250 mg as a single dose ORALLY in the morning; periodically reevaluate the need for continued therapy	Not FDA-approved, but included in Micromedex: Protriptyline (Adult, Evidence favors efficacy) "Protriptyline 5 mg/day was effective in treating disabling cataplexy in a 19-year-old female." ²²
Amphetamine IR 10 mg oral once daily; increase daily dose in 10 mg increments at weekly intervals until optimal response is obtained; usual dosage range: 5 to 60 mg daily in divided doses	Not FDA-approved & not included in Micromedex or Lexicomp under uses, but included in UpToDate and Ferri's:
Methylphenidate (IR, tablets, solution, and chewable tablets) 10 to 60 mg/day ORALLY divided 2 to 3 times daily, preferably 30 to 45 minutes before meals	Atomoxetine
Methylphenidate SR 18 to 54 mg 20 to 60 mg/day ORALLY divided every 8 hours	Fluoxetine
Dextroamphetamine IR 5 to 60 mg ORALLY in 2 to 3 divided doses daily	Sertraline
Dextroamphetamine SR 5 to 60 mg ORALLY as single daily dose	Venlafaxine
	Clomipramine
	Imipramine
	Desipramine
Not FDA-approved: Methamphetamine based on the American Academy of Sleep Medicine practice parameters ²¹ , but limited benefit-to-risk ratio information. Selegiline (Monoamine Oxidase Inhibitor): Micromedex: evidence inconclusive); Drug consult: only used as a last resort due to the high incidence of side effects and drug & food interactions. ³	

*"Ferri's Clinical Advisor 2016 is simply the fastest, most effective way to access up-to-date diagnostic and treatment information on more than 700 common medical conditions. The popular "5 books in 1" format provides quick guidance on diseases and disorders, differential diagnoses, medical algorithms, laboratory tests, and clinical practice guidelines. Yearly updates by experts in key clinical fields ensure that you're current with fast-changing medical knowledge, and extra electronic content delivers more than 100 exclusive topics, additional algorithms, and much more."²³

Clinical Guidelines and other recommendations

It is possible for people to need treatment for both cataplexy and daytime sleepiness and so may require more than one treatment.²⁰

European Academy of Neurology: Management of narcolepsy in adults, 2011 ²⁴
<p>Excessive Daytime Sleepiness and Irresistible Episodes of Sleep:</p> <ul style="list-style-type: none"> • First-line pharmacological treatment can vary, depending on comorbid conditions. Modafinil should be considered if excessive daytime sleepiness is the symptom of main concern (based on efficacy, limited adverse effects, and easiness of manipulation). • Sodium oxybate may be used in patients with cataplexy, excessive daytime somnolence, or poor sleep (based on sufficient evidence); however, caution should be exercised due to the nature of the drug. Closely monitor patients for development of side effects. <ul style="list-style-type: none"> ➢ Carefully titrate up-titrate dose over several weeks (optimal response on excessive daytime sleepiness may take as long as 8-12 weeks) ➢ Should not be used with other sedatives, respiratory depressants and muscle relaxants ➢ Not for depressed patients • Methylphenidate may be an option if modafinil is not effective or sodium oxybate not recommended

Cataplexy/Hallucinations/Sleep Paralysis:

- Sodium oxybate is the first-line pharmacological treatment based on current evidence (Class I evidence; Level A).
- Antidepressants are considered as second-line treatment.
 - The most potent anticataplectic available are tricyclic antidepressants, particularly clomipramine (10 to 75 mg). Initial dosing should start at the lower end of dosing (anticholinergic adverse effects).
 - Selective serotonin re-uptake inhibitors (SSRIs) can be considered due to fewer adverse effects, but are slightly less active.
 - Venlafaxine (serotonin/norepinephrine reuptake inhibitor) is commonly used today; however, it lacks clinical evidence of efficacy.
 - Reboxetine and atomoxetine (norepinephrine reuptake inhibitors) also lack published clinical evidence.

Poor Sleep:

- Sodium oxybate appears to be the most appropriate treatment of poor sleep based on several studies (**Level A**).
- Non-benzodiazepines/benzodiazepine hypnotics may be effective in treatment of poor sleep (**Level C**). Intermediate or long-term follow-up evidence is lacking. "The improvement in poor sleep reported by some patients once established on modafinil is noteworthy."

Parasomnias

- "Based on the available information it is difficult to provide guidance for prescribing in parasomnias associated with narcolepsy other than to recommend conventional medications."

Associated Features

- "Obstructive sleep apnoea/hypopnoea syndrome (OSAHS) should be treated no differently in narcoleptic patients than the general population, although it has been shown that continuous positive airway pressure (CPAP) does not improve excessive daytime sleepiness in most narcolepsy subjects. There is usually no need to treat periodic limb movements in sleep (PLMS) in narcoleptic patients. Antidepressants and psychotherapy should be used in depressed narcoleptic patients (**Level C**) as in non-narcoleptic depressed patients."

American Academy of Sleep Medicine Report: Practice Parameters for the Treatment of Narcolepsy and other Hypersomnias of Central Origin, 2007²¹

Effective pharmacologic treatment options for daytime sleepiness in narcolepsy

- Modafinil and sodium oxybate are effective for treating hypersomnia caused by narcolepsy based on several well controlled studies.
- Amphetamine, methamphetamine, dextroamphetamine, and methylphenidate are effective for treating daytime sleepiness caused by narcolepsy based on a long history of effective use in clinical practice (available in generic and are less expensive). Limited benefit-to-risk ratio evidence.

Effective pharmacologic treatment options for cataplexy in narcolepsy

- In addition to the effectiveness of sodium oxybate in daytime sleepiness or disrupted sleep, it is also effective for treatment of cataplexy.

Potentially effective treatment options

- Sodium oxybate may be effective for treatment of hypnagogic hallucinations and sleep paralysis
- Selegiline for cataplexy and daytime sleepiness (limited clinical experience and potential drug and diet interactions)
- Tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), and venlafaxine, may be effective treatment for cataplexy based on:
 - Reboxetine study (SNRI that is not available in US)
 - Fluoxetine (SSRI) level 2 and level 5 studies
 - Clinical experience of sleep specialists and committee consensus on other SSRIs (and more limited small open label studies that did not meet inclusion criteria)
 - Clinical experience of sleep specialists and committee consensus on venlafaxine (and a case study of 4 patients that did not meet inclusion criteria²⁵)
- TCAs, SSRIs, and venlafaxine, may be effective treatment for sleep paralysis and hypnagogic hallucinations based on anecdotal experience of committee members and committee consensus
- Ritanserin (5-HT₂ agonist not available in US) for daytime sleepiness due to narcolepsy

Lack of evidence/comparative evidence & additional research needed

- No studies were identified that compared modafinil or sodium oxybate to traditional stimulants (for hypersomnia due to narcolepsy)
- Modafinil and sodium oxybate provide moderate benefits in maintaining alertness, and does not provide full restoration of alertness so there is a need for new therapies.
- Sufficient evidence that sodium oxybate is effective for treating cataplexy in narcolepsy, but there is a lack of RCT evidence for use of antidepressants in cataplexy (and no comparative studies to sodium oxybate)
- Insufficient evidence in special populations e.g. children, older adults, or pregnant or nursing women.

UpToDate

According to UpToDate, nonpharmacological options in narcolepsy include a regular and adequate sleep schedule, scheduled daytime naps, avoidance of drugs that produce daytime sleepiness or insomnia, and a psychosocial support group.²⁰ It is also recommended to address coexisting sleep problems such as sleep apnea and periodic leg movements before initiating narcolepsy-specific medications.²⁰

Treatment recommendations for daytime sleepiness

- *“Patients with sleepiness severe enough to require medication can be treated with stimulant medications, such as modafinil, methylphenidate, or amphetamines. We suggest an initial trial of modafinil, rather than methylphenidate or an amphetamine (Grade 2B). The basis of this suggestion is that modafinil has been studied in patients with narcolepsy in randomized, placebo-controlled trials, and modafinil seems to produce fewer adverse effects. However, modafinil can be more expensive and there is no reason to suspect that its efficacy is superior to other stimulants.*
- *When prescribing methylphenidate, dextroamphetamine, or methamphetamine, clinicians should alert patients about the risks of serious cardiovascular and psychiatric side effects.”²⁰*

Treatment recommendations for cataplexy.

- *“We suggest a REM sleep-suppressing medication (eg, venlafaxine, fluoxetine, atomoxetine) as first line therapy for cataplexy (Grade 2C). We prefer extended release venlafaxine.*
- *For patients whose sleepiness or cataplexy does not improve with one of these medications, sodium oxybate may be of benefit.”²⁰*

Clinical Efficacy

Appendix 2 contains information on systematic reviews regarding sodium oxybate. No Cochrane systematic reviews were identified for sodium oxybate and the FDA-approved indication. Two other reviews that met the inclusion criteria for the Database of Abstracts of Reviews of effects (DARE) were identified in the Cochrane Library.

Alshaikh et al concluded that sodium oxybate was able to significantly improve daytime sleepiness and reduce cataplexy in narcolepsy. Sodium oxybate was generally well tolerated.²⁶ According to the Centre for Reviews and Dissemination (CRD), this was a generally well-conducted review.²⁷ However, it is recommended to interpret the conclusions of this review with caution because of the limited evidence base and uncertain long-term effects of sodium oxybate.²⁷

Boscolo-Berto et al concluded that gamma-hydroxybutyrate was effective and beneficial for patients with narcolepsy in reducing symptoms (e.g. daytime sleepiness, cataplexy), but the trials identified had limited quality assessments performed, and there was significant variation in the results of the trials (substantial heterogeneity and an absence of trial population details).^{28,29} The CRD therefore states that these factors make the reliability of the authors' conclusions uncertain.²⁹

Safety

“The primary effects of GHB use are those of a CNS depressant and therefore range from relaxation, to euphoria, confusion, amnesia, hallucinations, and coma.”¹³ Xyrem carries a black box warning regarding CNS depression and misuse and abuse.^{5,6,10} Adverse event information included in the Xyrem labeling include CNS depression, Abuse and Misuse, Respiratory Depression and Sleep-disordered Breathing, Depression and Suicidality, Other Behavioral or Psychiatric Adverse Reactions, Parasomnias, and Use in Patients Sensitive to High Sodium Intake (e.g., those with heart failure, hypertension, or renal impairment), because Xyrem has a high salt content (ranging from 550 mg sodium for a nightly Xyrem dose of 3 g to 1640 mg sodium per 9 g of Xyrem).¹⁰

Please refer to appendix 1 for additional drug information including the black box warning, contraindications, warnings/precautions, use in specific populations, and the Xyrem REMS Program (due to safety concerns and the high potential for misuse and abuse).

The long-term effects of sodium oxybate are uncertain.²⁷ According to Van Amsterdam et al. GHB, alcohol and ketamine show clear similarities in their mechanism of action, and ketamine and alcohol are known to cause neurotoxicity that leads to cognitive impairment.³⁰ The authors therefore reviewed the literature (PubMed) and reported that “An overdose of GHB, just like binge-drinking and a high dose of ketamine, may lead to a coma that probably harms the brain, particularly if comas occur repeatedly.”³⁰ The authors concluded that “The risk of neurotoxicity is likely to increase with chronic, intensive use of GHB, which is a feature of GHB-addiction. We therefore advocate research into the possible toxic effects of GHB in the long term, involving, for instance, the study of lasting effects on the cognitive functions of GHB users and former users.”³⁰

Misuse or abuse of GHB

Xyrem is a Schedule III controlled substance. Sodium oxybate (GHB) is a Schedule I controlled substance. There is high potential for abuse/diversion. Patients should be evaluated for history of drug abuse and closely monitored. Signs of abuse/misuse can include: increased size/frequency of dosing, drug-seeking behavior, feigned cataplexy.¹⁰

As mentioned before, gamma hydroxybutyrate (GHB) is a drug of abuse that is used for its euphoric, stimulant, sedative, and sexual effects.¹¹ UpToDate report that little is known of the prevalence of chronic GHB abuse or dependence (due to the absence of surveillance and systematic reporting mechanisms), but that cases of GHB dependence and withdrawal have been reported in the United States (US), Canada, Europe, and Australia.¹¹ Addicts use GBL, BD and GHB interchangeably and GHB tolerance, dependence, and withdrawal also develop subsequent to chronic BD and GBL use.^{11,31-34} Withdrawal symptoms include Insomnia, anxiety, tremors, sweating, increased heart rate and blood pressure, psychotic thoughts.³⁵

Abuse by bodybuilders or misuse for insomnia (not FDA approved) has been associated with a greater incidence of GHB dependence.^{11,36} Adverse outcomes (i.e. dependence, withdrawal, overdose, and death) are not only reported for patients who use GHB “supplements” or street products, but also for patients prescribed Xyrem.^{11,37-43}

From UpToDate:

“The Texas Department of State Health Services has reported a steady increase in the number of patients admitted for treatment of GHB dependence, from 2 in 1998 to a peak of 113 in 2008 and 91 in 2009⁴⁴. According to this report, GHB dependent users were slightly older than other users of club drugs (average age

29 to 32 years), often had a history of injection drug use, and frequently had primary dependency problems with amphetamines or methamphetamines. Users also reported using GHB's sedative effects to counteract the stimulant effects of methamphetamine, and vice versa. Combined data from Texas and the California Poison Control System (CPCS) suggest that GHB dependence is more common among men and occurs in a wide age range (17 to 60 years)^{44,45}. According to CPCS data, common reasons for starting to use GHB are bodybuilding and treatment of insomnia.

