



Pharmacological Treatment of GHB Withdrawal Syndrome

Laurent Karila¹ · Bernard Angerville^{1,2} · Amine Benyamina¹ · Joël Billieux^{3,4}

Accepted: 26 November 2023 / Published online: 26 January 2024
© The Author(s) 2024

Abstract

Purpose of Review Gamma-hydroxybutyrate (GHB) is an illicit drug used for many reasons: during music festivals or parties, for self-management of sleep and anxiety, or in combination with other drugs to facilitate chemsex. Most people who use GHB do so occasionally, without harm. However, a minority of users experience dependence or withdrawal symptoms. GHB withdrawal syndrome often has a specific course, with rapid onset and swift progression of severe complications. In this narrative review, we aimed to summarize recent evidence related to the pharmacological treatment of GHB withdrawal syndrome.

Recent Findings The management of GHB withdrawal syndrome is challenging due to the lack of specific evaluation tools and pharmacological treatment guidelines. From current findings, two pharmacological regimens could be considered for inpatients and outpatients with GHB dependence during detoxification: benzodiazepines and pharmaceutical GHB.

Summary Few detoxification protocols for GHB or its analogs have been reported in the literature. The main available evidence is based on case studies and uncontrolled open-label studies, which support the efficacy of pharmacological interventions, notably high-dose benzodiazepines and titration and tapering with pharmaceutical GHB, for the management of GHB withdrawal. Barbiturates such as phenobarbital and baclofen might also represent new therapeutic options. Future research should examine these pharmacological interventions with large-scale randomized trials, withdrawal scales, or validated treatment protocols.

Keywords Gamma-hydroxybutyrate · GHB · Dependence · Withdrawal syndrome · Delirium · Pharmacological treatment

Introduction

Gamma-hydroxybutyrate (GHB) was first synthesized in 1874 by the chemist Aleksandr Mikhaïlovitch Zaytsevin. In 1961, Henry Laborit synthesized GHB again in the context of his research on the gamma-aminobutyric acid (GABA) neurotransmitter. In 1963, Samuel P. Bessman and William

N. Fishbein discovered that GHB is naturally present in the brain, albeit in low concentration [1].

GHB and its chemical analogs, gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD), were labeled in the 1980s as dietary supplements purported to enhance muscle growth and aid sleep. GHB and its chemical analogs are typically used for the self-management of sleep and anxiety, as well as to facilitate chemsex, in combination with other drugs, in order to improve sexual performance. GHB was mainly misused in the 1980s, however, for its body building effects and in the 1990s as a recreational drug at electronic dance music venues. At that time, GHB was spotlighted in the general media for being related to sexual aggression and renamed the “date rape drug” [2]. Recently, the #BalanceTonBar movement, launched in Belgium, has gained momentum in France and more globally in Europe. Under this hashtag were collected many testimonies of persons who were raped after having consumed drinks containing GHB in bars, in clubs, or at student parties. Victims of GHB-related sexual aggression mostly described states of relaxation, euphoria, and sociability associated with a perceived feeling

✉ Joël Billieux
joel.billieux@unil.ch

¹ Centre d’Enseignement, de Recherche Et de Traitement Des Addictions, Hôpital Universitaire Paul Brousse (AP-HP), Université Paris Saclay, UR PSYCOMADD, Villejuif, France

² EPS Barthélemy Durand, Étampes, France

³ Institute of Psychology, University of Lausanne, Lausanne, Switzerland

⁴ Center for Excessive Gambling, Addiction Medicine, Lausanne University Hospital (CHUV), Lausanne, Switzerland

of abolished discernment, drowsiness, and amnesia. GHB and its chemical analogs have many street names, including “G” or “liquid ecstasy” [3, 4].

There are relatively few data about GHB use in nationally representative samples of adults and adolescents. A recent study conducted on a non-institutionalized sample of 241,675 US adults between 2015 and 2020 reported an estimated prevalence of GHB use during the last year of 0.05% [5]. The European Drug Emergencies Network reported that GHB was the fifth most frequently reported drug by health services in 2019, that it was found in 10.6% of acute drug toxicity cases, and that it was identified in 27% of intensive care admissions. In the same year, large seizures of GHB/GBL were reported by 18 European countries, amounting to 48 tons and 500 L [6]. Because of the extensive use of GBL for industrial purposes, these data are difficult to interpret. In 2019, the dismantling of nine laboratories involved in the production of GHB from GBL was reported by the Netherlands and Germany, and production sites have also been detected in Belgium and Estonia [6, 7].

GHB exists in liquid or powder form. Odorless, colorless, bitter in taste, GHB is usually taken with water mixed with syrup or fruit juice. When used as a recreational drug, GBL is a colorless viscous liquid. It is an acidic chemical, used in industry as a solvent or stripper for paints, or even as a cleaner for parquet floors. It is mostly ingested orally from small bottles, with intranasal or intravenous routes less frequently used [8]. One milliliter of liquid GHB is the common dosage and contains approximately 1 g of GHB. The GHB/GBL dose is often measured by users in imprecise capfuls, teaspoons, eye droppers, or vials. This imprecise dose measurement is generally considered to be one of the main causes of acute GHB/GBL-related harms [8, 9].

Classified as a narcotic since 1999, GHB was added in March 2001 to Schedule IV of the United Nations Convention on Psychotropic Substances. The member states of the European Union then had to monitor and control the use of this drug, implying that the GHB market, which was until then open, became restricted and that GHB was no longer legally available for sale. It has also become very difficult to obtain GHB from the Internet since it was banned at the international level. Yet, this is not the case for GBL, which remains in use as an industrial solvent [6, 7]. It is also worth noting that two pharmacological agents contain GHB: gamma-OH, used in general anesthesia, and sodium oxybate (Xyrem), indicated in the treatment of narcolepsy [10, 11]. From 2006 onward, the misuse of GBL gradually replaced that of GHB. Between 2005 and 2011, more than 200 cases of GBL poisoning were identified in France by the toxicovigilance and addictovigilance networks [9]. At present, GBL is not classified as a narcotic; however,

France decided in 2011 to prohibit its sale and its transfer to the public [9].

