

# $\gamma$ -Butyrolactone and 1,4-Butanediol

## Abused Analogues of $\gamma$ -Hydroxybutyrate

Robert B. Palmer<sup>1,2</sup>

1 Toxicology Associates, Prof LLC, Denver, Colorado, USA

2 Rocky Mountain Poison & Drug Center, Denver, Colorado, USA

### Contents

Abstract .....	21
1. Clinical Effects .....	23
2. Diagnosis and Management .....	25
3. Withdrawal .....	26
4. Conclusion .....	29

### Abstract

$\gamma$ -Hydroxybutyrate (GHB) is a GABA-active CNS depressant, commonly used as a drug of abuse. In the early 1990s, the US Drug Enforcement Administration (DEA) warned against the use of GHB and restricted its sale. This diminished availability of GHB caused a shift toward GHB analogues such as  $\gamma$ -butyrolactone (GBL) and 1,4-butanediol (1,4-BD) as precursors and surrogates. Both GBL and 1,4-BD are metabolically converted to GHB. Furthermore, GBL is commonly used as a starting material for chemical conversion to GHB. As such, the clinical presentation and management of GBL and 1,4-BD intoxication shares a great deal of common ground with that for GHB. This similarity exists not only for acute intoxication but also for withdrawal in those patients with a history of extended high-dose abuse. This review examines the history of GHB analogue abuse as well as the clinical presentation and management of acute intoxication and withdrawal associated with abuse of these compounds.

The pharmacological activity of  $\gamma$ -hydroxybutyrate (GHB) was discovered in 1960 by Henri Laborit while searching for therapeutically useful analogues of the inhibitory neurotransmitter,  $\gamma$ -aminobutyric acid (GABA).<sup>[1]</sup> It was later discovered that GHB is a naturally occurring substance in the mammalian brain.<sup>[2]</sup> Since that time, extensive study has been devoted to determining the function of endogenous GHB in normal brain physiology. The large body of current evidence suggests GHB functions as a neurotransmitter or neuromodulator.<sup>[3]</sup>

In Europe, GHB was used clinically as an anaesthetic agent since the 1960s.<sup>[4]</sup> However, in the US, GHB was initially marketed during the 1980s as an unregulated dietary supplement in health-food stores, weight-training gyms and fitness centres. Alleged anabolic effects were touted because of the ability of GHB to stimulate growth hormone release in both animals and humans.<sup>[5,6]</sup> This led to the use of GHB by body builders in order to increase

muscle bulk as well as for strength training. Use of GHB was also promoted as a 'natural' treatment for insomnia and to induce weight loss.

In the mid-1990s, illicitly marketed GHB became available on the Internet and has since developed notoriety as a substance of abuse at all-night dance parties called 'raves'.<sup>[7]</sup> Users of the drug claimed to experience an alcohol-like euphoria, disinhibition and sexual arousal without unpleasant hang-over effects; however, with the increase in GHB use, an increasing number of GHB users were experiencing overdoses serious enough to require hospital emergency department care. Many of these cases were the result of combining GHB with ethanol, which produced a synergistic and sometimes fatal CNS depression.<sup>[8-10]</sup>

The US FDA issued a warning against the use of GHB in 1990 after a series of reports of seizures and coma attributed to GHB overdose.<sup>[11]</sup> Later that year, the FDA banned the sale of GHB-

-containing nutritional supplements.<sup>[12]</sup> These FDA restrictions on GHB sales as well as increasingly tighter state regulations led to an increased interest in alternative supplies of the drug. New sources included not only illegally synthesised GHB but also GHB precursors or analogues. Although some of the related compounds have legitimate industrial uses, other products containing these compounds quickly became available through sources such as the Internet.

Numerous analogues of GHB exist (figure 1). However, the two most widely abused GHB analogues are  $\gamma$ -butyrolactone (GBL) and 1,4-butanediol (1,4-BD), which will be the focus of this review (table I). GBL was sold over-the-counter and on the Internet in kit form with instructions for the home synthesis of GHB. These kits typically packaged GBL with sodium hydroxide. When mixed, the lactone is saponified by the hydroxide anion to yield GHB (figure 2).<sup>[13,14]</sup> Synthesis of GHB from 1,4-BD is more difficult and does not seem to have been a common practice.

In addition to being a precursor for the home synthesis of GHB, GBL is metabolically converted to GHB.<sup>[15]</sup> *In vivo* conversion of 1,4-BD to GHB also occurs (figure 3).<sup>[16-18]</sup> As a result, both products have been abused as alternatives to GHB.<sup>[19,20]</sup> There are, however, some differences in potency and toxicokinetics between these agents. Commercially available products containing GHB analogues have often been marketed for use as an 'ink jet cleaner' or 'weight belt cleaner', which only thinly veiled the more common misuses of these products.