Although total exposures declined over the course of the CPCS study, the proportion of patients with severe outcomes from GHB withdrawal increased from 10 of 130 cases in 1999 to 2001 to 10 of 37 cases in 2002 to 2003⁴⁵. Of 167 total cases, 80 (48 percent) were admitted to a hospital for treatment of withdrawal. The median hospital stay was three days, with 27 of 80 (34 percent) admitted for five or more days. A review of 38 cases of withdrawal from GHB reported a mean duration of nine days (range 3 to 15)⁴⁶.¹¹

❖ **Please refer to appendix 3 for copies of recently published relevant abstracts on sodium oxybate and misuse/abuse/toxicity/ER visits.**

A recent report (2015) on acute recreational drug and new psychoactive substance (NPS) toxicity collected by a network of sentinel centres in 10 European countries (including Denmark, Estonia, France, Germany, Ireland, Norway, Poland, Spain, Switzerland and the UK; the European Drug Emergencies Network/Euro-DEN), includes GHB/GBL in the 'top five' drugs recorded.⁴⁷

The authors of a recent literature review (2015) that focused on UK fatalities related to non-medical use of GHB reported that misuse has increased greatly. They report on the “descriptive analyses of cases associated with GHB/GBL and 1,4-butanediol (1,4-BD) use extracted from the UK's National Programme on Substance Abuse Deaths database.” “From 1995 to September 2013, 159 GHB/GBL-associated fatalities were reported. Typical victims: White (92%); young (mean age 32 years); male (82%); with a drug misuse history (70%). Most deaths (79%) were accidental or related to drug use, the remainder (potential) suicides. GHB/GBL alone was implicated in 37%; alcohol 14%; other drugs 28%; other drugs and alcohol 15%. Its endogenous nature and rapid elimination limit toxicological detection. Post-mortem blood levels: mean 482 (range 0-6500; SD 758)mg/L. Results suggest significant caution is needed when ingesting GHB/GBL, particularly with alcohol, benzodiazepines, opiates, stimulants, and ketamine. More awareness is needed about risks associated with consumption.”⁴⁸

Additional evidence:

Authors of studies of patients presenting with acute poisonings (including self-poisoning) to emergency departments report that:

- GHB is one of the most frequent toxic agents (one-year observational study in Oslo, Norway)⁴⁹
- GHB presentations were most common overall out of ecstasy and related drug presentations, were commonly related to altered conscious state (89%), and more likely to require intubation (compared to ecstasy-related). Most presentations occurred on weekends placing a significant burden on EDs (Melbourne, Australia)⁵⁰
- There has been a drastic increase in the consumption of GHB (University Hospital Leipzig, Germany⁵¹, UK large inner-city ED⁵², among gay and bisexual men in eastern Australia⁵³, and the Netherlands³⁰)

Quednow and Herdener report that pharmacological treatment options for substance abuse disorder (SUD) can be separated in medications for (i) intoxication, (ii) withdrawal, and (iii) reduction of use together with relapse prevention.⁵⁴ According to Kamal et al. “GHB withdrawal symptoms cannot be related to a single mechanism or neurological pathway, which implies that different medication combinations are needed for treatment. A single drug class, such as benzodiazepines, gabapentin or antipsychotics, is unlikely to be sufficient to avoid life-threatening complications.”⁵⁵ Potential non FDA-approved use: It is interesting to note

that their conclusion also states “Detoxification by means of titration and tapering of pharmaceutical GHB can be considered as a promising treatment that could make polypharmacy redundant.”⁵⁵

2014 Annual Report of the American Association of Poison Control Centers’ National Poison Data System (NPDS): 32nd Annual Report includes 310 cases of single exposure to GHB (including analogs and precursors) in patients ranging from ≤5 to ≥20 years old; 270 were treated in a health care facility; 46 major outcomes (life-threatening) and no deaths reported.⁵⁶

- ❖ **Please refer to appendix 4 for information on cases from the Utah Poison Control Center (UPCC) where UPCC was consulted on the management of cases involving Xyrem and GHB exposures (January 1, 2011 – April 30, 2016).**

The Utah Poison Control Center (UPCC) was consulted on the management of 35 cases involving sodium oxybate (Xyrem®) or GHB between January 1, 2011 and April 30, 2016. The report in appendix 1 summarizes the 35 cases. GHB was included with sodium oxybate (Xyrem®) because it is not known if the illicit GHB was actually diverted sodium oxybate (Xyrem®). It is important to note that 2 sodium oxybate cases were pediatric patients orally exploring their environment who got into the medication that belonged to someone in the household. Six sodium oxybate cases were due to therapeutic error/misuse; taking both doses at the same time or too close together; which is particularly relevant because the Utah Medicaid Utilization Data shows early fills of prescriptions. Cases reported include misuse, abuse, attempted suicide, suspected they have been drugged, withdrawal, and inadvertent exposure. Calls originated from health care facilities and residences. Overall, 15 cases were treated in emergency departments (EDs) and 7 cases were admitted to the intensive care unit (ICU). Some refused referral and some were lost to follow-up and outcome was unknown but felt to be potentially toxic. Overall, 7 cases resulted in a major outcome (a life-threatening exposure that required a life-saving intervention).

The NIH National Institute on Drug Use National Survey of Drug Use and Health, Trends in Prevalence of Various Drugs Table (Results from a yearly survey of teenagers conducted by the University of Michigan's Institute for Social Research and funded by NIDA) include use of GHB in 12th graders in the past year (adapted from their table).⁵⁷

Monitoring the Future Study: Trends in Prevalence of Various Drugs for 8th Graders, 10th Graders, and 12th Graders; 2012 - 2015 (in percent)*													
Drug	Time Period	8th Graders				10th Graders				12th Graders			
		2012	2013	2014	2015	2012	2013	2014	2015	2012	2013	2014	2015
GHB	Past year	-	-	-	-	-	-	-	-	1.40	1.00	1.00	0.70

According to Wang et al. (2009) “Cumulative postmarketing and clinical experience indicates a very low risk of abuse/misuse of sodium oxybate.” Refer to appendix 4 for additional information.

Place in therapy and potential criteria to be reviewed

Factors and limitations to consider when considering Xyrem's place in therapy:

- **Referral:** "Because of the complexity of this disorder and its ever-changing management and treatment, patients should be referred to centers or programs with highly trained sleep specialists with expertise caring for these patients, especially if sodium oxybate (Xyrem) therapy is needed."²
- **Indication and other treatment options:** FDA-approved only for the treatment of cataplexy in narcolepsy or the treatment of excessive daytime sleepiness (EDS) in narcolepsy.¹⁰ Central Nervous system stimulants could be considered (weighing risks and benefits) in patients with narcolepsy and excessive sleepiness, or antidepressants (refer to recommendations; potentially effective, but not FDA-approved and no head-to-head comparative trials between sodium oxybate and antidepressants) in patients with cataplexy.
- **Fibromyalgia:** Not FDA-approved for use in fibromyalgia. "Xyrem was reviewed by the FDA for fibromyalgia, and this indication was rejected in October of 2010."⁵⁸
"At the joint meeting of the Arthritis Drug Advisory Committee and the Drug Safety and Risk Management Advisory Committee, the FDA advisory panel voted 20 to 2 against recommending that the FDA approve sodium oxybate for the treatment of fibromyalgia. Concerns cited by panel members included the possibility of increased illicit use with the expanded indication and a weak risk evaluation and mitigation strategy."⁵⁹
- **Maximum dosing:** Maximum FDA approved dosing is 9 g per night and it is available as a 500 mg/mL (180 mL) oral solution. This is equivalent to 540 mL or 3 bottles/30 days (at maximum dose).⁶
- **Adverse effects:** Refer to safety section & appendix 1
It is important to note that sodium oxybate rapidly produces deep sedation.²⁰ This could be deadly for children if the medication is not stored properly and taken by them (which has happened in Utah based on Poison Control data; refer to appendix 4). The general safety of everybody in the household should be considered and discussed.²⁰
- **Monitoring:** It is important to monitor patients for drug abuse, misuse, and addiction. Also, signs and symptoms of depression or suicidality; emergence of anxiety, confusion, thought disorders, or behavior abnormalities.⁶
- **Access & REMS:** Sodium oxybate is only available through the Xyrem REMS program due to safety concerns and the high potential for misuse and abuse. Access is restricted only to enrolled patients and prescribers. Sodium oxybate may only be dispensed to the patient by a specially certified pharmacy. Educational materials will be sent to the prescriber for review with the patient before the first prescription is dispensed, as well as forms for enrollment in the postmarketing surveillance program. Patients are required to be seen at every 3 months by their provider. The first prescription is limited to a one month supply. Prescriptions following the first month may be written for 3 months maximum.^{5,6,10}
- **Concomitant sedative hypnotics:** Use of alcohol and sedative hypnotics is contraindicated.⁶
- **Other GABA-receptor agonists:** For example, according to a recent case report by Kamal et al. "physicians should be alert to the danger of this combination because of the hazards of coma and respiratory distress."⁸ They reported on "a GHB-dependent patient, who ingested several days' doses of baclofen (80 mg) simultaneously with 0.3 L (215 g) of illicit GHB. Baclofen (40 mg/d) was prescribed to prevent relapse after a successful detoxification. The patient developed a rapid coma (E2M5V1 with oxygen support), bradypnea, and hypotonia."⁸ (baclofen is a GABA- β receptor agonist)
- **Overdose/intoxication/poisoning:** Could be lethal. GHB is not detectable on routine hospital toxicology screens and diagnosis is based on a clear history, clinical findings and exclusions of other etiologies.¹¹ GHB disappears from blood rapidly (within 4-6 hours) and a urine test will most likely be negative if collected longer than 6 to 12 hours after ingestion.¹¹ "Testing for other drugs of abuse can identify drug or alcohol codependency as well as the presence of alcohol, benzodiazepines, or opiates that may have been used for self-detoxification. Toxicologic screening may identify the presence of sympathomimetics,

whose effects can mimic GHB withdrawal.”¹¹ Acute GHB toxicity is associated with dose-related central nervous system (CNS) depression (often comatose and close monitoring of respiratory status and vital signs are required), and psychomotor agitation may also occur (stimulant effects may be treated with sedatives). “Abrupt onset of effects and sudden awakening and resolution of effects frequently occur.”¹¹ “Cointoxicants are common.”¹¹ Also, “GHB-dependent patients may present with acute toxicity and progress directly into GHB withdrawal.”¹¹

- **Dependence/Tolerance/Withdrawal:** Tolerance or withdrawal from discontinuation of sodium oxybate has not been evaluated and defined in clinical trials.^{11,20} Reported withdrawal/tolerance has occurred when used at larger doses for illicit purposes or with frequent dosing.^{5,6,10,11,20} Some users reported withdrawal symptoms following cessation of Xyrem for the treatment of cataplexy.^{11,60} It is important to note that GHB withdrawal symptoms occurs rapidly and the symptom course is often unpredictable.¹¹ Severe symptoms including hallucinations, delirium, and death could occur even after apparent improvement.^{11,31,61,62} Severe GHB withdrawal may require intensive care unit treatment up to 15 days and in-patient care for up to 32 days.^{11,63} According to UpToDate, data on the management of GHB withdrawal is limited to individual case reports and small case series and controlled prospective studies are needed.¹¹ Treatment of GHB withdrawal is aimed at controlling agitation and delirium, hyperthermia, seizures, and careful monitoring for respiratory depression and other potential complications.¹¹
- **After discontinuing Xyrem:** “Profound insomnia is common among patients with GHB withdrawal and has been reported to play a key role in ongoing use and relapse.”^{46,64-66} Severe insomnia, occurring prior to presentation and persisting for several days after hospitalization, despite the administration of antipsychotics (eg, haloperidol) and benzodiazepines, can occur and may exacerbate psychosis and delirium.^{32,40,62,67,11}
- “PITFALLS IN MANAGEMENT — Multiple drug dependencies have been reported among GHB dependent users and these must be addressed.⁶⁸ Codependencies may result from concurrent recreational abuse of GHB and other drugs, or from use of benzodiazepines, alcohol, or opiates for self-treatment of GHB withdrawal.^{61,67} Conversely, GHB may be used as an alcohol or drug substitute, or for self-treatment of alcohol or drug dependence or withdrawal.”^{31,61,69}¹¹
- **Age:**
 - Indicated in *adults 18 years or older (Safety and efficacy not established in pediatric patients)*^{5,10}
 - *Elderly:* Limited data exists in adults ≥65 years. Headache was experienced more frequently when compared to younger adults. Use with caution in elderly, and monitor cognitive/motor function as they may be at an increased risk for CNS side effects.⁶
- **Duration of treatment:** This is a chronic disorder (persist for life) that would require chronic treatment.² As discussed in the safety section, the long-term effects of sodium oxybate are uncertain and there are concerns about its potential to cause neurotoxicity and cognitive impairment (similar to alcohol and ketamine).²⁷
- **Emergency visits:** Patients on Xyrem could be visiting the ER department because of their condition (narcolepsy), overdose/poisoning (Xyrem or other drugs), withdrawal, or associated injuries/trauma especially when dependent (due to CNS effects e.g. falls, loss of consciousness, impaired driving and accidents). “People with narcolepsy have a three- to fourfold increased risk of having a car accident, and over one-third have had an accident due to sleepiness.”²⁰ Based on reports, misuse of GHB has increased greatly/drastically, and GHB is one of the drugs most frequently seen in poisonings in the emergency department.^{30,47-53} Also, it is reported that a significant amount of college students drive under the influence of nonmedical use of prescription drugs.⁷⁰ “Overall, 28.0% of participants reported lifetime NMUPD; 12.2% reported ever driving while engaging in NMUPD; and 7.9% reported this behavior in the past 3 months. Participants who reported engaging in NMUPD while driving were significantly more likely to report the use of alcohol, marijuana, ecstasy, cocaine, methamphetamine, ketamine, GHB (γ-hydroxybutyric acid), rohypnol, and mephedrone.”⁷⁰