Because GHB/GBL is generally used for the first time in young adulthood, most users are likely to have already tried other psychoactive substances before experimenting with GHB/GBL [12]. Psychotropic effects of GHB are comparable with those of alcohol or benzodiazepines [11]. These effects usually occur 15 min after ingestion and can last approximately 3 to 4 h. For GBL, it occurs more quickly, in 15–20 min and lasts about 1–2 h [2].

A 0.5-g dose of GHB is generally taken for relaxation and disinhibition, a 1-g dose for euphoric and some stimulant-like effects, and a 2- or 3-g dose for deep lethargy and sleep. Beyond 4 g, the use involves a deep coma and a risk of overdose (“G-hole”). This deep unresponsive coma is associated with a decreased HR, hypothermia, vomiting, respiratory distress, and neurological symptoms [13, 14]. Somatic, psychiatric, and social complications associated with chronic use of GHB/GBL have also been documented [1]. Moreover, these drugs worsen the sedative effects of other drugs such as alcohol and benzodiazepines. Cases of death have mainly been described following polyintoxication involving other substances [15, 16]. In addition to its sedative effects, GHB decreases the efficiency of self-control, thus increasing the risks of being the victim of sexual aggression and promoting risky sexual behaviors in general (e.g., unprotected sex) [17]. Regular GHB consumption can also be associated with an addictive usage pattern in which the withdrawal syndrome can be complicated by delirium [18]. In recent years, these clinical situations have been increasingly reported in outpatient medical consultation and can constitute reasons for hospitalization [7].

To our knowledge, no randomized clinical trials have to date been conducted to identify the best pharmacological treatment for GHB withdrawal or delirium. The evidence base supporting medication management of withdrawal is limited and for the most part consists of case reports, case series, or open-label studies.

Here, we aim to provide in a narrative format an update on the data on GHB withdrawal treatment, including recent findings, as the only available review on this topic was published in 2004 [19]. To achieve these objectives, a literature search was conducted on PubMed and Google Scholar with a timeframe between January 2012 and October 2023. The search was limited to articles in English or French (the languages known by the present authors). Notwithstanding the literature search identified a research letter published in Norwegian that we translated given its relevance. Search terms used included the keywords “GHB,” “gamma-hydroxybutyrate,” “GBL,” “gamma-butyrolactone,” “1,4-BD,” and “1,4-butanediol” combined with the keywords “use,” “dependence,” “addiction,” “harms,” “withdrawal,” “delirium,” and “treatment.” Reference lists of relevant

articles were also searched to identify additional potentially relevant articles. Evidence gathered through this literature was synthesized by the authors and reported here from a narrative review perspective. In the next sections, we briefly describe the pharmacology of GHB/GBL and review the evidence regarding GHB/GBL withdrawal syndrome. To address the growing demand of practitioners confronted with GHB/GBL withdrawal syndrome, we then synthesize the existing data concerning available pharmacological treatments.

Pharmacology

GHB is an endogenous short-chain fatty acid present in the central nervous system (CNS) [20]. It is synthesized from GABA, a major inhibitory neurotransmitter in the CNS, which originates from glutamate [11]. GHB is also found in peripheral tissues and other organs (heart, kidneys, muscle, brown fat) [21]. It binds to at least two distinct populations of sites in the brain. The physiological effects of GHB are mediated through binding to its GHB-specific receptor and to a subset GABA-A receptor. GHB acts as a neuromodulator in the brain at endogenous concentrations [22]. At physiological concentrations, it is thought to activate GHB and the GABA-A receptors but not the GABA-B receptors. The behavioral, pharmacological, and toxicological effects of GHB are attributed to its action on GABA-B receptors. Clinical effects of GHB may be mediated through modulation of a mixed GABA/GHB receptor mechanism of action in vivo and the GABA inhibitory neurotransmission system [23]. GHB, at high or low doses, affects the release of neurotransmitters in the brain (GABA, glutamate, dopamine, serotonin, opioids), which may contribute to its effect. It is in part metabolized to GABA via GABA transaminase. GBL and 1,4-BD are rapidly metabolized to GHB [11]. GBL can be converted to GHB prior to ingestion via lactonases. 1,4-BD is converted to 4-hydroxybutyraldehyde via alcohol dehydrogenase (ADH), which is subsequently converted to GHB via ADH. In the case of concomitant alcohol use, ADH can be saturated, delaying the transformation of 1,4-BD and the toxicity of GHB. GHB is rapidly absorbed, metabolized, and eliminated with a plasma half-life of 27 min. It is undetectable in the plasma after 6 h and in urine after approximately 12 h. GHB easily crosses the blood–brain barrier, and monocarboxylate transporters may facilitate that process. Hepatic metabolism is likely the primary route of metabolism for exogenous GHB with less than 2% excreted unchanged in urine. Discontinuation of the use of GHB results in unopposed excitatory neurotransmission due to decreased GABA- and GHB-mediated neuroinhibition, which results in withdrawal syndrome [24]. The addictive properties of GHB likely depend on its differential actions

on dopaminergic and GABA-B neurons. It is thus difficult to differentiate exogenous and endogenous GHB effects. To detect exogenous GHB, a threshold commonly used for samples taken from patients is 5 mg/mL in blood and 10 mg/L in urine. Screening for GHB in human samples can be difficult due to the lack of chemical stability of GHB, and its concentration can increase with time after sampling [11].