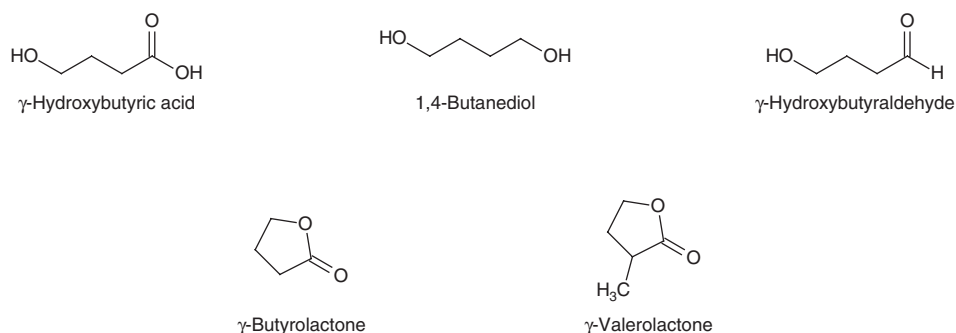
Despite the ban on sales, illegally produced GHB, together with GBL and 1,4-BD, continued to be abused. As with most other GABA agonists, GHB can cause anterograde amnesia. This effect seems to be especially pronounced when GHB is combined with ethanol. Largely as a result of its sedative and amnestic properties, GHB was implicated in an increasing number of drug-facilitated sexual assault cases throughout the 1990s and attained notoriety as a 'date rape' drug.<sup>[21]</sup> Prosecution of the cases was frequently difficult due to the inability of the victim to recall the assault, the analytical challenges in analysis of body fluids for GHB and

difficulties in interpreting the significance of measured GHB concentrations.

In 2000, the Hilary J. Farias and Samantha Reid Date-Rape Drug Prohibition Act of 2000 (Public Law 106-172) amended the federal Controlled Substances Act, making GHB a schedule I agent.<sup>[22]</sup> However, a pharmaceutical form of GHB (sodium oxybate) was simultaneously under investigation for treatment of cataplexy associated with narcolepsy which presented a unique legal challenge for the use of this drug. An equally unique solution was found when PL 106-172 created for the first time, a bifurcated schedule for GHB/sodium oxybate. Provisions of this act allowed sodium oxybate for medicinal purposes to be controlled under schedule III following FDA approval while the severe schedule I penalties were retained for illegal use.

In contrast to GHB, which has no legitimate use as an industrial chemical, GBL and 1,4-BD are used extensively in chemical manufacturing. The industrial consumption of 1,4-BD in the US was estimated at 338 million kilograms in 2000 where it is used extensively in the synthesis of tetrahydrofuran, polybutylene terephthalate resins, GBL and polyurethanes.<sup>[23]</sup> This creates a more complicated legal framework for the analogues as Federal listing of illicit GHB as a schedule I substance automatically made the intentional use of GBL and 1,4-BD as drugs a crime under the Controlled Substance Analogue Act of 1986. The Act states: "A controlled substance analogue shall, to the extent intended for human consumption, be treated, for the purposes of any Federal law as a controlled substance in schedule I" (PL 99-570, Sec 1201-1204, October 23, 1986). At present, due to its classification as a List 1 chemical, any industry involved in the import, export, manufacture or distribution of GBL must register with the US Drug Enforcement Administration (DEA) and follow specific record keeping and reporting requirements.<sup>[24]</sup>

It is difficult to assess the actual scope of GHB and GHB analogue abuse. Laboratory determination of GHB in urine has historically been difficult.<sup>[25]</sup> Further, ingested GBL and 1,4-BD are metabolised to GHB so urine tests will typically only be positive for GHB and not the analogue ingested. The increase in