- **Formulary examples:**

Insurance Plans	Tier	Restrictions
Federal Employee Program Basic ⁵	2	PA
Tricare Uniform Formulary ⁶	2	PA
Blue Shield California ²⁴	4	PA, QL, LA
Kaiser Permanente ²¹	NC	-
Select Health (RxCore) ²⁶	4	PA, QL
CVS Caremark ²⁸	3	None
Humana ⁷¹	4	PA, QL, SD

PA = Prior Authorization; QL = Quantity Limitation; LA = Limited Access; NC = Not Covered; SD = Specialty Drug

Utah Medicaid Utilization Data

ALL CLAIMS

GENERIC	DESCRIPTION	2013		2014		2015		2016*		ALL	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Sodium Oxybate	Xyrem Oral Solution 500MG/ML	40	9	25	8	49	8	8	3	122	16
TOTALS		40	9	25	8	49	8	8	3	122	16

PEDIATRIC CLAIMS (<18)

GENERIC	DESCRIPTION	2013		2014		2015		2016*		ALL	
		CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS	CLAIMS	PATIENTS
Sodium Oxybate	Xyrem Oral Solution 500MG/ML	10	3	9	3	11	1	2	1	32	4
TOTALS		10	3	9	3	11	1	2	1	32	4

- 1) **Do patients that filled prescriptions for Xyrem have diagnosis codes submitted for the FDA-approved indication?**
- 7 Patients did not have diagnosis codes submitted for narcolepsy (as defined in the table below) which could mean that codes were not submitted within the timeframe or Xyrem is being used for non FDA-approved indications
- 2) **If not, do they have a diagnosis code submitted for fibromyalgia (an off-label use)?**
- Of those 7 patients, none had a diagnosis code submitted for fibromyalgia (as defined in the table below).

NARCOLEPSY DIAGNOSIS*		ICD-9	ICD-10	
Cataplexy and Narcolepsy	347*		9	56%
Narcolepsy	3470*		9	56%
<i>Narcolepsy without Cataplexy</i>	34700	G47.419	5	31%
<i>Narcolepsy with Cataplexy</i>	34701	G47.411	8	50%
Narcolepsy in Conditions Classified Elsewhere	3471*		0	0%
<i>Narcolepsy in CCE without Cataplexy</i>	34710	G47.429	0	0%
<i>Narcolepsy in CCE with Cataplexy</i>	34711	G47.421	0	0%
ALL Narcolepsy without Cataplexy	34700 and 34710	G47.419 and G47.429	5	31%
ALL Narcolepsy with Cataplexy	34701 and 34711	G47.411 and G47.421	8	50%
TOTAL PATIENTS USING XYREM			16	

* Diagnosis date within 30 days of a prescription claim for Xyrem.

NO NARCOLEPSY DIAGNOSIS			7	44%
Fybromialgia	7291	M79.7	0	0%

3) Do patients filling prescriptions for Xyrem have diagnosis codes submitted for abuse? Patients should be evaluated for history of drug abuse and closely monitored.

➤ No patients had a diagnosis code submitted for abuse (as defined in the table below)

ABUSE DIAGNOSIS*	ICD-9	ICD-10		
ANY Substance Abuse Diagnosis	BELOW	BELOW	0	0%
Alcohol Dependence Syndrome	303		0	0%
Drug Dependence	304		0	0%
Non-Dependent Abuse of Drugs	305		0	0%
Alcohol Related Disorders		F10	0	0%
Opioid Related Disorders		F11	0	0%
Cannabis Related Disorders		F12	0	0%
Sedative Hypnotic or Anxiolytic Related Disorders		F13	0	0%
Cocaine Related Disorders		F14	0	0%
Other Stimulant Related Disorders		F15	0	0%
Hallucinogen Related Disorders		F16	0	0%
Nicotine Dependence		F17	0	0%
Inhalant Related Disorders		F18	0	0%
Other Psychoactive Substance Related Disorders		F19	0	0%
TOTAL PATIENTS USING XYREM			16	

* Diagnosis date within 30 days of a prescription claim for Xyrem.

4) How many patients filling prescriptions for Xyrem had emergency visits and how often (if applicable); poisoning or overdose ICD codes submitted? Poisoning/overdose/ER ICD or CPT codes specifically related to Xyrem were not identified. In general there are many diagnosis and procedure codes associated with this and we have included the basic codes (as defined in the tables below).

- 2 patients had emergency codes submitted (also refer to duration of use table)
 - One patient once in Oct 2013 (99281) and twice (same day 99282 & 99283) in Nov 2015
 - Another patient once in March 2015 (99283)
- 1 patient had a diagnosis code submitted for poisoning (Poisoning by Unspecified Drug or Medicinal Substance):
 - This is a different patient with a poisoning diagnosis than the two with ER visits.
 - Poisoning Dx in Oct 2013 - Xyrem fills in Sep, Oct and Dec 2013.

EMERGENCY DEPARTMENT VISITS*	ICD-9	ICD-10		
ANY ED Visit Type	BELOW	BELOW	2	13%
Emergency Department Visit	99281		1	6%
Emergency Department Visit	99282		1	6%
Emergency Department Visit	99283		2	13%
Emergency Department Visit	99284		0	0%
Emergency Department Visit	99285		0	0%
TOTAL PATIENTS USING XYREM			16	

* ED visit date within 30 days of a prescription claim for Xyrem.

POISONING DIAGNOSIS*	ICD-9	ICD-10		
ANY Poisoning Diagnosis	BELOW	BELOW	1	6%
Poisoning by Androgens and Anabolic Congeners	9621		0	0%
Poisoning by Opiates and Related Narcotics	9650		0	0%
Poisoning by Opium	96500		0	0%
Poisoning by Heroin	96501		0	0%
Poisoning by Methadone	96502		0	0%
Poisoning by Other Opiates and Related Narcotics	96509		0	0%
Poisoning by Anticonvulsants and Anti-Parkinsonism Drugs	966		0	0%
Poisoning by Sedatives and Hypnotics	967		0	0%
Poisoning by Other CNS Depressants and Anesthetics	968		0	0%
Poisoning by Psychotropic Agents	969		0	0%
Poisoning by CNS Stimulants	970		0	0%
Poisoning by Drugs Primarily Affecting the Autonomic Nervous System	971		0	0%
Poisoning by Skeletal Muscle Relaxants	9752		0	0%
Poisoning by Alcohol Deterrents	9773		0	0%
Poisoning by Unspecified Drug or Medicinal Substance	9779		1	6%
Poisoning by Opiates		T40*	0	0%
Poisoning by Sedative Hypnotics and Anti-Epileptics		T42*	0	0%
Poisoning by Psychostimulants and Psychotropics		T43*	0	0%
Poisoning by Skeletal Muscle Relaxants		T481*	0	0%
Poisoning by Androgens and Anabolic Congeners		T387*	0	0%
TOTAL PATIENTS USING XYREM			16	

* Diagnosis date within 30 days of a prescription claim for Xyrem.

5) **Did patients that filled prescriptions for Xyrem fill prescriptions for sedative hypnotics during the same month of Xyrem therapy (contraindicated)?** Sedative hypnotic is defined as per the FDA Sleep Disorder (Sedative-Hypnotic) Drug Information - Prescription Insomnia Drugs⁷² and Suvorexant (Belsomra)⁶ (new drug not yet in this FDA list). Note that this definition could include many medications and we have limited to the list as defined (it does not include for example all benzodiazepines)

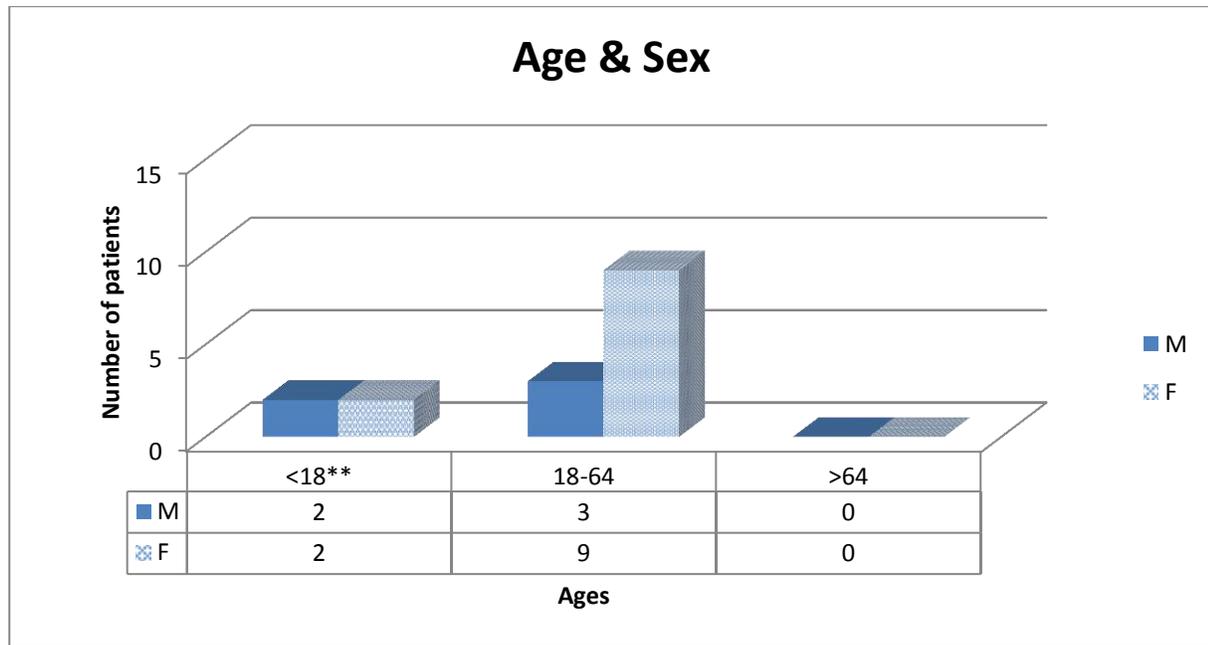
- One patient filled a prescription for a sedative hypnotic; Temazepam cap 30 mg (two fills, one within 30 days prior and one within 30 days after, a Xyrem claim):
 - Xyrem fill on 12/13/2013 and temazepam fills on 11/22/2013 and 12/23/2013.
- 5 patients had a history of sedative hypnotic use

Sedative Hypnotics DURING Same Month as Xyrem Therapy	1	6%
ANY History of Sedative Hypnotic Use 2013-2016	5	31%
Modafinil or Armodafinil PRIOR TO Xyrem Therapy	9	56%
ANY History of Modafinil or Armodafinil Use 2013-2016	11	69%
TOTAL PATIENTS USING XYREM	16	

6) Did patients that filled prescriptions for Xyrem fill prescriptions for modafinil or armodafinil prior to filling prescriptions for Xyrem?

- 9/16 patients filled a prescription for modafinil or armodafinil prior to filling a prescription for Xyrem (ranging from approximately 3 months to 3 years prior)
- 11/16 patients had a history of modafinil or armodafinil fills (any time during the review period; 2013-2016)

7) Age and Sex

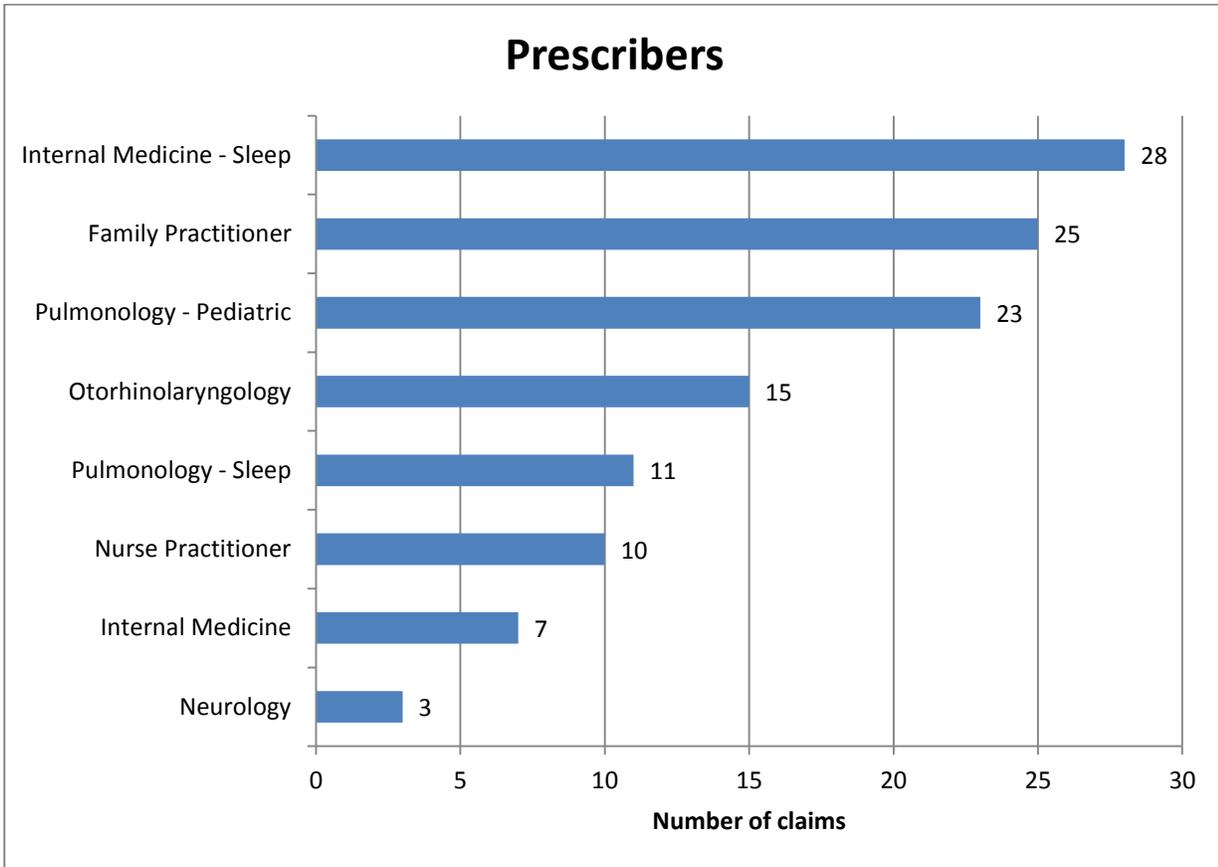


- No geriatric patients filled prescriptions for Xyrem (may be at an increased risk for CNS side effects)
- 4 Pediatric patients ranging between 6 and 17 years old have been receiving Xyrem and it is not FDA-approved for use in pediatric patients.