GHB Acute Toxicity and Withdrawal Syndrome

Acute Toxicity

GHB intoxication is difficult to diagnose, as it is not detected by routine urine drug testing. Thus, treatment is often guided by patient history and clinical presentation [25].

GHB users are at risk of acute toxicity and overdose. Toxicity is dose dependent. Mild effects include nausea, hyper-salivation, vomiting, diarrhea, drowsiness, headache, ataxia, dizziness, confusion, amnesia, urinary incontinence, tremor, myoclonus, hypotonia, agitation, euphoria, and hypothermia [26]. Severe effects include coma, convulsions, bradycardia, abnormal electrocardiogram results, hypotension, and bradypnea, often accompanied by type 2 respiratory failure [8]. At doses over 60 mg/kg, coma and respiratory depression can occur [27•]. Hyponatremia, hypokalemia, hyperglycemia, and metabolic acidosis have also been reported [8].

Tolerance is not necessarily a protective factor for overdose (G-hole). Overdose typically occurs when large concentrations are used over a short period or when GHB/GBL is used in combination with other drugs, such as alcohol or benzodiazepines. Harm often results from imprecise dosing of illicit GHB/GBL, which cannot be easily measured [28]. Risk factors for overdose include higher levels of GHB use, polysubstance use, and being male. CNS depression usually persists for 1 to 3 h, with patients typically being completely recovered within 4 to 8 h. Death generally results from medical complications such as aspiration, asphyxia, or pulmonary edema, or from intoxication-related accidents [26].

GHB Withdrawal Syndrome

GHB withdrawal syndrome (GWS) can occur after withdrawal from GHB or its analogs and is comparable to other withdrawal syndromes, especially those encountered with alcohol and benzodiazepines. Because of the limited time of GHB action and its rapid elimination, GWS often has a fulminant course, with rapid onset (1 to 6 h after the last use) and swift progression to severe withdrawal symptoms [29]. Fast oral absorption of GHB and a half-life of 20–30 min likely explains why regular users typically use the drug every 1 to 4 h to prevent the onset of withdrawal [30]. GHB

withdrawal can last from 3–5 to 14–21 days (9 days on average). The predictors of GHB withdrawal include the amount and frequency of use (i.e., > 4 mL of GBL on a daily basis or GBL use > 6 times daily every day or using GHB/GBL > 4 times per day during 2–4 weeks in higher doses [31], or a daily minimum GHB dose being 18 g and 10 g for GBL [19]), previous withdrawal(s) syndrome(s) [32] and poly-drug use [33]. The median time for chronic GHB users to experience withdrawal syndrome is 18 months [34]. Most individuals with GWS have been taking GHB and/or its analogs for less than 2 years, the first manifestations appearing as early as 8–13 weeks into their use [14]. Withdrawal symptoms in the context of GHB thus appear much sooner than do withdrawal symptoms in the context of alcohol use [34].

Early symptoms of GHB/GBL withdrawal include insomnia, tremors, confusion, nausea, and vomiting. Over the next 12 to 48 h, other symptoms include tachycardia, hypertension, agitation, convulsions and/or myoclonic jerks, and visual or auditory hallucinations [26]. Disorientation and paranoia are also described [31]. The more severe GHB withdrawal symptoms resolve within 2 weeks, but as with other sedative agents, insomnia, anxiety, and mood disruption may persist for some time after the end of an acute episode [8].

A major adverse event occurring in certain cases of GWS consists of acute delirium comparable to what happens in the context of severe alcohol withdrawal [34]. Yet, the prevalence in GHB withdrawal is up to 12% higher than it is in alcohol withdrawal (about 5%) [34]. Risk factors for such delirium are not well identified but include a pattern of consumption of GHB every 8 h or less [35]. Symptoms associated with delirium episodes include generalized tremors, tachycardia, polypnea, sweats, agitation, anxiety, visual hallucinations, paranoid ideas, and confusion [36]. A recent study found that co-use of stimulants can cause an add-on effect on GHB withdrawal manifestations, including more intense and prolonged muscle twitching, agitation, and restlessness [37].

Management of Withdrawal from GHB and Its Analogs

Since the first case of GWS reported in the medical literature in the mid-nineties, there has been uncertainty about the most effective pharmacotherapy to manage this life-threatening condition [30]. No formal detoxification protocols exist for GHB or its analogs. The available evidence is based on case studies and uncontrolled open-label studies. Similarities to alcohol or benzodiazepine withdrawal syndrome tend to call for a comparable treatment approach.

First-line pharmacological treatment is the use of a high-dose long-acting benzodiazepine such as diazepam [38, 39]. However, high-dose benzodiazepines are not always sufficient to manage GHB withdrawal [40–42]. In the case

of benzodiazepine resistance, barbiturates such as phenobarbital [43], propofol [24], and baclofen [40] can be considered. Antipsychotics such as quetiapine, olanzapine, or haloperidol can be considered when delusional symptoms are observed [29, 44]. Although not legally possible in all countries, immediate-release pharmaceutical GHB may be used to manage withdrawal symptoms [45•]. The management of severe GHB withdrawal is more complicated than it is for alcohol withdrawal because of the higher risk of delirium and the higher doses of medication needed [46]. Detoxification approaches combining fixed dosing and a symptom-triggered dosing regimen have been proposed [34].

To the authors' knowledge, there is no validated assessment instrument to measure GHB withdrawal symptoms. Yet, given the similarities to alcohol withdrawal symptoms, scales such as the Clinical Institute Withdrawal Assessment-Alcohol revised could be used in the context of GHB withdrawal [34], as this scale has proven useful in guiding benzodiazepine dosing of alcohol withdrawal for decades [47]. The Subjective and Objective Withdrawal Scale was also developed on the basis of a scale used in the context of opioid withdrawal [48].