**Fig. 1.** Chemical structures of  $\gamma$ -hydroxybutyrate and analogues.

**Table 1.** Analogues of  $\gamma$ -hydroxybutyrate

	Chemical synonyms	Street/trade names
<b><math>\gamma</math>-Butyrolactone</b>		
[CAS: 96-48-0]	1,4-Butanolide	Blue Nitro
Formula: C <sub>4</sub> H <sub>6</sub> O <sub>2</sub>	1,4-Lactone	Blue Nitro Vitality
MW: 86.1 g/mol	4-Butyrolactone	Fire Water
Density: 1.13 g/mL	4-Butanolide	Gamma-G
Description: colourless liquid	4-Deoxytetronic acid	GH Revitalizer
Solubility: water, alcohols, ketones and esters	4-Hydroxybutyric acid lactone	Remforce
	4-Hydroxybutyric acid, $\gamma$ -lactone	RenewTrient
	Dihydro-2(3H)-furanone	Revivariant
	Butyrl lactone	Revivariant-G
	Butyric acid lactone	
	Butyrolactone	
	Butyrylactone	
	Hydroxybutanoic acid lactone	
	Tetrahydro-2-furanone	
	$\gamma$ -Hydroxybutyric acid lactone	
<b>1,4-Butanediol</b>		
[CAS: 110-63-4]	1,4-Dihydroxybutane	BlueRaine
Formula: C <sub>4</sub> H <sub>10</sub> O <sub>2</sub>	1,4-Butanediol	Dream On
MW: 90.1 g/mol	1,4-Butylene glycol	Fubar
Density: 1.02 g/mL	1,4-Tetramethylene	Pine Needle Oil
Description: colourless viscous liquid	1,4-Tetramethylene glycol	Rejuv@Nite
Solubility: water, alcohols	Butane-1,4-diol	SomatoPro
	Butylene glycol	Thunder
	Tetramethylene-1,4-diol	
	Tetramethylene glycol	

**CAS** = Chemical Abstracts Service; **MW** = molecular weight.

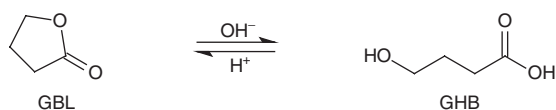
the number of DEA investigations into illegal GBL and 1,4-BD activities during the past several years suggest that the GHB analogues are responsible for many of the current reports of GHB abuse and overdose. The Drug Abuse Warning Network (DAWN) tracks emergency department mentions of various drugs in a series of US cities and may provide some indication of the extent of GHB abuse if GHB and its analogues are considered as a group. The number of emergency department mentions of GHB reported to DAWN peaked at 5542 mentions in 2000 but dropped to 3330 within 2 years of the passage of PL106-172.<sup>[26]</sup>

## 1. Clinical Effects

As stated, the focus of this paper is the two most commonly reported GHB analogues, GBL and 1,4-BD. The number of confirmed cases of GBL and 1,4-BD intoxication is small relative to GHB. This is likely due to a combination of factors including the

longer period of GHB availability, inaccurate or unknown identity of the substance ingested by intoxicated persons, lack of ability to perform necessary analytical investigations, metabolic conversion of GBL and 1,4-BD to GHB and the similarity of symptoms caused by GHB and its analogues.

The clinical hallmark of GHB analogue intoxication is CNS depression with relatively short duration of action, which may be clinically indistinguishable from that of GHB intoxication. This may be largely a result of the *in vivo* conversion of the analogues to GHB (figure 3). CNS depression may be accompanied with a labile level of consciousness and patients have presented with confusion or agitation as well as coma in cases of GBL and 1,4-BD intoxication. A general dose-response relationship exists with the level of CNS involvement becoming progressively greater with increasing dose. At very high doses, significant respiratory depression with apnoea may occur.



**Fig. 2.** The chemical interconversion of  $\gamma$ -butyrolactone (GBL) and  $\gamma$ -hydroxybutyrate (GHB) and its dependence upon pH.

Although GHB has been used as a model in animal studies of absence seizures, major motor seizures have not been well documented clinically. Similarly, major motor seizures have been inconsistently associated with reports of GBL and 1,4-BD intoxication. However, myoclonus may occur and myoclonic movements may be mistaken for seizure activity. In addition, generalised seizures may be the result of hypoxia secondary to severe intoxication or as a result of withdrawal from these agents. Hypoglycaemia or co-ingestants including amphetamine and derivatives (e.g. methylenedioxymethamphetamine [MDMA]), or cocaine may also cause seizures.

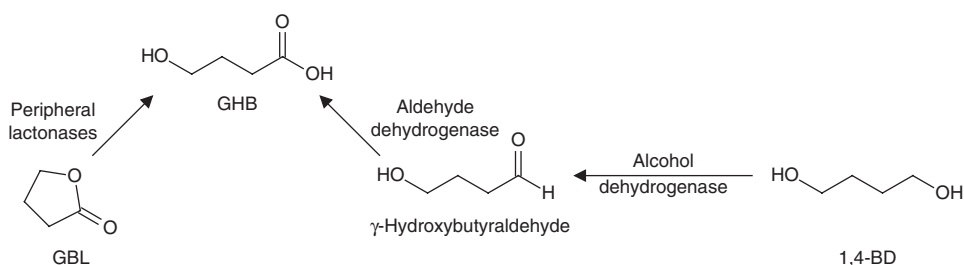
Isolated case reports describing generalised seizures as a primary manifestation of GBL or 1,4-BD intoxication should be interpreted with care. Most often, case reports have a viable alternative cause of the seizure (e.g. co-ingestant or hypoxia), failure to prove seizure activity with EEG evidence or failure to establish exposure to GBL or 1,4-BD with blood or urine measurements of the compound. One case claims to be the first report to have seizure activity following ingestion of 1,4-BD with EEG documentation and blood and urine concentrations of both 1,4-BD and GHB with no other metabolic or toxic causes for seizures based on routine laboratory analyses. Unfortunately, the authors provide no analytical data confirming the identity or composition of the 'homemade' product. Based on the primary pharmacological mechanism of action (GABA agonism) and the irregularity with which it is reported, primary tonic-clonic seizure activity as a result of GBL or 1,4-BD intoxication appears unlikely.