Pediatric Patients

Sex	Age
F	17
F	17
M	16
M	6

8) Prescribers



PRESCRIBER TYPE	TOTAL CLAIMS 2013-16	
Neurology	3	2.46%
Internal Medicine	7	5.74%
Nurse Practitioner	10	8.20%
Pulmonology - Sleep	11	9.02%
Otorhinolaryngology	15	12.30%
Pulmonology - Pediatric	23	18.85%
Family Practitioner	25	20.49%
Internal Medicine - Sleep	28	22.95%
TOTAL CLAIMS	122	

- Prescribers of Xyrem to pediatric patients are physicians with specialties in Orthorhinolaryngology (2), Pediatric Pulmonary, and Internal Medicine-Sleep.
- Prescribers of 7 patients with no narcolepsy diagnosis (25 of the total 122 claims):

PRESCRIBER TYPE - No Narcolepsy DX	TOTAL CLAIMS 2013-16	
Pulmonology - Pediatric	2	8.00%
Neurology	3	12.00%
Internal Medicine - Sleep	3	12.00%
Internal Medicine	6	24.00%
Family Practitioner	11	44.00%
TOTAL CLAIMS	25	

9) Quantity and duration of use

- It does not appear that patients are using more than the maximum daily dose.
- 10 patients had more than one course of treatment (more than one prescription) of which 5 patients could be attributed to early or late fills within 30 days (the other 5 had more separate courses or the gap in treatment was bigger than 30 days)
- 9 patients had early or late fills ranging from 1-6 days early and 1-12 days late (only considering consecutive months and not if there was a gap of >1 month) indicating potential abuse/misuse or adherence issues.
- Several patients had more than one fill on their first prescription. The REMS program information include that the first prescription is limited to a one month supply. Prescriptions following the first month may be written for 3 months maximum.^{5,6,10}
- It also appears that many patients had fills exceeding the 3 months maximum limit.

Conclusions

Even though sodium oxybate is only available through the REMS program and Wang et al. (2009)⁴² reported that cumulative postmarketing and clinical experience indicates a very low risk of abuse/misuse of sodium oxybate, we have noticed inappropriate use in the Utah Medicaid Utilization Data. Also, the Utah Poison Control Center (UPCC) report is reason for concern especially considering the fact that 2 of the cases were pediatric patients.

This is a complex disorder and it is important to ensure that highly trained sleep specialists with expertise in caring for these patients are involved in the care of these patients especially if sodium oxybate (Xyrem) therapy is needed.

Based on the limited evidence base, the high potential for misuse and abuse, reports that misuse of GHB has increased greatly, the uncertain long-term effects of sodium oxybate, and the potential inappropriate use and issues identified in the Utah Medicaid Utilization data and the UPCC report, it is important to ensure that sodium oxybate is used appropriately only when medically necessary, and only if benefits outweigh the risks and other options have been considered.

Potential clinical criteria

Due to the scheduling of the drug and high potential for misuse/abuse, you may wish to consider the following Prior Authorization (PA) criteria:

1. Age requirement: 18 years or older
 2. Prescribed by or in consultation with a highly trained sleep specialists
 3. Must have documented diagnosis of cataplexy in narcolepsy or EDS in narcolepsy (due to multiple off label uses).
 4. Must have documented prior use of modafinil or armodafinil. You may also wish to consider a trial of other Central Nervous system stimulants (weighing risks and benefits) in patients with narcolepsy and excessive sleepiness, or antidepressants (refer to recommendations; potentially effective, but not FDA-approved and no head-to-head comparative trials between sodium oxybate and antidepressants) in patients with cataplexy.
- Also, a quantity limit: 9 g/day (due to safety concerns, high potential for misuse/abuse, and possibility of alternate dosing). Some plans have it as a limit per 30 days (e.g. 540 mL or 3 bottles/30 days) or 810 g per 90 days
 - As part of the REMS, patients must be seen at least every 3 months; the first prescription may only be written for a 1-month supply and then prescriptions can be written for a maximum of 3 months. You may therefore wish to require a prior authorization every 3 months.

Appendix 1 – Drug information

Xyrem (Sodium oxybate)	
FDA Labeled Indications and Approved Dosing	<ol style="list-style-type: none"> 1. Cataplexy in narcolepsy^{5,6,10} <ol style="list-style-type: none"> a. Initial dose (oral): 2.25 g at bedtime after the patient is in bed, and 2.25 g 2.5 to 4 hours later (4.5 g/night) b. Titration: Increase dose by 1.5 g/night (0.75 g/dose) in weekly intervals. Titrate to effect. c. Maintenance dose (oral): 6-9 g/day in 2 divided doses d. Maximum dose (oral): 9 g/day in 2 divided doses 2. Excessive daytime sleepiness (EDS) in narcolepsy^{5,6,10} <ol style="list-style-type: none"> a. Initial dose (oral): 2.25 g at bedtime after the patient is in bed, and 2.25 g 2.5 to 4 hours later (4.5 g/night) b. Titration: Increase dose by 1.5 g/night (0.75 g/dose) in weekly intervals. Titrate to effect. c. Maintenance dosing (oral): 6-9 g/day in 2 divided doses d. Maximum dose (oral): 9 g/day in 2 divided doses
Off-Label Use⁵	<ul style="list-style-type: none"> • Alcoholism • Alcohol withdrawal syndrome • Breathing-related sleep disorder • Fibromyalgia • General anesthesia • Opioid withdrawal • Sedation during cardiac catheterization in children
Dose Adjustments	<p>Hepatic Insufficiency</p> <ul style="list-style-type: none"> • Hepatic impairment: reduce starting doses to 1.13 g orally^{5,6,10} • Cirrhosis: 25-50 mg/kg/day⁵ <p>Concomitant use with divalproex sodium</p> <ul style="list-style-type: none"> • Currently stable on sodium oxybate: initially reduce nightly dose of sodium oxybate by at least 20% when adding divalproex sodium; adjustments guided by patient response^{5,6,10} • Currently stable on divalproex sodium: initiate sodium oxybate at a lower starting dose; adjustments guided by patient response^{5,6,10}
Safety	<p>Black Box Warning:^{5,6,10}</p> <ul style="list-style-type: none"> • <i>CNS depression:</i> In patients treated with sodium oxybate during clinical trials, significant respiratory depression and obtundation occurred with recommended dosing. Most of the patients being treated with sodium oxybate were also taking CNS stimulants. • <i>Misuse and abuse:</i> Sodium oxybate is the sodium salt of gamma hydroxybutyrate (GHB). CNS adverse reactions such as respiratory depression, seizures, decreased level of consciousness, coma, or death have been associated with use of GHB, either alone or combined with other CNS depressants. <p>Contraindications: Concurrent use with sedative hypnotics, use with alcohol, use in patients with succinic semialdehyde dehydrogenase deficiency.^{5,6,10}</p> <p>Xyrem REMS Program: Sodium oxybate is only available through the Xyrem REMS program due to safety concerns and the high potential for misuse and abuse. Access is restricted only to enrolled patients and prescribers. Sodium oxybate may only be dispensed to the patient by a specially certified pharmacy. Educational materials will be sent to the prescriber for review with the patient before the first prescription is dispensed, as well as forms for enrollment in the postmarketing surveillance program. Patients are required to be seen at every 3 months by their provider. The first prescription is limited to a one month supply. Prescriptions following the first month may be written for 3 months maximum.^{5,6,10}</p> <p>Additional Warnings/Precautions:</p> <ul style="list-style-type: none"> • <i>CNS depression:</i> Has been known to cause agitation, anxiety, confusion, depression, hallucinations, paranoia, psychosis, sleepwalking and suicidality. Use cautiously if patients have a history of depression or suicide attempts. Patients should not engage in hazardous activities for 6 hours or more after taking their second nightly dose. There is an increased risk of excessive sedation, hypotension, respiratory depression, syncope, and death when used concomitantly with other CNS depressants, and should be avoided if possible. If use is required, consider discontinuing sodium oxybate temporarily. Use of alcohol and sedative hypnotics is contraindicated.⁶ • <i>Respiratory depression:</i> In patients treated with sodium oxybate during clinical trials, significant respiratory depression and obtundation occurred with recommended dosing. Most of the patients being treated with sodium oxybate were also taking CNS stimulants. Use cautiously in compromised respiratory function.⁶ • <i>Sleep-related breathing disorders:</i> May occur during therapy, and may be more common in obesity, narcolepsy, and postmenopausal women without hormone replacement therapy.^{5,6,10} • <i>Cardiovascular disease:</i> Use cautiously in heart failure or hypertensive patients due to significant amounts of sodium. Increased risk of hypotension and syncope when used with other CNS depressants. Consider dose adjustment.⁶ • <i>Patients with sodium restrictions (e.g. heart failure, hypertension, compromised renal function):</i> Sodium oxybate

contributes approximately 550 mg sodium per 3 g dose.^{5,6,10}

- *Dependence/Tolerance*: Tolerance or withdrawal from discontinuation of sodium oxybate in clinical trials has not been defined. Reported withdrawal/tolerance has occurred when used at larger doses for illicit purposes.^{5,6,10}

Use in Specific Populations:

- *Pregnancy*: FDA Category C. Adverse effects have been reported. It has been shown to cross the placenta at $\leq 25\%$ concentration of maternal levels. Minor decreases in Apgar scores have been observed in neonates due to sleepiness. Sodium oxybate was absent in infant blood approximately 30 minutes after delivery.⁶ Increased incidences of malformations and stillbirths have been reported in animal studies when given concentrations equal to the maximum recommended human dose.⁵
- *Breast-feeding*: It is unknown if sodium oxybate is excreted in breast milk. Use caution when administering sodium oxybate to women who are nursing.⁶
- *Elderly*: Limited data exists in adults ≥ 65 years. Headache was experienced more frequently when compared to younger adults. Use with caution in elderly, and monitor cognitive/motor function as they may be at an increased risk for CNS side effects.⁶
- *Renal impairment*: A significant amount of sodium is contained in sodium oxybate. Use cautiously in patients that have renal impairment.⁶
- *Hepatic impairment*: Use cautiously in hepatic impairment. Recommended dose adjustment stated previously.⁶