Benzodiazepines

From a review of available evidence, McDonough and colleagues conducted the first review of all published clinical studies to evaluate the clinical course of GHB withdrawal and its treatment with a view to propose practical management guidelines. They proposed treatment and dosage that depends on the amount taken and frequency per day of GHB and/or its analogs [19]. The following recommendations were proposed by these authors:

- If there are less than three regular doses of GHB or less than 30 g GHB or 15 g GBL, outpatient treatment is recommended with diazepam 20–40 mg/day for 7 days with medical supervision (blood pressure (BP) and heart rate (HR)).
- If there are three regular doses of GHB or more than 30 g/day GHB or 15 g/day GBL or medical complications, hospitalization is recommended for therapeutic withdrawal.
- If there is no delirium, diazepam 80–150 mg/day can be prescribed for 7 days.
- If delirium is present, for first-line treatment, a medical cause/complication must be investigated and excluded. A high dose of diazepam 150–200 mg/day can be prescribed.
- If there is benzodiazepine resistance after 24 h, phenobarbital must be added while the patient is in the intensive care unit.

Beurmanjer and colleagues proposed to adjust the treatment (using diazepam or lorazepam) based on vital parameters in case of severe liver damage [45•]. In this case, vital parameters are first measured every 30 min. If BP is > 140/90 mmHg and/or HR is > 100 bpm, diazepam 10 mg or lorazepam 2.5 mg can be prescribed. If there is an increase in systolic or diastolic BP of > 20 mmHg and/or an increase in HR of 20 bpm, diazepam must be increased by 20 mg or lorazepam by 5 mg. Benzodiazepine doses can be adjusted every 30 min for BP < 140/90 mmHg and HR < 100 bpm. Vital parameters must be monitored every 30 min for the first 48 h, and then every 3–4 h until withdrawal treatment is completed. Unfortunately, this protocol provides no information regarding previous medical conditions that may have influenced standard vital parameters, such as idiopathic hypertension. As close monitoring is required, it is recommended that this protocol is implemented in the context of a hospitalization. Of note, Craig et al. reported a case that required an equivalent total dose of 2655 mg of diazepam over the course of almost 4 days of GHB detoxification [49].

Pharmaceutical GHB

Pharmaceutical GHB is characterized by the same pharmacological properties as street GHB but is characterized by a milder withdrawal syndrome. It was, for example, reported that delirium occurs in 20% of cases during withdrawal from street GHB managed with benzodiazepines versus 2.5% for withdrawal from the consumption of pharmaceutical GHB. There are fewer side effects with pharmaceutical GHB [45•].

In some countries (e.g., France or Belgium), physicians cannot prescribe pharmaceutical GHB in the context of GHB withdrawal, and benzodiazepines are generally considered the gold standard treatment. In the Netherlands, GHB titration and tapering has acceptance as first-line therapy for GHB withdrawal [45•].

GHB-assisted tapering requires up to 12 doses, every 2 h per day. It leads to a high success rate of 85%, and more limited adverse events have been reported during detoxification (mainly hypertension and, for a small percentage of patients, delirium) [45•]. A disadvantage of GHB tapering is its shorter half-life, requiring GHB administration throughout the night, which interferes with sleep [44, 45•, 50].

An open-label study that included 23 GHB-dependent inpatients has shown that this treatment is feasible, efficient, and secure [51]. De Jong and colleagues also proposed treatment guidelines based on a large naturalistic study in treatment-seeking GHB users, including 274 patients who had followed a pharmaceutical GHB treatment protocol [52]. A case series of 229 patients indicated completion rates in acute withdrawal management of up to 85% [44]. A cohort study comparing pharmaceutical GHB to diazepam showed that GHB was superior in reducing delirium and

severity of withdrawal. In this multicenter, nonrandomized, indirect comparison of two treatments as usual, withdrawal decreased over time in both groups. Withdrawal severity was higher in patients who received benzodiazepine tapering than in patients who received pharmaceutical GHB tapering. No difference in GHB craving levels was found during withdrawal with tapering of pharmaceutical GHB versus benzodiazepines [45•]. Optimization of the duration of detoxification and whether some patients could profit more from one method or the other should be evaluated in future studies. From the reviewed evidence, it appears that benzodiazepine tapering is efficient to counteract GHB withdrawal in patients with relatively low levels of GHB use. However, pharmaceutical GHB appears to be the preferred treatment approach in patients using high levels of GHB.

Baclofen

Preclinical evidence supports the potential of baclofen, an anti-spasticity agent and a muscle relaxant, for the management of GHB withdrawal [53]. This GABA-B receptor agonist, with its longer half-life than GHB, could be a relevant alternative for benzodiazepine and/or GHB tapering in the context of GHB withdrawal [54]. Although there is limited research related to the use of baclofen in the treatment of GHB withdrawal, initial evidence (including data retrieved from gray literature) suggests its potential relevance and clinical utility [39, 55].

Despite a low level of evidence, UK medical guidelines have included a recommendation to initiate GHB withdrawal management with baclofen and diazepam [26]. This use for the management of GHB/GBL withdrawal is off label, but for other indications, the British National Formulary recommended a starting dose of 5 mg with titration to a maximum daily dose of 100 mg in 2017 [55]. It was suggested that baclofen tapering might prevent withdrawal and allow patients to abstain from using GHB with only three to four daily dosages [26]. Doses greater than 200 mg are associated with a reduced level of consciousness, hypotonia, and respiratory depression, with death previously reported after ingestion of 1.25–2.5 g baclofen [56]. Baclofen has also been proposed as an adjunct to benzodiazepines in the treatment of GHB withdrawal [40, 57]. LeTourneau and colleagues described the case of a 61-year-old patient with GHB withdrawal who experienced witnessed seizures despite treatment with lorazepam combined with pharmaceutical GHB, whose symptoms improved within hours of administration of 20 mg of baclofen [40].