GHB is known to affect temperature regulation,<sup>[27,28]</sup> which may also be expected following exposure to GBL and 1,4-BD. In one animal study, rats exposed to lower doses (5–10 mg/kg) of GHB developed hyperthermia; however, when the dose was increased to 300–500 mg/kg, hypothermia was observed.<sup>[27]</sup> Similarly, mild hypothermia is frequently reported in hospitalised cases of

GBL and 1,4-BD intoxication.<sup>[20,29,30]</sup> The incidence of hypothermia in human cases of GHB abuse has been reported to be as high as approximately 30% in some series but not observed in others.<sup>[8,31,32]</sup> It is possible that this apparent discrepancy is the result of sampling bias in these reports in that overdosed patients are more likely to be seen in the hospital and, because of the larger doses ingested, are more likely to be hypothermic. However, these patients represent the population about which the toxicologist is most likely to be consulted. In any case, these temperature variations appear to be nominal and respond well to noninvasive warming techniques. The clinician must be mindful of other factors possibly affecting body temperature, such as environmental conditions (e.g. high ambient temperature plus physical exertion in rave parties or CNS depression outdoors with low ambient temperature) and co-ingestants (e.g. MDMA, cocaine).

Other central effects of GBL and 1,4-BD intoxication include nausea and vomiting as well as changes in pupillary response. Although the usual route of administration of these agents is ingestion, the unpleasant gastrointestinal adverse effects do not appear to be solely the result of local irritant effects. Nausea and vomiting have been noted with intravenous administration of GHB, suggesting the response may also have a central component. Notably, GHB-intoxicated patients with lower Glasgow Coma Scale scores appear to be more likely to vomit, increasing the possibility of aspiration<sup>[9,31]</sup> and a similar dose-related response appears to occur following GHB analogue intoxication.<sup>[20,29]</sup> Variable pupillary responses have been reported and include reports of non-reactive miosis, equal but sluggishly reactive pupils 2–3mm in size as well as non-reactive mydriasis in GHB analogue poisoning.<sup>[29,30,33]</sup>

The effects of GHB analogues on cardiovascular function are also variable. Bradycardia and tachycardia have both been reported, as have both hypotension and hypertension. Due to the clinical response of hypotension when atropine has been administered for symptomatic bradycardia, at least some component of hypotension appears to be related to heart rate. Animal studies have shown that a demonstrable loss in systemic vascular tone may also be present in cases of GHB intoxication; however, at least one report describes a patient with bradycardia and hypertension, although



**Fig. 3.** The *in vivo* conversion pathways of  $\gamma$ -butyrolactone (GBL) and 1,4-butanediol (1,4-BD) to  $\gamma$ -hydroxybutyrate (GHB).

laboratory results in that patient were also positive for three amphetamine derivatives and cocaine.<sup>[34]</sup> There does not appear to be strong evidence for direct myocardial depression from GHB or its analogues.

Nonspecific ECG changes seen in cases of GHB use include right bundle branch block, transient atrial fibrillation, P-wave inversion and appearance of U-waves. Though one report of 1,4-BD poisoning describes junctional bradycardia<sup>[35]</sup> and another involving GBL ingestion displayed a widened QRS,<sup>[33]</sup> no specific ECG abnormalities have been consistently associated with either GBL or 1,4-BD poisoning. However, it is reasonable to suspect that ECG changes similar to those observed in cases of GHB intoxication may also be seen in cases of GHB analogue abuse.