Appendix 2 – Systematic reviews

Table 3: Cochrane Reviews

Author(s)	Title	Objectives	Main Results	Author's Conclusions
Leone MA et al. (2010) ⁷³ (Assessed as up-to-date: 17 February 2011)	Gamma-hydroxybutyrate (GHB) for treatment of alcohol withdrawal and prevention of relapses	“To evaluate the efficacy and safety of GHB for the treatment of AWS and the prevention of relapse.”	<p>“Thirteen RCTs were included, 11 of which had been conducted in Italy.</p> <p>For alcohol withdrawal syndrome, comparing GHB 50mg versus placebo, results from 1 study (23 participants) favour GHB for withdrawal symptoms: MD -12.1 (95% CI -15.9 to -8.29), but tolerated side effects were more frequent in the GHB group: RR 16.2 (95% CI 1.04 to 254.9; based on 7 of 11 patients in the GHB group developing transitory vertigo compared to none in the placebo group). In the comparison of GHB 50mg versus Clomethiazole, results from 1 study (21 participants) favour GHB for withdrawal symptoms: MD -3.40 (95% CI -5.09 to -1.71). For GHB 100mg versus Clomethiazole, results from 1 study (98 participants) favour Clomethiazole for side effects: RR 1.84 (95% CI 1.19 to 2.85).</p> <p>At mid-term, comparing GHB 50mg/day with placebo, 1 study (71 participants, 3 months follow-up) favour GHB for abstinence rate (RR 5.35, 95% CI 1.28 to 22.4), controlled drinking (RR 2.13, 95% CI 1.07 to 5.54), relapses (RR 0.36, 95% CI 0.21 to 0.63), and number of daily drinks (MD -4.60, 95% CI -6.18 to -3.02). On abstinence, GHB performed better than Naltrexone (NTX) (2 studies, 64 participants) (RR 2.59, 95% CI 1.35 to 4.98 at 3 months) and then Disulfiram (1 study, 59 participants) (RR 1.66, 95% CI 0.99 to 2.80 at 12 months, slightly significant). The combination of GHB and NTX was better than NTX for abstinence (RR 12.3, 95% CI 1.79 to 83.9 at 3 months; 1 study, 35 participants). The combination of NTX, GHB and Escitalopram was better than Escitalopram alone for abstinence (RR 2.02 95% CI 1.03 to 3.94 at 3 months; RR 4.58, 95% CI 1.28 to 16.5 at 6 months; 1 study, 23 participants). For Alcohol Craving Scale, results favour GHB over placebo (MD -4.50, 95% CI -5.81 to -3.19 at 3 months; 1 study, 71 participants) and over Disulfiram at 12 months (MD -1.40, 95% CI -1.86 to -0.94, from 1 study with 41 participants).</p>	<p>“There is insufficient randomised evidence to be confident of a difference between GHB and placebo, or to determine reliably if GHB is more or less effective than other drugs for the treatment of alcohol withdrawal or the prevention of relapses. The small amount of randomised evidence available suggests that GHB 50mg may be more effective than placebo in the treatment of AWS, and in preventing relapses and craving in previously detoxified alcoholics during the first 3 months of follow-up. This review does not provide evidence in favour or against GHB compared to benzodiazepines and Clomethiazole for treatment of AWS; but, again based on a small amount of randomised evidence, GHB appears better than NTX and Disulfiram in maintaining abstinence and preventing craving in the medium term (3 to 12 months). The review does not provide evidence of a difference in side effects between GHB and benzodiazepines, NTX or Disulfiram. These findings should be considered alongside concerns that have been raised about GHB regarding the risk of developing addiction, and the misuse or abuse of the drug, suggesting to use GHB only under strict medical surveillance.”</p>

			All other comparisons and outcomes did not show significant differences.”	
	<p>Additional Information from Abstract</p> <p>“Background</p> <p>Chronic excessive alcohol consumption may lead to dependence, and to alcohol withdrawal syndrome (AWS) in case of abrupt drinking cessation. Gamma-hydroxybutyric acid (GHB) can prevent and suppress withdrawal symptoms, and improve the medium-term abstinence rate. However, clear estimates of its beneficial and harmful effects have not been yet established.”</p>			
<p><i>Mason M, et al. (2015)⁴</i> <i>(Assessed as up-to-date: 4 March 2015)</i></p>	<p>Effects of opioid, hypnotic and sedating medications on sleep-disordered breathing in adults with obstructive sleep apnoea</p>	<p>“To investigate whether administration of sedative and hypnotic drugs exacerbates the severity of OSA (as measured by the apnoea-hypopnoea index (AHI) or the 4% oxygen desaturation index (ODI)) in people with known OSA.”</p>	<p>“Fourteen studies examining the effects of 10 drugs and including a total of 293 participants contributed to this review. Trials were small, with only two trials, which used sodium oxybate, recruiting more than 40 participants, and all but three trials were of only one to three nights in duration. Most participants had mild to moderate OSA with a mean AHI of 11 to 25 events/h, and only two trials recruited patients with severe OSA. Two trials investigating the effects of ramelteon, a treatment option for insomnia, recruited adults over 60 years of age with OSA and concomitant insomnia. The drugs studied in this review included remifentanyl (infusion) 0.75 mcg/kg/h, eszopiclone 3 mg, zolpidem 10 and 20 mg, brotizolam 0.25 mg, flurazepam 30 mg, nitrazepam 10 mg to 15 mg, temazepam 10 mg, triazolam 0.25 mg, ramelteon 8 mg and 16 mg and sodium oxybate 4.5 g and 9 g. We were unable to pool most of the data, with the exception of data for eszopiclone and ramelteon.</p> <p>None of the drugs in this review produced a significant increase in AHI or ODI. Two trials have shown a beneficial effect on OSA. One study showed that a single administration of eszopiclone 3 mg significantly decreased AHI compared with placebo (24 ± 4 vs 31 ± 5; P value < 0.05), and a second study of sodium oxybate 4.5 g showed a significant decrease in AHI compared with placebo (mean difference (MD) -7.41, 95% confidence interval (CI) -14.17 to -0.65; N = 48). Only four trials reported outcome data on ODI. No significant increase, in comparison with placebo, was shown with eszopiclone (21 (22 to 37) vs 28.0 (15 to 36); P value = NS), zolpidem (0.81 ± 0.29 vs 1.46 ± 0.53; P value = NS), flurazepam (18.6 ± 19 vs 19.6 ± 15.9; P value = NS) and temazepam (6.53 ± 9.4 vs 6.56 ± 8.3; P value = 0.98).</p>	<p>“The findings of this review show that currently no evidence suggests that the pharmacological compounds assessed have a deleterious effect on the severity of OSA as measured by change in AHI or ODI. Significant clinical and statistical decreases in minimum overnight SpO₂ were observed with remifentanyl, zolpidem 20 mg and triazolam 0.25 mg. Eszopiclone 3 mg and sodium oxybate 4.5 g showed a beneficial effect on the severity of OSA with a reduction in AHI and may merit further assessment as a potential therapeutic option for a subgroup of patients with OSA. Only one trial assessed the effect of an opioid (remifentanyl); some studies included CPAP treatment, whilst in a significant number of participants, previous treatment with CPAP was not stated and thus a residual treatment effect of CPAP could not be excluded. Most studies were small and of short duration, with indiscernible methodological quality. Caution is therefore required when such agents are prescribed for patients with OSA, especially outside the severity of the OSA cohorts and the corresponding dose of compounds given in the particular studies. Larger, longer trials involving patients across a broader spectrum of OSA severity are needed to clarify these results.”</p>

A significant decrease in minimum nocturnal peripheral capillary oxygen saturation (SpO₂) was observed with zolpidem 20 mg (76.8 vs 85.2; P value = 0.002), flurazepam 30 mg (81.7 vs 85.2; P value = 0.002), remifentanyl infusion (MD -7.00, 95% CI -11.95 to -2.05) and triazolam 0.25 mg in both rapid eye movement (REM) and non-REM (NREM) sleep (MD -14.00, 95% CI -21.84 to -6.16; MD -10.20, 95% CI -16.08 to -4.32, respectively).

One study investigated the effect of an opiate (remifentanyl) on patients with moderate OSA. Remifentanyl infusion did not significantly change AHI (MD 10.00, 95% CI -9.83 to 29.83); however it did significantly decrease the number of obstructive apnoeas (MD -9.00, 95% CI -17.40 to -0.60) and significantly increased the number of central apnoeas (MD 16.00, 95% CI -2.21 to 34.21). Similarly, although without significant effect on obstructive apnoeas, central apnoeas were increased in the sodium oxybate 9 g treatment group (MD 7.3 (18); P value = 0.005) in a cross-over trial.

Drugs studied in this review were generally well tolerated, apart from adverse events reported in 19 study participants prescribed remifentanyl (n = 1), eszopiclone (n = 6), sodium oxybate (n = 9) or ramelteon (n = 3)."

Plain language for sodium oxybate:
"Sodium oxybate (a treatment for narcolepsy, a condition causing excessive sleepiness during the day)
Sodium oxybate was compared with placebo in two trials. Results showed that sodium oxybate did not worsen OSA as measured by the numbers and duration of pauses in breathing during sleep. In one study, sodium oxybate 4.5 g reduced the severity of OSA and might have proved beneficial in treating this condition, although further studies are needed to assess this effect."

"Bottom line
The long-term effect and potential side effects of sedative drugs in people with OSA need to be assessed in larger, longer and methodologically robust studies."

Additional Information from Abstract

“Background

Obstructive sleep apnoea (OSA) is a common sleep disorder characterised by partial or complete upper airway occlusion during sleep, leading to intermittent cessation (apnoea) or reduction (hypopnoea) of airflow and dips in arterial oxygen saturation during sleep. Many patients with recognised and unrecognised OSA receive hypnotics, sedatives and opiates/opioids to treat conditions including pain, anxiety and difficulty sleeping. Concerns have been expressed that administration of these drugs to people with co-existing OSA may worsen OSA.”

Table 4: Other Reviews (in Cochrane Library: Critical abstracts of systematic reviews that meet the criteria for inclusion on DARE. “Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.”)

Author(s)	Title	Objectives	Main Results	Author’s Conclusions
<p><i>Centre for Reviews and Dissemination Structured Abstract</i>²⁷ Original article: <i>Alshaikh MK, et al. (2012)</i>²⁶</p>	<p>Sodium oxybate for narcolepsy with cataplexy: systematic review and meta-analysis (Structured abstract)</p>	<p>To assess the efficacy and safety of sodium oxybate in adults with excessive daytime sleeping and sudden loss of muscle tone (narcolepsy-cataplexy).</p>	<p>“Six RCTs (741 participants; range 20 to 278) were included in the review. All studies were blinded, and all reported that incomplete outcome data had been addressed. Five studies reported freedom from selective reporting, but all other criteria were not addressed or it was unclear whether they had been addressed. Compared to placebo, sodium oxybate (4.5g per night) statistically significantly reduced cataplexy attacks (MD -8.5, 95% CI -15.3 to -1.6; two of four trials) measured using diaries. Compared to placebo, sodium oxybate (9g per night) statistically significantly increased wakefulness (MD 5.18, 95% CI 2.59 to 7.78; two trials), significantly decreased mean number of sleep attacks (MD -9.65, 95% CI -17.72 to -1.59; two trials), and significantly increased the proportion of patients who were much improved or very much improved as measured on the Clinical Global Impression of Change (MD 2.42, 95% CI 1.77 to 3.32; three trials). There were no statistically significant differences between treatment groups in the percentage of restful eye movement sleep before and after sodium oxybate. Sodium oxybate (9g per night) statistically significantly increased the number of adverse events compared to placebo, including nausea, vomiting and dizziness. There was no evidence of statistical heterogeneity for any outcomes. Other results were reported in the review.”</p>	<p>“Sodium oxybate significantly reduced cataplexy (based on diaries) and significantly improved daytime sleepiness, as measured using objective and subjective assessment methods. Sodium oxybate was well tolerated and most adverse events were mild-to-moderate in severity.”</p> <p>“CRD summary The authors concluded that sodium oxybate significantly reduced cataplexy, significantly improved daytime sleepiness, and was well tolerated. This was a generally well-conducted review, but given the limited evidence base and uncertain long-term effects of sodium oxybate, the authors’ conclusions should be interpreted with caution as the findings may not be reliable.”²⁷</p>

Additional Information from Abstract

“Searching

Five electronic databases, including the Cochrane Central Register of Controlled Trials (CENTRAL) and MEDLINE were searched up to October 2010 without restrictions on language or publication status. A search strategy was presented. In addition, ClinicalTrials.gov was scanned, along with reference lists of included studies, and authors’ personal files. Experts in the field and relevant manufacturers were also contacted to find additional studies.

Study selection

Eligible for inclusion were randomised controlled trials (RCTs) that compared the safety and efficacy of sodium oxybate to any comparator in adults with narcolepsy and cataplexy. The primary outcome of interest was elimination of excessive daytime sleeping, assessed according to subjective or objective measures (as stated in the review). Secondary outcomes included quality of life and adverse events. Included trials were conducted in clinics in the USA, Canada and Europe (where reported), and were published after 2002. The proportion of females ranged from 46% to 65% and the mean age ranged from 36 to 48 years. Where reported, the mean weight of participants ranged between 80.5 and 87.5kg. None of the patients had concurrent sleep disordered breathing. The occurrence of narcolepsy/cataplexy varied between studies. Various assessment methods were used to measure some outcomes, while others were based on diaries. The duration of most interventions ranged from four to eight weeks, and the dose of sodium oxybate in most studies ranged between 4.5 and 9g per night. Two reviewers independently screened studies for inclusion. Discrepancies were resolved through discussion or referral to a third reviewer.

Validity assessment

Two reviewers independently assessed study quality based on the Cochrane risk of bias tool criteria. Discrepancies were resolved through discussion or referral to a third reviewer.

Data extraction

Two reviewers independently extracted outcome data to calculate relative risks or mean differences and their 95% confidence intervals. Any discrepancies were resolved through discussion or referral to a third reviewer.

Methods of synthesis

Where possible, a random-effects model was used to combine relative risks, mean differences and their 95% confidence intervals. Where it was not possible to combine studies in meta-analysis, data were briefly discussed narratively. Statistical heterogeneity was assessed through visual inspection of forest plots and using I^2 and X^2 . The authors planned to assess publication bias using funnel plots.

Cost information

The review question and supporting inclusion criteria were clearly stated. A number of sources were searched to identify relevant articles. The authors could not formally assess publication bias due to the small number of studies involved. Trial risk of bias was assessed using appropriate criteria, but this indicated potential for some risk of bias. Each stage of the review process was performed in duplicate, which reduced potential for reviewer error and bias. There was some variability in the methods used to measure outcomes, some of which were subjective, which reduced the robustness of the findings. Meta-analyses were generally based on two small trials and confidence intervals were wide for some outcomes, which again reduced the reliability of the findings. This was a generally well-conducted review, but given the limitations of the evidence and uncertain long-term effects of sodium oxybate, the authors' conclusions should be interpreted with caution as the findings may not be reliable.