Treatment with baclofen has been reported in several case studies, which emphasized better efficacy compared to the standard use of benzodiazepines [58, 59]. Baclofen's targeted GABA-B activity proved efficacious in reversing specific withdrawal-related symptoms such as somnolence and aggression [59]. However,

baclofen-based treatment approaches to GHB withdrawal have to date not been largely adopted in clinical practice, and when they are, generally require additional advice from an addiction specialist [57, 60, 61].

GHB targets the GABA-B receptor and downregulates it when the drug is abused. Most anesthetic agents affect the GABA-A receptor. A case report of severe delirium following GHB abuse has prompted the claim that baclofen could reduce the need for anesthetic agents and facilitate recovery [62]. Successful management of GHB withdrawal by using baclofen as standalone therapy has been reported in a 26-year-old woman [58]. The treatment protocol was as follows: She received 130 mg each day with a subsequent dose reduction to 90 mg daily on days 3 and 4. She then reported being very comfortable, and her symptoms were completely resolved with no objective signs of GHB withdrawal. Therefore, the care team decided to taper baclofen on day 5 to 40 mg, day 6 to 30 mg, and day 7 to 20 mg. No diazepam or phenobarbital was necessary at any time during hospitalization. No significant baclofen side effects were observed, and only mild drowsiness was reported. The detoxification process was completed over 7 days with no prescription for baclofen [58]. Another case report of GHB intoxication in a 57-year-old man, which resulted in an 11-day hospitalization due to GWS, showed that baclofen was successfully used to facilitate patient sedation reversal [59].

Baclofen has been suggested as a potential candidate for GHB substitution therapy and suggested to constitute relapse prevention in the treatment of GHB use disorder [60, 61]. A case series of patients who were supported through an off-label treatment with baclofen (doses ranging from 30 to 60 mg per day) for a period of 12 weeks to avoid a relapse into GHB abuse suggests that baclofen was well tolerated, although mild side effects such as fatigue, nausea, dry mouth, excessive sweating, and depressive feelings were reported [63].

In an outpatient, multicenter, open-label, nonrandomized, controlled trial in patients with GHB use disorder conducted in the Netherlands, the patients treated with baclofen after detoxification showed no reduced lapse rates, but reduced relapse and dropout rates, compared with patients receiving treatment as usual only [60].

Further controlled studies are necessary to establish the exact efficacy and safety of baclofen as a relapse prevention approach in GHB use disorder [63]. Despite this, online pharmacies are readily offering prescription-only medication without an actual prescription due to inadequate regulation, which is a dangerous practice [64].

Other Treatments

Because of the challenges in managing GHB withdrawal, other medications have been commonly used in conjunction

with or substituted for benzodiazepines, including anticonvulsants, valproic acid, carbamazepine, and gabapentin [41, 65].

Patients who are poorly responsive to benzodiazepines can be tested with barbiturates, which also act on GABA-A receptors. Recent studies have found that GBL and its analogs possess a high affinity for a specific form of extrasynaptic GABA-A receptors that are strongly activated by barbiturates, such as phenobarbital, but are insensitive to benzodiazepines [66]. Administration of benzodiazepines and phenobarbital successfully treated withdrawal symptoms in a case report [67].

Patients with GWS who have clinical signs of neuroleptic malignant syndrome can be treated with dantrolene because it regulates the distorted calcium secretion and affects the serotonin and cholinergic system [68]. A published case study suggests barbiturate coma therapy might be considered in the case of severe GHB withdrawal not responding to conventional treatment [69]. Sedative-hypnotic drugs can be continued and tapered gradually for several weeks after acute withdrawal syndrome resolves. Pharmacological agents such as clonazepam or phenobarbital may be preferable during this stage to decrease the likelihood of interdose symptoms of a prolonged withdrawal syndrome [70].

One case series suggested that phenobarbital is safe for the management of benzodiazepine-resistant GHB withdrawal, even in general inpatient settings, and may avert the progression of delirium [71]. Another case series suggested that for patients demonstrating severe withdrawal, resistant to benzodiazepines, the treatment of choice is pentobarbital titrated to sedation and normalization of vital signs [43]. Prospective trials are, however, needed to establish an evidence base for such treatment approaches, including a validated assessment measure of withdrawal severity and more information related to the safe and effective dosing of phenobarbital.

Conclusion

GHB and its precursors GBL and 1,4-BD are used for many reasons, including self-management of sleep and anxiety and in combination with other drugs to facilitate chemsex. There is growing evidence of GHB-related adverse effects among people who use GHB on a regular basis. Harms associated with the consumption of GHB, including severe withdrawal syndrome, delirium, overdose, and addictive use, are increasing worldwide. Case studies and reviews describe similarities between withdrawal symptoms for GHB and those for alcohol or benzodiazepines. Inpatient medical management of GHB withdrawal may be warranted for people who regularly use high amounts. Outpatient withdrawal management has also been documented.

To date, there are no formal detoxification protocols for GHB or its analogs. The main available evidence is based on case studies and uncontrolled open-label studies. Pharmacological interventions for the management of GHB withdrawal include high-dose benzodiazepines, titration and tapering with pharmaceutical GHB (not available in many countries), barbiturates such as phenobarbital, and baclofen. Future research should examine these interventions with large-scale randomized trials, withdrawal scales, or validated treatment protocols.

Funding Open access funding provided by University of Lausanne

Declarations

Joël Billieux is editorial board member and section editor (Internet Use Disorders) for *Current Addiction Reports*. Please note, however, that he was not involved at any stage during the editorial process.