Miscellaneous symptoms seen with GBL and 1,4-BD intoxication include diaphoresis as well as urinary and faecal incontinence.<sup>[20]</sup> One example of an indirect toxicity associated with GBL describes a 19-year-old woman who developed caustic burns resulting in oesophageal strictures that required repeated dilations after swallowing a liquid in which the sodium hydroxide used to convert GBL to GHB had not been fully neutralised.<sup>[36]</sup>

## 2. Diagnosis and Management

The differential diagnosis of GHB analogue poisoning is lengthy and includes any one of a myriad traumatic, medical (e.g. CNS infections or masses, hypo/hyperglycaemia, stroke, thyroid disease, hepatic encephalopathy) and toxicological (e.g. carbon monoxide, opioid, benzodiazepine, toxic alcohol, barbiturate) causes of diminished mental status. Furthermore, there are no true pathognomonic signs or symptoms to separate GBL or 1,4-BD intoxication from poisoning due to GHB. Some helpful, but not diagnostic, considerations in distinguishing GHB or GHB analogue poisoning from that due to other sedative hypnotic agents include trunk or extremity myoclonus or agitated or combative response to painful stimuli such as laryngoscopy or Foley catheter placement, followed by relapse into coma. Information from emergency medical services personnel, family, friends or bystanders including the circumstances of the poisoning, containers or labels from products used or a past history of GHB or analogue use might provide valuable insight into the agent(s) involved.

Management of symptomatic ingestion of GBL or 1,4-BD is supportive. Initially, the airway may be managed non-invasively and supplemental oxygen should be provided. Intubation and mechanical ventilation should be considered but may not be necessary.<sup>[31]</sup> Continuous cardiac, pulse oximetry and blood pressure monitoring should be initiated and intravenous access with crystalloid fluids should be obtained. Bedside fingerstick glucose should be evaluated and dextrose administered if needed. Naloxone and

thiamine administration may also be considered where clinically appropriate to manage effects from other agents or medical conditions such as malnutrition, but are not likely to have any significant benefit in the management of the clinical effects of GBL or 1,4-BD.

Due to rapid absorption of the liquid GBL and 1,4-BD preparations, gastrointestinal decontamination is unlikely to be beneficial. Further, because of the high likelihood of CNS depression, induction of emesis is not recommended. No studies have examined the relative binding of GHB analogues to activated charcoal; however, the administration of activated charcoal may be considered in cases of very large ingestions presenting within 1 hour or less or in cases of suspected ingestion of multiple substances without other contraindications to this therapy. Based on clinical experience with GHB, there is no role for gastric lavage, whole bowel irrigation or extracorporeal methods of elimination enhancement in the management of GBL or 1,4-BD poisoning.

A variety of pharmacological antidotes have been examined for their ability to reverse the clinical effects of GHB intoxication. In two animal studies, naloxone appeared to reverse the dopaminergic, EEG and behavioural effects of GHB intoxication,<sup>[37,38]</sup> although another study reported a lack of response in mice even with high dose naloxone.<sup>[39]</sup> Physostigmine reportedly reversed GHB-induced anaesthesia<sup>[40]</sup> and may have reversed sedation in some GHB-intoxicated patients, but the results in other patients are equivocal.<sup>[41,42]</sup> When flumazenil is given to mice before administration of GHB, it appears to mitigate intoxication.<sup>[43]</sup> Further, flumazenil also attenuates the GHB-mediated release of growth hormone in humans.<sup>[44]</sup> Unfortunately, no reliable antagonist effects were found with any of these prospective antidotes in the clinical management of actual GHB or GHB analogue intoxication. Therefore, it is difficult to make a strong case for empirical administration of these drugs in cases of known sole agent GHB or GHB analogue poisoning.

Significant respiratory depression may warrant airway protection with endotracheal intubation; however, patients with GHB poisoning have reacted violently to attempts at intubation and this is also possible in GBL- and 1,4-BD-intoxicated patients. There is also evidence that patients with GHB poisoning may do well without invasive airway management, provided aspiration can be prevented.<sup>[31]</sup> If airway protection is indicated because of the risk of aspiration or the need for mechanical ventilation, rapid sequence intubation has been used, especially in combative patients. Most case reports of GBL and 1,4-BD intoxication suggest that the duration of depressed respiration is relatively brief (3–6 hours).<sup>[29,33,35,45]</sup>

Bradycardia is typically mild and often does not require drug therapy. Anaesthetic doses of GHB demonstrate an average drop



in heart rate of only 8 beats/min below baseline and haemodynamic compromise is rarely seen.<sup>[46,47]</sup> In cases of GHB intoxication in which bradycardia becomes symptomatic, increased heart rate has been achieved with atropine<sup>[31]</sup> and the same is expected for GHB analogues. No reports of GBL or 1,4-BD intoxication requiring pressor support were located.