Authors' conclusions

Sodium oxybate significantly reduced cataplexy (based on diaries) and significantly improved daytime sleepiness, as measured using objective and subjective assessment methods. Sodium oxybate was well tolerated and most adverse events were mild-to-moderate in severity.

CRD commentary

The review question and supporting inclusion criteria were clearly stated. A number of sources were searched to identify relevant articles. The authors could not formally assess publication bias due to the small number of studies involved. Trial risk of bias was assessed using appropriate criteria, but this indicated potential for some risk of bias. Each stage of the review process was performed in duplicate, which reduced potential for reviewer error and bias. There was some variability in the methods used to measure outcomes, some of which were subjective, which reduced the robustness of the findings. Meta-analyses were generally based on two small trials and confidence intervals were wide for some outcomes, which again reduced the reliability of the findings. This was a generally well-conducted review, but given the limitations of the evidence and uncertain long-term effects of sodium oxybate, the authors' conclusions should be interpreted with caution as the findings

	<p>may not be reliable.</p> <p>Implications of the review for practice and research Practice: The authors stated that caution was advised when treating narcoleptics with concurrent sleep disordered breathing, and health care professionals should confirm that these patients were compliant with positive airway pressure therapy before starting sodium oxybate. Research: The authors stated that future research should explore the long-term efficacy and tolerability of sodium oxybate, the effect of sodium oxybate in patients with concurrent sleep disordered breathing, and the effect of different dosages on patients with milder narcolepsy.</p> <p>Funding National Plan for Science and Technology.”²⁷</p>			
<p><i>Centre for Reviews and Dissemination Structured Abstract</i>²⁹ Original article: Boscolo-Berto R, et al.(2012)²⁸</p>	<p>Narcolepsy and effectiveness of gamma-hydroxybutyrate (GHB): a systematic review and meta-analysis of randomized controlled trials (Structured abstract)</p>	<p>“To evaluate the effectiveness of gamma hydroxybutyrate on the clinical and neurological features of narcolepsy”</p>	<p>“Nine randomised controlled trials (1,154 participants) were included in the review. Seven studies scored 4 on the Jadad scale and two studies scored 3. Statistically significant benefits were observed with treatment with gamma hydroxybutyrate doses of 4g, with reductions in cataplexy attacks on a daily (WMD -1.10, 95% CI -1.29 to -0.90; I²=0%; two trials) and weekly basis (WMD -7.04, 95% CI -12.45 to -1.63; I²=93%; three trials) and daytime sleep attacks on a weekly basis (WMD -9.30, 95% CI -15.92 to -2.68; I²=15%; two trials). Statistically significant improvements were observed across doses that ranged from 3.0g to 9.0g in subjective daytime sleepiness (WMD -2.81, 95% CI -4.13 to -1.49; I²=94%; six comparisons) and on the clinical global impression changes scale (OR 3.45, 95% CI 2.47 to 4.80; I²=0%; seven comparisons). There were statistically significant changes showing benefits of gamma hydroxybutyrate compared to placebo in stage 3 and 4 sleep (WMD 4.11, 95% CI 0.07 to 8.16; I²=0%; two trials), stage shifts in sleep (WMD -9.69, 95% CI -17.14 to -2.24; I²=0%; two trials) and in subjective nocturnal awakenings (WMD -1.33, 95% CI -1.78 to -0.88; I²=0%; two trials) No statistically significant differences observed between gamma hydroxybutyrate and placebo in daytime sleep attacks on a daily basis, night-time sleep latency, total sleep time or percentages of stage 1 or stage 2 sleep or REM sleep (two trials for each outcome). There was no evidence of publication bias observed in the appraisals of the funnel plots for the comparisons in the review.”</p>	<p>“The results showed that gamma hydroxybutyrate was effective in the treatment of major clinically relevant symptoms of narcolepsy and sleep architecture abnormalities.”</p> <p>“CRD summary This review found that gamma hydroxybutyrate provided statistically significant benefits in patients with narcolepsy. Limited quality assessment of the included trials and significant variation across the results make the reliability of the authors' conclusions uncertain.”²⁹</p>
<p>Additional Information from Abstract “Searching PubMed, EMBASE, Web of Science, Scirus, Scopus, Cochrane Central Register of Controlled Trials (CENTRAL) and ClinicalTrials.gov were searched for relevant studies to August 2010; search terms were reported.</p>				

Study selection

Randomised controlled trials that evaluated oral administration of gamma hydroxybutyrate compared to orally administered placebo in patients with narcolepsy were eligible for inclusion. Eligible trials were required to report at least one outcomes: cataplexy attacks, excessive daytime sleepiness attacks, hypnagogic hallucinations, sleep paralysis, clinical global impression change, quality of life, neurophysiological outcomes on the multiple sleep latency test or the maintenance of wakefulness test, or nocturnal somnographic data. Studies that did not present sufficient data to enable calculation of summary estimates were excluded from the review. The included studies were published between 1989 and 2009. Gamma hydroxybutyrate dose ranged from 3.0g to 9.0g. Treatment duration ranged from four to eight weeks. Concomitant medications were stimulants, antidepressants or hypnotics and low-dose propranolol. It appeared that three reviewers performed the study selection; any discrepancies between reviewers were resolved by consensus.

Validity assessment

Methodological quality was assessed using the five-point Jadad scale of randomisation, blinding and treatment of withdrawals and drop-outs. An overall score of 3 points was indicative of a high quality study. The authors did not state how many reviewers assessed study quality.

Data extraction

Odds ratios (OR) were calculated for dichotomous outcomes and mean differences were calculated for continuous outcomes, each with 95% confidence intervals (CI) for the estimates. Study authors were contacted for additional data. Data were extracted by two reviewers and checked by a third. Any disagreements between reviewers were resolved by consensus.

Methods of synthesis

Pooled odds ratios, weighted mean differences (WMD) and 95% CIs for the summary estimates were calculated using a fixed-effect model. Statistical heterogeneity was assessed using X^2 and I^2 . Where statistical heterogeneity was detected the results were combined using a random-effects model. Potential for publication bias was evaluated by visual appraisal of funnel plots.

Cost information

The review addressed a clearly specified question. Study inclusion criteria were stipulated. Appropriate databases were searched for relevant studies. Attempts were made to identify unpublished studies. The authors used validated methods to examine potential for publication bias. Steps were taken to minimise reviewer error and bias during study selection and data extraction; methods were not reported for the assessment of methodological quality. Jadad scores indicated that the studies were of good quality. No data were presented on long term follow-up. Important quality criteria such as the reporting of allocation concealment were not evaluated. Many studies had a crossover design but this aspect of study quality was not assessed and further details were not provided. There was substantial heterogeneity in the results of the trials; the authors acknowledged that these were due to variations in doses, durations of treatment, follow-up durations, concomitant medications, clinical baseline features and sample sizes. The authors also acknowledged the absence of adequate information for subgroup analyses. The clinical value of the numerous pooled results in which significant statistical heterogeneity was present was questionable. Limited assessment of study quality, substantial heterogeneity and an absence of trial population details make the reliability of the authors' conclusions uncertain.

Authors' conclusions

The results showed that gamma hydroxybutyrate was effective in the treatment of major clinically relevant symptoms of narcolepsy and sleep architecture abnormalities.

CRD commentary

The review addressed a clearly specified question. Study inclusion criteria were stipulated. Appropriate databases were searched for relevant studies. Attempts were made to identify unpublished studies. The authors used validated methods to examine potential for publication bias. Steps were taken to minimise reviewer error and bias during study selection and data extraction; methods were not reported for the assessment of methodological quality. Jadad scores indicated that the studies were of good quality. No data were presented on long term follow-up. Important quality criteria such as the reporting of allocation concealment were not evaluated. Many studies had a crossover design but this aspect of study quality was not assessed and further details were not provided. There was substantial heterogeneity in

	<p>the results of the trials; the authors acknowledged that these were due to variations in doses, durations of treatment, follow-up durations, concomitant medications, clinical baseline features and sample sizes. The authors also acknowledged the absence of adequate information for subgroup analyses. The clinical value of the numerous pooled results in which significant statistical heterogeneity was present was questionable. Limited assessment of study quality, substantial heterogeneity and an absence of trial population details make the reliability of the authors' conclusions uncertain.</p> <p>Implications of the review for practice and research Practice: The authors stated that gamma hydroxybutyrate was effective for cataplexy attacks, subjective daytime sleepiness, subjective nocturnal awakenings and daytime sleep attacks. Research: The authors stated that further well-designed placebo-controlled studies with adequate power were required. New research should use standardised outcomes with adequate follow-up and no other medication to investigate the effects of gamma hydroxybutyrate on night-time sleep disturbances in narcolepsy. The role of gamma hydroxybutyrate in sleep paralysis and hypnagogic hallucinations should be verified.</p> <p>Funding No external funding.”</p>			
<p><i>Centre for Reviews and Dissemination Structured Abstract</i>⁷⁴</p> <p>Original article: Traub S J, et al. (2002)⁷⁵</p>	<p>Physostigmine as a treatment for gamma-hydroxybutyrate toxicity: a review (Structured abstract)</p>	<p>“To assess the effect of physostigmine in the treatment of sedation caused by gamma-hydroxybutyrate (GHB).”</p>	<p>“Four case series (73 patients) were included.</p> <p>Methodological limitations included the lack of a control group, the use of unblinded studies, and the concurrent use of diazepam in 90% of the patients.</p> <p>Small case series: there were 2 case series with a total of six patients with GHB overdose. Five of the six patients were reported as improving after the administration of physostigmine.</p> <p>Larger case series: there were 2 case series with a total of 67 patients undergoing surgery. The first case series reported that 24 of the 25 patients awoke within 10 minutes of being given physostigmine. The second case series found that 36 of the 42 patients awoke within 10 minutes of being given physostigmine.”</p>	<p>“There was insufficient evidence to assess whether physostigmine should be used routinely for treating toxicity due to GHB.”</p> <p>“CRD commentary The review question was clear in terms of the intervention, participants and outcomes. The inclusion criteria were not defined in terms of the study design. Studies in any language were included and the search terms were stated. The authors acknowledged that limiting the search to studies listed in only one database may have resulted in the omission of other relevant studies. Three reviewers independently selected the studies and this reduced the potential for bias and errors. The methods used to extract the data were not described, so it is not known whether efforts were made to reduce errors and bias. Validity was not formally assessed, but some methodological limitations of the studies were discussed in the text. A narrative synthesis was appropriate given the small number of studies. The evidence presented appears to support the authors' conclusions.”⁷⁴</p>

Additional Information from Abstract

“Searching

MEDLINE was searched for studies published in any language. The reference lists of identified studies were also checked.

Study selection: study designs

The inclusion criteria were not explicitly defined in terms of the study design. All of the included studies were case series.

Study selection: specific interventions

Studies of physostigmine were eligible for inclusion. In the included studies, physostigmine was administered intravenously at doses of 2 mg one or more times, 1.0 mg, and 0.5 mg times three doses.

Study selection: participants

Studies of patients with GHB-induced sedation were eligible for inclusion. The included studies were of patients with GHB poisoning who were being treated in emergency departments and surgical patients who had been given GHB as part of an anaesthetic regimen. Some patients with GHB poisoning were given naloxone or flumazenil. In the studies of surgical patients, the cointerventions included combinations of diazepam, regional anaesthesia, morphine, alcuronium, neostigmine, naloxone, and thiopentone or althesin.

Study selection: outcomes

Studies that reported the reversal or attenuation of sedation were eligible for inclusion. The included studies appeared to assess time till 'awake', 'regained consciousness' or 'recovered' and respiratory rate.

Study selection: how were decisions on the relevance of primary studies made?

Three authors selected the studies for inclusion

Validity assessment

Validity was not formally assessed, but some aspects of validity were discussed in the text, e.g. study design, blinding and confounding by cointerventions.

Data extraction

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The data extracted included study design, sample size, study setting and cointerventions.

Methods of synthesis: how were the studies combined?

A narrative synthesis of the studies was undertaken.

Methods of synthesis: how were differences between studies investigated?

The differences between the included studies were described in the text.

Authors' conclusions

There was insufficient evidence to assess whether physostigmine should be used routinely for treating toxicity due to GHB.

CRD commentary

The review question was clear in terms of the intervention, participants and outcomes. The inclusion criteria were not defined in terms of the study design. Studies in any language were included and the search terms were stated. The authors acknowledged that limiting the search to studies listed in only one database may have resulted in the omission of other relevant studies. Three reviewers independently selected the studies and this reduced the potential for bias and errors. The

methods used to extract the data were not described, so it is not known whether efforts were made to reduce errors and bias. Validity was not formally assessed, but some methodological limitations of the studies were discussed in the text. A narrative synthesis was appropriate given the small number of studies. The evidence presented appears to support the authors' conclusions.

Implications of the review for practice and research

Practice: The authors stated that there was insufficient evidence to recommend the routine use of physostigmine in toxicity due to GHB.

Research: The authors stated that further research is required to assess whether physostigmine should be used to treat toxicity due to GHB.

Record status

This record is a structured abstract written by CRD reviewers. The original has met a set of quality criteria. Since September 1996 abstracts have been sent to authors for comment. Additional factual information is incorporated into the record. Noted as [A:.....].”