Conflict of Interest Laurent Karila has given talks and received honoraria from Ethypharm and Zentiva laboratories. Amine Benyamina has received honoraria from Indivior and Ethypharm laboratories. Bernard Angerville has no conflict of interest to declare.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by/4.0/>.

References

Papers of particular interest, published recently, have been highlighted as: • Of importance

- Karila L, Reynaud M. GHB and synthetic cathinones: clinical effects and potential consequences. *Drug Test Anal.* 2011;3(9):552–9.
- Karila L, Novarin J, Megarbane B, Cottencin O, Dally S, Lowenstein W, et al. Gamma-hydroxybutyric acid (GHB): more than a date rape drug, a potentially addictive drug. *Presse Med.* 2009;38(10):1526–38.
- Karila L. <https://theconversation.com/drogues-connaissiez-vous-le-gbl-nouvel-agent-de-soumission-chimique-171904>. Last Access May 18th, 2022. 2022.
- Trombley TA, Capstick RA, Lindsley CW. DARK Classics in Chemical Neuroscience: Gamma-Hydroxybutyrate (GHB). *ACS Chem Neurosci.* 2020;11(23):3850–9.
- Palamar JJ. Prevalence and correlates of GHB use among adults in the United States. *J Psychoactive Drugs.* 2022;26:1–6.
- EMCDDA. European Monitoring Centre for Drugs and Drug Addiction (2021), European Drug Report 2021: trends and developments, publications office of the European Union, Luxembourg. 2021. https://www.emcdda.europa.eu/publications/edr/trends-developments/2021_en. Retrieved 29 December 2023.
- EMCDDA. Observatoire européen des drogues et des toxicomanies - Rapport européen sur les drogues 2022: Tendances et évolutions, Office des publications de l'Union européenne, Luxembourg. 2022. https://www.emcdda.europa.eu/publications/edr/trends-developments/2022_en. Retrieved 29 December 2023.
- Tay E, Lo WKW, Murnion B. Current insights on the impact of gamma-hydroxybutyrate (GHB) abuse. *Subst Abuse Rehabil.* 2022;13:13–23.
- Gerome C, Chevallier C. Surdoses de GHB/GBL : mise en perspective et état des lieux des données récentes. http://www.ofdt.fr/BDD/publications/docs/Note_GHB-GBL.pdf Note N° 2018-01 - Saint-Denis, avril 2018. Retrieved 29 December 2023.
- Guiraud J, Addolorato G, Antonelli M, Aubin HJ, de Bejczy A, Benyamina A, et al. Sodium oxybate for the maintenance of abstinence in alcohol-dependent patients: an international, multicenter, randomized, double-blind, placebo-controlled trial. *J Psychopharmacol.* 2022;36(10):1136–45. **This recent study was the first large double-blind, randomized, placebo-controlled trial investigating the efficacy of sodium oxybate for the maintenance of abstinence in detoxified adult alcohol-dependent outpatients. It shows that sodium oxybate had a significant clinical effect on cumulative abstinence duration in alcohol-dependent patients.**
- Felmlee MA, Morse BL, Morris ME. Gamma-hydroxybutyric acid: pharmacokinetics, pharmacodynamics, and toxicology. *AAPS J.* 2021;23(1):22.
- Brunetti P, Umani RF. Recreational use of GHB and prescribed drugs: the challenge in forensic and clinical toxicology. *Clin Ter.* 2021;172(5):423–4.
- Abid M, Kietzerow J, Iwersen-Bergmann S, Schnitgerhans T, Andresen-Streichert H. Characteristics and dose-effect relationship of clinical gamma-hydroxybutyrate intoxication: a case series. *J Forensic Sci.* 2022;67(1):416–27.
- Marinelli E, Beck R, Malvasi A, Lo Faro AF, Zaami S. Gamma-hydroxybutyrate abuse: pharmacology and poisoning and withdrawal management. *Arh Hig Rada Toksikol.* 2020;71(1):19–26.
- Mortali C, Berretta P. GHB concentration in a related post-mortem case. *Clin Ter.* 2020;171(3):e235–6.
- Ferrara SD, Tedeschi L, Frison G, Rossi A. Fatality due to gamma-hydroxybutyric acid (GHB) and heroin intoxication. *J Forensic Sci.* 1995;40(3):501–4.
- Busardo FP, Jones AW. Interpreting gamma-hydroxybutyrate concentrations for clinical and forensic purposes. *Clin Toxicol (Phila).* 2019;57(3):149–63.
- Donnadiou-Rigole H, Peyrière H, Benyamina A, Karila L. Complications related to sexualized drug use: what can we learn from literature? *Front Neurosci.* 2020;14:548704.
- McDonough M, Kennedy N, Glasper A, Bearn J. Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. *Drug Alcohol Depend.* 2004;75(1):3–9.
- Bay T, Eghorn LF, Klein AB, Wellendorph P. GHB receptor targets in the CNS: focus on high-affinity binding sites. *Biochem Pharmacol.* 2014;87(2):220–8.
- Maitre M, Klein C, Mensah-Nyagan AG. Mechanisms for the specific properties of gamma-hydroxybutyrate in brain. *Med Res Rev.* 2016;36(3):363–88.