GHB and its analogues are not detected by most immunoassay urine drug screens. Chromatographic methods for detection of GHB do exist,<sup>[48,49]</sup> although they are time and labour intensive and therefore not routinely available at many hospitals. Therefore, laboratory confirmation in cases of GBL or 1,4-BD exposure, is typically not available in a clinically meaningful time frame. Further, many analytical methods are incapable of distinguishing between GHB and the various analogues.<sup>[49]</sup> Realistically, even if laboratory results confirm the presence of GHB or analogues, this information is unlikely to alter management or disposition of the patient intoxicated. A urine drug screen may be useful in determining the presence of other substances ingested and assist in sorting out a conflicting or complicated clinical picture due to polysubstance poisoning.

A 12-lead ECG may be useful, primarily for ruling out co-intoxication with cardioactive substances. Likewise, chest radiography is not empirically necessary unless there is evidence of aspiration, respiratory distress or after endotracheal intubation. In cases where the index of suspicion for GHB or GHB analogue poisoning is high and the comatose patient is otherwise stable and appropriately supported, additional procedures, such as lumbar puncture and head CT, may often be deferred. However, if level of consciousness does not improve substantially within a short period of time (i.e. 4–6 hours), other possible aetiologies should be considered and worked up appropriately. Serum creatine phosphokinase (CPK) may be elevated in cases of prolonged unconsciousness following GHB intoxication and monitoring of renal function is appropriate. Other clinical laboratory assessments should be performed as clinically indicated.

The CNS depression associated with GHB and GBL intoxication may be potentiated by concomitant ingestion of ethanol. This circumstance is less clear in the case of 1,4-BD, primarily due to the enzymatic conversion of this compound to GHB. Metabolically, 1,4-BD first undergoes alcohol dehydrogenase mediated oxidation to 4-hydroxybutanal followed by either enzymatic (aldehyde dehydrogenase) or auto-oxidation to form GHB.<sup>[16,50,51]</sup> Consequently, it has been suggested that preventing metabolic transformation of 1,4-BD to GHB by blocking alcohol dehydrogenase with ethanol or fomepizole (4-methylpyrazole) might be of benefit in the management of 1,4-BD ingestion. When studied in mice, pretreatment with fomepizole prevented development of toxicity from 1,4-BD;<sup>[51]</sup> however, when ethanol and 1,4-BD were simulta-

neously administered to rats, the CNS effects of 1,4-BD were potentiated.<sup>[52]</sup> Though these observations are academically interesting, the application of alcohol dehydrogenase inhibition in the management of human cases of 1,4-BD ingestion cannot be recommended based on the currently available data.

### 3. Withdrawal

Withdrawal from GHB is well established and can be severe and prolonged.<sup>[53]</sup> The most frequently observed symptoms of GHB withdrawal include anxiety, tremor, insomnia and tachycardia.<sup>[54,55]</sup> Confusion, paranoia, agitation, delirium and hallucinations as well as autonomic instability are also known to occur with GHB withdrawal. The onset of withdrawal symptoms in patients with a significant history of GHB use is typically within 1–6 hours of last use and can persist for 3–15 days.<sup>[54,56]</sup> Although, as with all illicitly prepared drugs of abuse, estimation of dose is difficult, it is clear that those experiencing withdrawal are heavy users over extended periods of time. No reports of withdrawal symptoms exist following therapeutic use of GHB.

As is seen with the presentation of acute GHB intoxication, the clinical picture of withdrawal from GBL and 1,4-BD is similar to that seen with withdrawal from GHB. A total of five papers<sup>[55,57–60]</sup> describing 12 cases (11 male) of reported GBL withdrawal were located (table II). One of these 12 patients was treated on three separate occasions for GBL-related withdrawal; however, since all three episodes were reported in the same paper, he is counted herein as only a single case. Ten of the patients reported using GBL for 3–18 months. The remaining two patients reported regular use for much longer, one for 4 years<sup>[60]</sup> and the other for 11 years.<sup>[59]</sup> The onset of signs and symptoms of withdrawal generally began within a few hours of cessation of dosing. Most patients attempted self-management as an initial approach and typically requested medical assistance for continued withdrawal symptoms 3–7 days after the last dose.

Insomnia, anxiety and tremors were common in patients withdrawing from GBL. More severe cases also manifested various combinations of confusion, disorientation, paranoid delusions, psychosis as well as visual, auditory and tactile hallucinations. Hyper-religious delusions, terrifying nightmares, depression and fatigue were also intermittently reported. Of the ten cases in which vital sign data were presented, seven had elevated blood pressure and six were tachycardic. All patients with tachycardia had elevated blood pressure. Only one case describes tonic-clonic seizure activity.<sup>[59]</sup> Alterations of temperature, when seen, were mild and required no intervention.