Appendix 3 – PubMed results for sodium oxybate and abuse or misuse

Postmarketing and clinical safety experience with sodium oxybate (Xyrem)

Wang et al. (2009) Safety overview of postmarketing and clinical experience of sodium oxybate (Xyrem): abuse, misuse, dependence, and diversion

“STUDY OBJECTIVES:

This study reviewed the cumulative postmarketing and clinical safety experience with sodium oxybate (Xyrem), a treatment approved for cataplexy and excessive daytime sleepiness in narcolepsy. Study objectives were to investigate the occurrence of abuse/misuse of sodium oxybate since first market introduction in 2002, classify cases using DSM-IV criteria for substance abuse and dependence, and describe specific characteristics of these cases.

METHODS:

We retrospectively reviewed postmarketing spontaneous adverse event (AE) reports from 15 countries for all cases containing reporting terminology related to abuse/misuse to determine its occurrence. All death cases independent of causality were reviewed to identify associated risk factors.

RESULTS:

Approximately 26,000 patients worldwide received sodium oxybate from first market introduction in 2002 through March 2008. Of those 26,000 patients, 0.2% reported ≥ 1 of the events studied. These included 10 cases (0.039%) meeting DSM-IV abuse criteria, 4 cases (0.016%) meeting DSM-IV dependence criteria, 8 cases (0.031%, including 3 of the previous 4) with withdrawal symptoms reported after discontinuation of sodium oxybate, 2 confirmed cases (0.008%) of sodium oxybate-facilitated sexual assault, 8 cases (0.031%) of overdose with suicidal intent, 21 deaths (0.08%) in patients receiving sodium oxybate treatment with 1 death known to be related to sodium oxybate, and 3 cases (0.01%) of traffic accidents involving drivers taking sodium oxybate. During this period, approximately 600,000 bottles of sodium oxybate were distributed, and 5 incidents (0.0009%) of diversion were reported.

CONCLUSION:

Cumulative postmarketing and clinical experience indicates a very low risk of abuse/misuse of sodium oxybate.”

Neurological Pathways causing GHB dependency and withdrawal

Kamal et al. (2016) The Neurobiological Mechanisms of Gamma-Hydroxybutyrate Dependence and Withdrawal and Their Clinical Relevance: A Review.⁵⁵

“OBJECTIVE:

γ -Hydroxybutyrate (GHB) has gained popularity as a drug of abuse. In the Netherlands the number of patients in treatment for GHB dependence has increased sharply. Clinical presentation of GHB withdrawal can be life threatening. We aim, through this overview, to explore the neurobiological pathways causing GHB dependency and withdrawal, and their implications for treatment choices.

METHODS:

In this work we review the literature discussing the findings from animal models to clinical studies focused on the neurobiological pathways of endogenous but mainly exogenous GHB.

RESULTS:

Chronic abuse of GHB exerts multifarious neurotransmitter and neuromodulator effects on γ -aminobutyric acid (GABA), glutamate, dopamine, serotonin, norepinephrine and cholinergic systems. Moreover, important effects on neurosteroidogenesis and oxytocin release are wielded. GHB acts mainly via a bidirectional effect on GABAB receptors (GABABR; subunits GABAB1 and GABAB2), depending on the subunit of the GIRK (G-protein-dependent ion inwardly rectifying potassium) channel involved, and an indirect effect of the cortical and limbic inputs outside the nucleus accumbens. GHB also activates a specific GHB receptor and β 1-subunits of α 4-GABAAR. Reversing this complex interaction of neurobiological mechanisms by the abrupt cessation of GHB use results in a withdrawal syndrome with a diversity of symptoms of different intensity, depending on the pattern of GHB abuse.

CONCLUSION:

The GHB withdrawal symptoms cannot be related to a single mechanism or neurological pathway, which implies that different medication combinations are needed for treatment. A single drug class, such as benzodiazepines, gabapentin or antipsychotics, is unlikely to be sufficient to avoid life-threatening complications. Detoxification by means of titration and tapering of pharmaceutical GHB can be considered as a promising treatment that could make polypharmacy redundant.”

Acute toxicity & Emergency Room visits – Accidental, related to drug use, or suicide and Trends in drug abuse

Dines et al. (2015) Acute recreational drug and new psychoactive substance toxicity in Europe: 12 months data collection from the European Drug Emergencies Network (Euro-DEN).⁴⁷

“CONTEXT:

Despite the potential for recreational drugs and new psychoactive substances (NPSs) to cause significant morbidity and mortality, there is limited collection of systematic data on acute drug/NPS toxicity in Europe.

OBJECTIVE:

To report data on acute drug/NPS toxicity collected by a network of sentinel centres across Europe with a specialist clinical and research interest in the acute toxicity of recreational drugs and NPS to address this knowledge gap.

METHODS:

Sixteen sentinel centres in 10 European countries (Denmark, Estonia, France, Germany, Ireland, Norway, Poland, Spain, Switzerland and the UK) collected data on all acute drug toxicity presentations to their Emergency Rooms (ERs) for 12 months (October 2013-September 2014); information on the drug(s) involved in the presentations was on the basis of patient self-reporting.

RESULTS:

Data were collected on a total of 5529 presentations involving 8709 drugs (median (interquartile range [IQR]): 1 (1-2) drugs per presentation), a median of 0.3% of all ER attendances. Classical recreational drugs were most common (64.6%) followed by prescription drugs (26.5%) and NPS (5.6%). The 'top five' drugs recorded were heroin (1345 reports), cocaine (957), cannabis (904), GHB/GBL (711) and amphetamine (593). 69.5% of individuals went to hospital by ambulance (peak time between 19:00 and 02:00 at weekends); the median (IQR) age was 31 (24-39) years and 75.4% were male. Although serious clinical features were not seen in most presentations and 56.9% were medically discharged from the ER (median length of stay: 4.6 hours), a significant number (26.5%) was agitated, in 10.5% the GCS was 8 or less and 35 presented in cardiac arrest. There were 27 fatalities with opioids implicated in 13.

CONCLUSION:

The Euro-DEN dataset provides a unique insight into the drugs involved in and clinical pattern of toxicity/outcome of acute recreational drug toxicity presentations to hospitals around Europe. This is complimentary to other indicators of drug-related harm and helps to build a fuller picture of the public health implications of drug use in Europe.

KEYWORDS:

Acute toxicity; Emergency Room; epidemiology; prescription medicines"

*Vallersnes, et al. (2015) Patients presenting with acute poisoning to an outpatient emergency clinic: a one-year observational study in Oslo, Norway.*⁴⁹

"BACKGROUND:

In Oslo, the majority of patients with acute poisoning are treated in primary care, at an emergency outpatient clinic with limited diagnostic and treatment resources. We describe the poisonings currently seen in this setting. We compare our findings with previous studies, with special concern for the appearance of new toxic agents, and changes in overall numbers and patterns of poisoning.

METHODS:

Observational study. Patients above the age of 12 years presenting at Oslo Accident and Emergency Outpatient Clinic (Oslo Legevakt) with acute poisoning were included consecutively from October 2011 through September 2012. Physicians and nurses registered data on preset forms. Main outcome measures were toxic agents, age, sex, intention, referral and time of presentation.

RESULTS:

There were 2923 episodes of acute poisoning in 2261 patients. Median age of the patients was 32 years, and 1430 (63%) were males. The most frequent toxic agents were ethanol in 1684 (58%) episodes, heroin in 542 (19%), benzodiazepines in 521 (18%), amphetamine in 275 (9%), fire smoke in 192 (7%), gamma-hydroxybutyrate (GHB) in 144 (5%), and cannabis in 143 (5%). In 904 (31%) poisonings there were more than one toxic agent. In 493 episodes (17%), the patient was hospitalised, and in 60 episodes (2%) admitted to a psychiatric ward. Most poisonings, 2328 (80%), were accidental overdoses with substances of abuse, 276 (9%) were suicide attempts, and 312 (11%) were accidents. Among ethanol poisonings in patients above the age of 26 years, 685/934 (73%) were in males, and 339/934 (36%) presented during weekends. However, among ethanol poisonings in patients under the age of 26 years, 221/451 (49%) were in females, and 297/451 (66%) presented during weekends.

CONCLUSIONS:

The poisonings treated in this primary care setting were mostly due to accidental overdoses with ethanol or other substances of abuse. There is a disconcerting weekend drinking pattern among adolescents and young adults, with young females presenting as often as young males with ethanol poisoning."

*Sorge et al. (2015) Self-poisoning in the acute care medicine 2005-2012.*⁵¹

"OBJECTIVE:

To describe the trend of acute self-poisoning in the emergency and intensive care.

METHODS:

Electronic charts of adults who presented to the emergency department of the University Hospital Leipzig with self-poisoning following a suicide attempt (suicide group), intoxication (intoxication group), drug overdose for relief of pain or discomfort (drug overdose group) between 2005 and 2012 were analyzed.

RESULTS:

3533 adults (62.6% males) were identified, with the yearly admissions increasing from 305 in 2005 to 624 in 2012. The admission rate in relation to the total emergency department admissions also increased, from 1.2% in 2005 to 1.9% in 2012. 31.7% of the patients were younger than 25 years. The reasons for self-poisoning were suicide attempt (18.1%), intoxication (76.8%) and drug overdose (2.9%). The reason could not be clearly classified in 80 patients. Psychotropic drugs were used in

71.6% of suicide attempts, while alcohol was the sole cause of intoxication in 80.1% of cases in the intoxication group. Self-poisoning using at least two substances was observed in 52.0% of the suicide attempts, 10.3% of those with intoxication and 29.7% of those with drug overdose. While alcohol remains the most common cause of intoxication, there was a drastic increase in the consumption of cannabinoids, Crystal Meth and gamma-hydroxybutyrate in the years 2011 and 2012. ICU admission was necessary in 16.6% of the cases. There were 22 deaths (0.6% of the study population), of whom 15 were in the suicide group (2.3%), four (0.15%) in the intoxication group, and three in the not clearly classified group (3.8%).

CONCLUSION:

Acute self-poisoning is an increasing medical issue. Psychotropic drugs remain the most common means of suicide attempt. Although alcohol intoxication is very frequent, intake of illicit drugs as the cause of emergency admission is increasing.”

***Corkery et al. (2015) Gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL) and 1,4-butanediol (1,4-BD; BDO): A literature review with a focus on UK fatalities related to non-medical use.*⁴⁸**

“Misuse of gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) has increased greatly since the early 1990s, being implicated in a rising number of deaths. This paper reviews knowledge on GHB and derivatives, and explores the largest series of deaths associated with their non-medical use. Descriptive analyses of cases associated with GHB/GBL and 1,4-butanediol (1,4-BD) use extracted from the UK’s National Programme on Substance Abuse Deaths database. From 1995 to September 2013, 159 GHB/GBL-associated fatalities were reported. Typical victims: White (92%); young (mean age 32 years); male (82%); with a drug misuse history (70%). Most deaths (79%) were accidental or related to drug use, the remainder (potential) suicides. GHB/GBL alone was implicated in 37%; alcohol 14%; other drugs 28%; other drugs and alcohol 15%. Its endogenous nature and rapid elimination limit toxicological detection. Post-mortem blood levels: mean 482 (range 0-6500; SD 758)mg/L. Results suggest significant caution is needed when ingesting GHB/GBL, particularly with alcohol, benzodiazepines, opiates, stimulants, and ketamine. More awareness is needed about risks associated with consumption.”

***Horyniak, et al. (2014) Pattern and characteristics of ecstasy and related drug (ERD) presentations at two hospital emergency departments, Melbourne, Australia, 2008-2010.*⁵⁰**

“OBJECTIVE:

To describe patterns and characteristics of emergency department (ED) presentations related to the use of ecstasy and related drugs (ERDs) in Melbourne, Australia.

METHODS:

Retrospective audit of ERD-related presentations from 1 January 2008 to 31 December 2010 at two tertiary hospital EDs. Variation in presentations across years was tested using a two-tailed test for proportions. Univariate and multivariate logistic regressions were used to compare sociodemographic and clinical characteristics across groups.

RESULTS:

Most of the 1347 presentations occurred on weekends, 24:00-06:00. Most patients arrived by ambulance (69%) from public places (42%), private residences (26%) and licensed venues (21%). Ecstasy-related presentations decreased from 26% of presentations in 2008 to 14% in 2009 ($p < 0.05$); γ -hydroxybutyrate (GHB) presentations were most common overall. GHB presentations were commonly related to altered conscious state (89%); other presentations were due to psychological concerns or nausea/vomiting. Compared with GHB presentations, patients in ecstasy-related presentations were significantly less likely to require intubation (OR 0.04, 95% CI 0.01 to 0.18), but more likely to result in hospital admission (OR 1.77, 95% CI 1.08 to 2.91). Patients in amphetamine-related cases were older than those in GHB-related cases (median 28.4 years vs 23.9 years; $p < 0.05$), and more likely to have a history of substance use (OR 4.85, 95% CI 3.50 to 6.74) or psychiatric illness (OR 6.64, 95% CI 4.47 to 9.87). Overall, the median length of stay was 3.0 h (IQR 1.8-4.8), with most (81%) patients discharged directly home.

CONCLUSIONS:

Although the majority of ERD-related presentations were effectively treated, with discharge within a short time frame, the number and timing of presentations places a significant burden on EDs. ERD harm reduction and improved management of minor harms at licensed venues could reduce this burden.”

***Wood et al. (2013) Five-year trends in self-reported recreational drugs associated with presentation to a UK emergency department with suspected drug-related toxicity.*⁵²**

“OBJECTIVE:

User surveys show that there have been significant changes over the last decade in the recreational drugs that are available and being used. This study aims to determine whether there have been similar trends in the drug(s) used by individuals presenting to the emergency department (ED) with acute recreational drug toxicity.