22. Cash CD. Gamma-hydroxybutyrate: an overview of the pros and cons for it being a neurotransmitter and/or a useful therapeutic agent. *Neurosci Biobehav Rev.* 1994;18(2):291–304.
23. Maitre M, Klein C, Mensah-Nyagan AG. A proposed preventive role for gamma-hydroxybutyrate (Xyrem(R)) in Alzheimer's disease. *Alzheimers Res Ther.* 2016;8(1):37.
24. Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med.* 2001;37(2):147–53.
25. Van Sassenbroeck DK, De Neve N, De Paepe P, Belpaire FM, Verstraete AG, Calle PA, et al. Abrupt awakening phenomenon associated with gamma-hydroxybutyrate use: a case series. *Clin Toxicol (Phila).* 2007;45(5):533–8.
26. Abdulrahim D, Bowden-Jones O. The NEPTUNE Expert Group. Guidance on the management of acute and chronic harms of club drugs and novel psychoactive substances. Novel Psychoactive Treatment UK Network (NEPTUNE). London, 2015. 2015.
27. • Phan V, Arunogiri S, Lubman DI. The assessment and management of gamma hydroxybutyrate use in general practice. *Aust J Gen Pract.* 2020;49(1–2):73–8. **This article describes and highlights the challenges of the assessment and management of individuals with GHB-related harms in general practice. The authors urge clinicians to be aware of the context of use, familiarity with targeted harm-minimization advice, and cognizance of markers of risk indicating onward referral to specialist addiction services when appropriate.**
28. Busardo FP, Jones AW. GHB pharmacology and toxicology: acute intoxication, concentrations in blood and urine in forensic cases and treatment of the withdrawal syndrome. *Curr Neuropharmacol.* 2015;13(1):47–70.
29. Kamal RM, van Noorden MS, Wannet W, Beurmanjer H, Dijkstra BA, Schellekens A. Pharmacological treatment in gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL) dependence: detoxification and relapse prevention. *CNS Drugs.* 2017;31(1):51–64.
30. Galloway GP, Frederick SL, Staggers FE Jr, Gonzales M, Stalcup SA, Smith DE. Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. *Addiction.* 1997;92(1):89–96.
31. Brunt TM, van Amsterdam JG, van den Brink W. GHB, GBL and 1,4-BD addiction. *Curr Pharm Des.* 2014;20(25):4076–85.
32. Delic M. Inpatient management of GHB/GBL withdrawal. *Psychiatr Danub.* 2019;31(Suppl 3):354–6.
33. Bell J, Collins R. Gamma-butyrolactone (GBL) dependence and withdrawal. *Addiction.* 2011;106(2):442–7.
34. Liao PC, Chang HM, Chen LY. Clinical management of gamma-hydroxybutyrate (GHB) withdrawal delirium with CIWA-Ar protocol. *J Formos Med Assoc.* 2018;117(12):1124–7.
35. Wu LT, Schlenger WE, Galvin DM. Concurrent use of methamphetamine, MDMA, LSD, ketamine, GHB, and flunitrazepam among American youths. *Drug Alcohol Depend.* 2006;84(1):102–13.
36. Wolf CJH, Beurmanjer H, Dijkstra BAG, Geerlings AC, Spoelder M, Homberg JR, Schellekens AFA. Characterization of the GHB Withdrawal Syndrome. *J Clin Med.* 2021;10(11):2333.
37. Kamal RM, Dijkstra BA, Loonen AJ, De Jong CA. The effect of co-occurring substance use on gamma-hydroxybutyric acid withdrawal syndrome. *J Addict Med.* 2016;10(4):229–35.
38. Schep LJ, Knudsen K, Slaughter RJ, Vale JA, Megarbane B. The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol. *Clin Toxicol (Phila).* 2012;50(6):458–70.
39. Siefried KJ, Freeman G, Roberts DM, Lindsey R, Rodgers C, Ezard N, Brett J. Inpatient GHB withdrawal management in an inner-city hospital in Sydney, Australia: a retrospective medical record review. *Psychopharmacology (Berl).* 2023;240(1):127–35.
40. LeTourneau JL, Hagg DS, Smith SM. Baclofen and gamma-hydroxybutyrate withdrawal. *Neurocrit Care.* 2008;8(3):430–3.
41. McDaniel CH, Miotto KA. Gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) withdrawal: five case studies. *J Psychoactive Drugs.* 2001;33(2):143–9.
42. Acciani J, Kao L. Severe GHB withdrawal treated with baclofen. *Clin Toxicol.* 2010;48(6):617.
43. Sivilotti ML, Burns MJ, Aaron CK, Greenberg MJ. Pentobarbital for severe gamma-butyrolactone withdrawal. *Ann Emerg Med.* 2001;38(6):660–5.
44. Dijkstra BA, Kamal R, van Noorden MS, de Haan H, Loonen AJ, De Jong CA. Detoxification with titration and tapering in gamma-hydroxybutyrate (GHB) dependent patients: the Dutch GHB monitor project. *Drug Alcohol Depend.* 2017;170:164–73.
45. • Beurmanjer H, Luykx JJ, De Wilde B, van Rompaey K, Buwalda VJA, De Jong CAJ, et al. Tapering with pharmaceutical GHB or benzodiazepines for detoxification in GHB-Dependent patients: a matched-subject observational study of treatment-as-usual in Belgium and The Netherlands. *CNS Drugs.* 2020;34(6):651–9. **This study aimed to compare benzodiazepines or pharmaceutical GHB tapering methods on withdrawal, craving, and adverse events during detoxification in GHB-dependent patients. This multicenter nonrandomized trial shows that tapering with pharmaceutical GHB could be considered for patients with GHB dependence during detoxification, as it has potentially less severe withdrawal and fewer complications than BZD tapering.**
46. Busardo FP, Kyriakou C, Napoletano S, Marinelli E, Zaami S. Clinical applications of sodium oxybate (GHB): from narcolepsy to alcohol withdrawal syndrome. *Eur Rev Med Pharmacol Sci.* 2015;19(23):4654–63.
47. Sullivan J, Sykora K, Schneiderman J, Naranjo C, Sellers E. Assessment of alcohol withdrawal: the revised clinical institute withdrawal assessment for alcohol scale (CIWA-Ar). *Br J Addict.* 1989;84(11):1353e7.
48. Handelsman L, Cochrane KJ, Aronson MJ, Ness R, Rubinstein KJ, Kanof PD. Two new rating scales for opiate withdrawal. *Am J Drug Alcohol Abuse.* 1987;13(3):293–308.
49. Craig K, Gomez HF, McManus JL, Bania TC. Severe gamma-hydroxybutyrate withdrawal: a case report and literature review. *J Emerg Med.* 2000;18(1):65–70.
50. Beurmanjer H, Verbrugge C, Schrijen S, DeJong CD. Treatment of patients with GHB dependence: end report of the GHB Monitor 2.0 [in Dutch]. Nijmegen: NISPA. 2016.
51. de Jong CA, Kamal R, Dijkstra BA, de Haan HA. Gamma-hydroxybutyrate detoxification by titration and tapering. *Eur Addict Res.* 2012;18(1):40–5.
52. de Jong CA, Kamal R, van Noorden M, Broers B. Treatment of GHB withdrawal syndrome: catch 22 or challenge for addiction medicine? *Addiction.* 2013;108(9):1686.
53. Smith M, Gergans S, Lyle M. The motor-impairing effects of GABA(A) and GABA(B) agonists in gamma-hydroxybutyrate (GHB)-treated rats: cross-tolerance to baclofen but not flunitrazepam. *Eur J Pharmacol.* 2006;552:83–9.
54. Vacher CM, Bettler B. GABA(B) receptors as potential therapeutic targets. *Curr Drug Targets CNS Neurol Disord.* 2003;2(4):248–59.
55. Floyd CN, Wood DM, Dargan PI. Baclofen in gamma-hydroxybutyrate withdrawal: patterns of use and online availability. *Eur J Clin Pharmacol.* 2018;74(3):349–56.
56. Leung N, Whyte I, Isbister G. Baclofen overdose: defining the spectrum of toxicity. *Emerg Med Australas.* 2006;18(1):77–82.
57. Lingford-Hughes A, Patel Y, Bowden-Jones O, Crawford MJ, Dargan PI, Gordon F, et al. Improving GHB withdrawal with baclofen: study protocol for a feasibility study for a randomised controlled trial. *Trials.* 2016;17(1):472.