The duration of hospital stay ranged from 6 hours to 13 days in the ten cases where it is known. One additional case was managed

**Table II.** Cases of  $\gamma$ -butyrolactone (GBL) and 1,4-butanediol (1,4-BD) withdrawal

Case no.	Agent	Age (y) and sex	Peak dose and duration of use	Last dose prior to presentation	Signs/symptoms	Duration of hospital stay	Outcome	Reference
1	GBL	33 F	2 sips qhs 4mo	5d	Insomnia, paranoid delusions BP: 125/75mm Hg; HR: 66 beats/min Temp: 36.6°C	6h	Recovered	57
2	GBL	25 M	15–30mL tid 9mo	4d	Insomnia, tremor, agitation, disorientation BP: 170/91mm Hg; HR: 120 beats/min Temp: 37.6°C	4d	Recovered	57
3	GBL	27 M	15mL q3h and 30mL qhs 4mo	3d	Anxiety, confusion, hallucinations, paranoid delirium, disorientation BP: 170/100mm Hg; HR: 94 beats/min Temp: 36.8°C	9d	Recovered	57
4	GBL	25 M	120–150 mL/day 4mo	5d	Insomnia, auditory and command hallucinations, paranoid delusions BP: 140/100mm Hg; HR: 100 beats/min Temp: 37.3°C	6d	Recovered	57
5	GBL	23 M	15mL qhs 2mo	8d	Insomnia, anxiety, tremor BP: 208/138mm Hg; HR: 78 beats/min Temp: 37.4°C	5d	Recovered	57
6	GBL	36 M	360 mL/day 8mo	10h	Agitation, hallucinations, delirium, nystagmus, tremor, clonus BP: 132/84mm Hg; HR: 127 beats/min Temp: 37.1°C	3d	Recovered	58
7	GBL	35 M	300–900 mL/day 11y	8d	Insomnia, agitation, paranoia, diaphoresis, seizure in ICU BP: 172/102mm Hg; HR: 104 beats/min	11d	Recovered	59
8	GBL	49 M	Dose not stated 3mo	3d	Agitation, psychosis, hyper-religious delusions No data on vital signs	Not stated	Recovered	59
9	GBL	34 M	240 mL/day 18mo	1d	Agitation, confusion, psychosis, visual and tactile hallucinations BP: 134/84mm Hg; HR: 87 beats/min Temp: 36.7°C	8d	Recovered	59

*Continued next page*

Table II. Contd

Case no.	Agent	Age (y) and sex	Peak dose and duration of use	Last dose prior to presentation	Signs/symptoms	Duration of hospital stay	Outcome	Reference
10	GBL	21 M	1.5 capfuls q2h daytime and 4.5 capfuls qhs 18mo	3d	Anxiety, agitation, paranoid delusions, catatonic periods, odd posturing BP: 165/98mm Hg; HR: 130 beats/min	13d	Relapsed	55
11	GBL	57 M	30–40 tablets in divided doses daytime plus additional tablets 1–2 times at night 3mo	Unknown last dose	Insomnia, anxiety, tremor, depression, fatigue BP: 166/98mm Hg; HR: 130 beats/min	3d	Relapsed	55
			5mo	Unknown last dose	Similar to above BP: 158/92mm Hg; HR: 122 beats/min	>2d	Relapsed	
			6mo	Unknown last dose	Insomnia, anxiety, tremor, confusion, disorientation Vitals not listed	>3d	Entered rehab	
12	GBL	27 M	30mL q2h 4y	NA	Insomnia, craving, dysphoria, sweating, tremor, palpitations Vital signs reported as 'normal'	NA	Recovered	60
13	1,4-BD	31 M	480 mL/day 5w	4d	Anxiety, palpitations, abdominal cramps, nystagmus, tremor BP: 138/90mm Hg; HR: 115 beats/min Temp: 37.0°C	6h	Discharged from ED with lorazepam	61
14	1,4-BD	28 F	480 mL/day 5w	4d	Anxiety, palpitations, abdominal cramps, nystagmus, tremor BP: 140/60mm Hg; HR: 120 beats/min Temp: 37.2°C	6h	Discharged from ED with lorazepam	61
15	1,4-BD	37 F	30mL q4h around the clock for 3w plus acute OD of 90mL 12mo	3d withdrawal occurred while in hospital recovering from acute OD	Refractory agitation Vitals not listed		2 more acute ODs before entering rehab	20

**BP** = blood pressure; **ED** = emergency department; **F** = female; **HR** = heart rate; **ICU** = intensive care unit; **M** = male; **NA** = not available; **OD** = overdose; **qhs** = every night; **qxx** = every x hours; **rehab** = rehabilitation; **temp** = temperature; **tid** = three times daily.



pharmacologically as an outpatient. All but two cases reportedly did well after discharge. Of the two cases that had difficulty after discharge, one restarted GBL use with 48 hours of discharge and was lost to follow up. The other relapsed into GBL use twice following inpatient treatment for withdrawal before he began psychiatric treatment and a 12-step programme.