METHODS:

Data on all poisoned patients presenting to our large inner-city ED are recorded prospectively on a dedicated clinical toxicology database. Presentations relating to the use of classical recreational drugs and/or novel psychoactive substances were identified retrospectively between 1 January 2006 and 31 December 2010.

RESULTS:

There was a significant increase between 2006 and 2010 in the number of individuals reporting the use of cocaine (119-222), γ -hydroxybutyrate/ γ -butyrolactone (158-270), ketamine (58-81) and cannabis (18-68) and novel psychoactive substances (seven to 98). In particular, there was an increase in cathinones reported from none in 2006 to 82 in 2010. Only 3,4-methylenedioxyamphetamine (MDMA) was associated with a downward trend in reported use from 140 in 2006 to 103

in 2010.

CONCLUSION:

Data collection on the drug(s) used in individuals presenting to specialist clinical toxicology centres and/or sentinel EDs across Europe with acute recreational drug toxicity would help to determine the true pattern(s) of drug use and the acute harm associated with this use across Europe and trends over time.”

Kelly et al. (2014) Is there any evidence of changes in patterns of concurrent drug use among young Australians 18-29 years between 2007 and 2010?⁷⁶

“BACKGROUND:

A significant minority of Australians engage in concurrent drug use (using more than one drug in a given period). We examined clusters and correlates of concurrent drug use using the latest available nationally representative survey data on Australian young adults.

SAMPLE:

3836 participants aged 18-29 years (mean age 24 years) from the 2010 National Drug Strategy Household Survey (NDSHS).

METHOD:

Clusters were distilled using latent class analysis of past year use of alcohol, tobacco, cannabis, cocaine, hallucinogens, ecstasy, ketamine, GHB, inhalants, steroids, barbiturates, meth/amphetamines, heroin, methadone/buprenorphine, other opiates, painkillers and tranquillisers/sleeping pills.

RESULTS:

Concurrent drug use in this sample was best described using a 4-class solution. The majority (87.5%) of young adults predominantly used alcohol only (50.9%) or alcohol and tobacco (36.6%). 10.2% reported using alcohol, tobacco, marijuana, and ecstasy, and 2.3% reported using an extensive range of drugs.

CONCLUSION:

Most drug use clusters were robust in their profile and stable in their prevalence, indicating little meaningful change at the population level from 2007. The targeting of alcohol and tobacco use remains a priority, but openness to experiencing diverse drug-related effects remains a significant concern for 12.5% of young people in this age group.”

Lea et al. Trends in drug use among gay and bisexual men in Sydney, Melbourne and Queensland, Australia.⁵³

“INTRODUCTION AND AIMS:

The findings of Australian drug surveys are typically not stratified by sexual orientation, despite the higher prevalence of drug use generally reported among gay and bisexual men. This paper aims to examine trends in drug use among gay and bisexual men in eastern Australia between 2004 and 2011.

DESIGN AND METHODS:

Data from the cross-sectional, ongoing Gay Community Periodic Surveys (GCPS) were used to analyse drug trends among gay and bisexual men in Sydney, Melbourne and Queensland. Between 2004 and 2011, 45,273 eligible questionnaires were completed.

RESULTS:

There was a downward trend in recent drug use (previous 6 months) between 2004 and 2011 from 62.2% to 57.5%. However, this trend was not found among men in Queensland, bisexual men, men aged over 40 years or HIV-positive men. Club drug use peaked in 2006 (45.1%), before steadily declining to 32.4% in 2011. There were significant reductions in use of ecstasy, methamphetamine, ketamine and cannabis, increased use of cocaine, gamma hydroxybutyrate, erectile dysfunction medications, amyl nitrite and lysergic acid diethylamide, and no change in heroin use. Recent injecting drug use fluctuated over time but experienced an overall downward trend from 5.5% in 2004 to 4.0% in 2011.

DISCUSSION AND CONCLUSIONS:

Drug use trends among gay and bisexual men in Australia are broadly consistent with downward and upward drug trends reported in other Australian drug surveys. The risks associated with drug use in this population and high rates of use supports the ongoing role of the GCPS in monitoring drug trends among homosexually active men.”

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Long-term effects

Van Amsterdam, et al. (2012) [Cognitive impairment due to intensive use and overdoses of gammahydroxybutyric acid (GHB)].³⁰

“In several countries, including the Netherlands, the use of GHB seems to be increasing. Many recreational users of GHB consider the drug to be harmless and to have no serious side effects. In recent years the number of patients with GHB addiction has been increasing steadily.

AIM:

To draw attention to the possible development of neurotoxicity due to chronic and intensive use of GBH.

METHOD:

We reviewed the literature using PubMed.

RESULTS:

Several studies point to an increase in the number of incidents arising from the risky use of GHB or from a GHB overdose. Other drugs, such as ketamine and alcohol, are known to cause neurotoxicity, leading to cognitive impairment. As outlined in this review article, GHB, alcohol and ketamine show clear similarities in their mechanism of action. This suggests that GHB

might have almost the same neurotoxic effects as ketamine and alcohol. An overdose of GHB, just like binge-drinking and a high dose of ketamine, may lead to a coma that probably harms the brain, particularly if comas occur repeatedly.

CONCLUSION:

The risk of neurotoxicity is likely to increase with chronic, intensive use of GHB, which is a feature of GHB-addiction. We therefore advocate research into the possible toxic effects of GHB in the long term, involving, for instance, the study of lasting effects on the cognitive functions of GHB users and former users.”

Accidents or potential accidents

***Benotsch, et al. (2015) Driving under the influence of prescription drugs used nonmedically: associations in a young adult sample.*⁷⁰**

“BACKGROUND:

Over the past 20 years, there has been a dramatic increase in the nonmedical use of prescription drugs (NMUPD). However, minimal attention has been given to driving under the influence of prescription drugs used nonmedically.

METHODS:

This study examines attitudes and characteristics that might be associated with driving while engaging in NMUPD. College students (N = 763) aged 18-25 years completed online surveys assessing demographic information, NMUPD, recreational use of other drugs, psychological variables, attitudes towards NMUPD and driving, and driving behavior.

RESULTS:

Overall, 28.0% of participants reported lifetime NMUPD; 12.2% reported ever driving while engaging in NMUPD; and 7.9% reported this behavior in the past 3 months. Participants who reported engaging in NMUPD while driving were significantly more likely to report the use of alcohol, marijuana, ecstasy, cocaine, methamphetamine, ketamine, GHB (γ-hydroxybutyric acid), rohypnol, and mephedrone. These participants also scored higher on measures of hopelessness, impulsivity, and sensation seeking. Individuals who engaged in NMUPD while driving also reported lower perceptions of the risks of this behavior and believed that NMUPD is more common in young adults.

CONCLUSIONS:

A significant percentage of college students engage in driving under the influence of prescription drugs. Public health interventions designed to increase driving safety may wish to focus attention on this type of drugged driving.”

***Delaveris, et al. (2014) Non-natural manners of death among users of illicit drugs: Substance findings.*⁷⁷**

“The aim of the study was to explore differences and similarities between the various non-natural manners of death (accident, suicide, homicide) regarding toxicological findings in illicit drug users. Medicolegal autopsy reports from the Institute of Forensic Medicine University of Oslo concerning deaths from 2000 to 2009 were investigated. Those aged 20-59 whose manner of death was non-natural and who tested positive for any narcotic drug (morphine/heroin, amphetamines, ecstasy, cannabis, LSD, PCP, and high levels of GHB in addition to methadone and buprenorphine) were selected. All substance findings were registered and categorized (narcotics, ethanol, and medicinal products). Of the 1603 autopsies that met the selection criteria, 1204 were accidental intoxications, 122 accidents other than intoxication, 114 suicides by intoxication, 119 non-intoxication suicides, and 44 victims of homicide. Poly drug use was found in all manners of death. The drug profile as well as the mean number of substances (illicit drugs and medicinal products) varied from 2.9 to 4.6 substances per case, depending on the manner of death. Intoxication suicides had the highest number of substances and a total drug profile similar to accidental intoxications. Non-intoxication suicides had a total drug profile similar to homicide and accidents other than intoxication. The number of substances found per case increased during the decade, mainly due to increased findings of methadone, cannabis, amphetamines, and benzodiazepines. Methadone findings increased much more than buprenorphine. Methadone was found 20 times more often than buprenorphine in accidental intoxication cases. In summary, poly drug findings are common in adults who suffer a non-natural death while using illicit drugs. The different manners of death have some specific characteristics and significant differences regarding drug profile.”

Different forms of GHB

***Van Amsterdam et al. (2014) Risk assessment of GBL as a substitute for the illicit drug GHB in the Netherlands. A comparison of the risks of GBL versus GHB.*⁷⁸**

“In the Netherlands, γ-hydroxybutyric acid (GHB) was recently banned, but γ-butyrolactone (GBL) was not. As such, GBL remained a legal alternative to GHB. This review compares the risks of GBL and GHB. Pure GBL is per unit of volume about threefold stronger and therefore threefold more potent than currently used GHB-preparations in the Netherlands. Like GHB, GBL use hardly leads to organ toxicity, although, as with GHB, frequent GBL use may lead to repeated comas that may result in residual impairments in cognitive function and memory. Little is known about the prevalence of GBL use in Europe, but the recent increase in improper trading in GBL confirms that users of GHB gradually switch to the use of GBL. This shift may result in an increase in the number GBL dependent users, because the dependence potential of GBL is as great as that of GHB. Severe withdrawal symptoms and a high relapse rate are seen following cessation of heavy GBL use. GBL-dependent users seem to be severe (dependent, problematic) GHB users who started using GBL, the legal GHB substitute. Subjects who are solely dependent to GBL are rarely reported. About 5-10% of the treatment seeking GHB dependent subjects also use GBL and this subpopulation forms a vulnerable group with multiple problems. Fatal accidents with GBL are rarely reported, but non-fatal GHB (or GBL) overdoses frequently occur for which supportive treatment is needed. It is recommended to monitor the recreational use of GBL, the rate of GBL dependence treatment, and the improper trading of GBL.”

Appendix 4 – Utah Poison Control Center

Utah Poison Control Center

Xyrem and GHB exposures

January 1, 2011 – April 30, 2016

The Utah Poison Control Center (UPCC) was consulted on the management of 35 cases involving sodium oxybate (Xyrem®) or GHB between January 1, 2011 and April 30, 2016. This reports summarizes the 35 cases. Note: GHB was included with sodium oxybate (Xyrem®) because it is not known if the illicit GHB was actually diverted sodium oxybate (Xyrem®).

Year	Sodium Oxybate	GHB	Total
2011	5	9	14
2012	2	8	10
2013	1	1	2
2014	3	0	3
2015	3	1	4
2016	1	1	2
Total	15	20	35

I. Sodium Oxybate (Xyrem®)

A. Reason for exposure

- 6/15: therapeutic error/misuse –taking both doses at the same time or too close together
- 4/15: adverse reaction – patient experienced an untoward reaction from the medication
- 2/15: unintentional general – pediatric patients orally exploring their environment who got into the medication that belonged to someone in the household
- 1/15: used to get high
- 1/15: unknown
- 1/15: attempted suicide
- This was the patients medication in all but the 2 pediatric cases

- B. Age and Gender
 - Age ranged from 2-66 years
 - 11/13 cases where it was the patient's medication were women
- C. Caller, Exposure and Management Site
 - 9/15 cases involving sodium oxybate originated from a health care facility
 - 5/9 were treated and released from the emergency department (ED)
 - 3/9 were admitted to an intensive care unit
 - 1/9 was admitted to a non-critical care unit
 - In 6/15 the UPCC was contacted from someone at the residence
 - 5/6 were referred to a health care facility for evaluation
 - 1 was treated and released from the ED
 - 1 was admitted to a critical care unit
 - 3 refused the referral
- D. Medical Outcome
 - 2/15 resulted in a major outcome. A major outcome is defined as a life-threatening exposure that required a life-saving intervention
 - 6/15 resulted in a moderate outcome
 - 5/15 resulted in a minor outcome
 - 2/15 resulted in no effect or the exposure was deemed unlikely to result in an effect

II. GHB

- A. Reason for exposure
 - 10/20: individual reported to use GHB for illicit benefit
 - 1/20: therapeutic error – drank inadvertently; thought it was water
 - 5/20: suspected they had been drugged by GHB
 - 1/20: attempted suicide with GHB
 - 1/20: experiencing withdrawal from GHB
 - 2/20: unknown reason
- B. Age and Gender
 - Age ranged from 16-42 years
 - Overall 11/20 reporting GHB as substance were men
 - 50% of those illicitly using GHB were men
 - 3/5 reporting they were drugged by GHB were women

- C. Caller, Exposure and Management Site
 - 11/20 cases involving GHB originated from a healthcare facility
 - 7/11 were treated and released from emergency department (ED)
 - 3/11 were required admission to an intensive care unit for monitoring and treatment
 - 1/11 was admitted to a non-critical care unit
 - In 9/20 cases the UPCC was contacted from someone at the residence
 - 6/9 were referred to a health care facility for evaluation
 - 2/6 were treated and released from ED
 - Remaining 4 refused referral
 - 2/9 were managed onsite as all symptoms had resolved at the time of the call
 - Management site was unknown in one case
 - Site of exposure was residence in 17/20; a public area in 1 and unknown in 2

- D. Medical Outcome
 - 5/20 cases resulted in a major outcome. 8/20 cases resulted in a moderate outcome.
 - 4/20 cases resulted in a minor outcome
 - 3/20 were lost to follow-up and outcome was unknown but felt to be potentially toxic

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