58. Habibian S, Ahamad K, McLean M, Socias ME. Successful management of gamma-hydroxybutyrate (GHB) withdrawal using baclofen as a standalone therapy: a case report. *J Addict Med.* 2019;13(5):415–7.
59. Lai W, Raposa JT, Parlapalli R. Treatment of poorly responsive gamma-hydroxybutyrate withdrawal with baclofen: a case report. *Cureus.* 2022;14(6):e25728.
60. Beurmanjer H, Kamal RM, de Jong CAJ, Dijkstra BAG, Schellekens AFA. Baclofen to prevent relapse in gamma-hydroxybutyrate (GHB)-dependent patients: a multicentre, open-label, non-randomized, controlled trial. *CNS Drugs.* 2018;32(5):437–42.
61. Kamal RM, Schellekens A, De Jong CA, Dijkstra BA. Baclofen as relapse prevention in the treatment of gamma-hydroxybutyrate (GHB) dependence: an open label study. *BMC Psychiatry.* 2015;15:91.
62. Sundal EV, Giil LM. [Severe delirium after GHB abuse]. *Tidsskr Nor Laegeforen.* 2020;140(2). <https://doi.org/10.4045/tidsskr.19.0558>.
63. Kamal RM, Loonen AJ, Dijkstra BA, De Jong CA. Baclofen as relapse prevention in the treatment of gamma-hydroxybutyrate dependence: a case series. *J Clin Psychopharmacol.* 2015;35(3):313–8.
64. Floyd C, Wood D, Dargan P. Baclofen in gamma-hydroxybutyrate withdrawal: patterns of use and online availability. *Eur J Clin Pharmacol.* 2018;74(3):349–56.
65. Schep L, Knudsen K, Slaughter R, Vale J, Megarbane B. The clinical toxicology of gamma-hydroxybutyrate, gamma-butyrolactone and 1,4-butanediol. *Clin Toxicol.* 2012;50:458–70.
66. Ghio L, Cervetti A, Respino M, BelvederiMurri M, Amore M. Management and treatment of gamma butyrolactone withdrawal syndrome: a case report and review. *J Psychiatr Pract.* 2014;20(4):294–300.
67. Schneir AB, Ly BT, Clark RF. A case of withdrawal from the GHB precursors gamma-butyrolactone and 1,4-butanediol. *J Emerg Med.* 2001;21(1):31–3.
68. Röell A, Ramnarain D, Kamal R. Successful treatment of severe gamma-hydroxybutyric acid withdrawal syndrome with dantrolene. *Cureus.* 2021;13(7):e16398.
69. Vos CF, Pop-Purceleanu M, van den Berg MJW, Schellekens AFA. Successful treatment of severe, treatment resistant GHB withdrawal through thiopental-coma. *Subst Abus.* 2021;42(1):33–8.
70. Rosenberg MH, Deerfield LJ, Baruch EM. Two cases of severe gamma-hydroxybutyrate withdrawal delirium on a psychiatric unit: recommendations for management. *Am J Drug Alcohol Abuse.* 2003;29(2):487–96.
71. Freeman G, Siefried KJ, Roberts DM, Rodgers C, Nic Ionmhain U, Ramanathan J, Ezard N, Brett J. Phenobarbital to manage severe gamma-hydroxybutyrate withdrawal: A case series. *Drug Alcohol Rev.* 2023;42(1):27–32.

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.