Of three cases (one male) in two papers of withdrawal following 1,4-BD abuse, the clinical picture seems analogous (table II).<sup>[20,61]</sup> Anxiety and tremors with nystagmus, tachycardia and mild elevation of blood pressure were seen in two patients (a man and his female companion) who reported escalating use of 1,4-BD for 5 weeks prior to sudden cessation of use in an attempt to 'get unhooked'.<sup>[61]</sup> Signs and symptoms of withdrawal began within 6 hours of the last dose. Both patients unsuccessfully attempted self-management of symptoms with vodka before presenting to the emergency department 4 days after their last dose. They were both observed in the emergency department for 6 hours before being discharged with a 5-day course of lorazepam and instructions for follow up.

The third case of reported 1,4-BD withdrawal is more complex as this woman was also using GHB and GBL and was admitted multiple times for acute intoxication with these substances.<sup>[20]</sup> One instance of note involved the development of refractory agitation on the third day of hospitalisation after an acute overdose of 1,4-BD. This incident required high doses of sedatives and resulted in a total hospital stay of 8 days. Following this episode, she enrolled in an intensive treatment programme but returned to the emergency department twice more in the subsequent 10 weeks for acute 1,4-BD intoxication. Eventually, she completed an inpatient substance dependence programme followed by outpatient addiction management.

Cases of GBL and 1,4-BD withdrawal are managed in much the same fashion as withdrawal from GHB or ethanol. Benzodiazepines are typically the first-line agents for management of anxiety, agitation, hallucinations and psychosis. This is also appropriate initial therapy for tachycardia and hypertension. Large doses of benzodiazepines are often required to control withdrawal symptoms. However, some cases of GHB and GHB analogue withdrawal appear resistant to even high-dose benzodiazepines.

Sivilotti et al. reported the successful management of a series of patients with severe GBL withdrawal refractory to high dose benzodiazepine therapy with pentobarbital.<sup>[57]</sup> According to the same report, it was not uncommon for patients to have a recurrence of agitation, paranoia, delirium and hallucinations with attempted weaning from pentobarbital as late as 3–4 days after initiation of pentobarbital therapy. However, all five of these patients were weaned from pentobarbital prior to discharge from the hospital with the longest hospital stay being 9 days. In addition to pentobar-

bital and various benzodiazepines, other medications used in the management of reported cases of GBL and 1,4-BD withdrawal include haloperidol, propofol, baclofen, atenolol, physostigmine, phenobarbital (phenobarbitone), gabapentin, risperidone, carbamazepine and clonidine.

Not all cases of GHB analogue withdrawal appear to require emergency department or inpatient management. A 27-year-old man was reportedly successfully treated for a 4-year dependence on GBL as a family medicine outpatient.<sup>[60]</sup> Attempts by this patient to discontinue use without medical assistance resulted in the development of insomnia, dysphoria, tremor, nausea, sweating and other typical signs and symptoms of withdrawal. He reportedly responded well to therapy with clonidine for craving and dysphoria, propranolol for sweating, tremors and palpitations, paroxetine for depression and diazepam for insomnia. The most troublesome issue for this patient was insomnia, which did not respond to amitriptyline or zaleplon and required him to continue to use 45mL of GBL at bedtime. The insomnia and use of GBL at bedtime persisted for approximately 4 weeks prior to the successful use of diazepam, which allowed the patient to successfully taper off his nightly dose of GBL.

#### 4. Conclusion

The most commonly abused analogues of GHB are GBL and 1,4-BD. These two compounds, though DEA Schedule 1 when used as drugs, also have legitimate industrial uses. Both GBL and 1,4-BD are metabolically converted to GHB and GBL can also be used as a starting material for chemical conversion to GHB. There are no profound differences in the clinical presentation and management of persons intoxicated with GHB or one of the GHB analogues. In all cases, no specific antidote exists and care is supportive. As with GHB, heavy abusers of GBL and 1,4-BD may experience significant withdrawal with cessation of use. The withdrawal syndrome may persist for over a week and management may require large doses of benzodiazepines or pentobarbital.

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Correspondence and offprints: Dr *Robert B. Palmer*, Toxicology Associates, Prof LLC, 2555 South Downing, Suite 260, Denver, CO 80210, USA.  
E-mail: RPalmer@ToxicologyAssoc.com