Novel Psychoactive Treatment UK Network

NEPTUNE

Guidance on the Clinical Management of Acute and Chronic Harms of Club Drugs and Novel Psychoactive Substances

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Inspiring Improvement

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Chapter 3

Gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL)

Drug group: depressants

This chapter discusses GHB (gamma-hydroxybutyrate) and its precursor GBL (gamma-butyrolactone). Another precursor of GHB, 1,4-BD (1,4-butanediol), has not been widely available in recent times, but is mentioned in the literature. In the UK, GBL is used more than the other two.

3.1. Street names

Street names at the time of publication include G, GHB, GBL, Gina, liquid E, liquid ecstasy, liquid X, Gamma-O, Blue Verve, Gobbe, Charisma. Other street names are used in particular localities.

3.2. Legal status

GHB, GBL and 1,4-BD are controlled in the UK as Class C Scedule 2 drugs under the Misuse of Drugs Act 1971. However, GBL and 1,4-BD are controlled under that Act only when supplied or possessed with the intention for human consumption, but not when available for legitimate use in industry (see section 3.5).

3.3. Quality of the research evidence

The international evidence on the management of the acute and chronic harms related to the use of GHB and GBL is limited; randomised control trials in particular are not available. Evidence mainly consists of case reports and series and a small number of prospective observational studies, retrospective cohort studies and analysis of patient records. Despite these limitations, data/evidence from these sources is relatively consistent.

3.4. Brief summary of pharmacology

GHB acts primarily as a CNS depressant but at low doses can also produce euphoric effects and effects that appear to be like those of stimulants. GHB is both a metabolite and a precursor of the inhibitory neurotransmitter gamma-aminobutyric acid (GABA)

and acts as a neuromodulator in the GABA system, acting on both GABA-B and its own so-called GHB receptors. GBL and 1,4-BD are converted into GHB after they are absorbed.[1]

A number of studies have looked at GHB pharmacokinetics in healthy volunteers.[2–6] GHB is absorbed rapidly, is extensively metabolised to carbon dioxide and rapidly eliminated,[7] mainly through the lungs (less than 5% is excreted in the urine as GHB, although this may be greater in overdose). It has a half-life of only 20–30 minutes.[8] The effects of GHB usually occur 15–20 minutes after ingestion and can last for up to three to four hours,[9] with peak effects at 30–60 minutes after ingestion.[8] It is undetectable in urine after approximately 12 hours.[10]

GBL is a precursor of GHB and is non-enzymatically converted in the body into GHB. GBL is absorbed more rapidly than GHB and potentially has a faster onset of action. Its duration of action may also be longer.[10] Some users report that GBL is more potent than GHB. 1,4-BD is another precursor to GHB; it is converted in the liver through a two-step conversion, via hepatic alcohol dehydrogenase to gamma-hydroxybutyraldehyde followed by metabolism into GHB via hepatic acetaldehyde dehydrogenase.[11,12] Animal studies have shown that both ethanol and fomepizole competitively block the metabolism of 1,4-BD to GHB.[13,14]

GHB (and therefore GBL and 1,4-BD) has a steep dose–response curve and narrow therapeutic threshold. It can readily cross both the placenta and the blood–brain barrier, leading to profound CNS and respiratory depression.[8,9] Daily use of GHB/GBL can lead to dependence and the possibility of withdrawal syndrome on cessation of use, which can be severe, with agitation and delirium. Acute GHB/GBL toxicity and acute withdrawal can be life threatening.

3.5. Clinical and other uses

Clinical uses of GHB have included alcohol and opiate detoxification regimens, anti-craving medication after alcohol detoxification,[9] and as an anaesthetic agent in some European countries (although this latter use is now declining). The sodium salt of GHB, sodium oxybate (Xyrem SPC), is approved for the treatment of narcolepsy with problematic catalepsy in specialist sleep centres the US and Europe.*

GHB was sold in US health food stores for weight control and sedation, until the over-the-counter sales were banned in 1990, following reports of acute intoxication.[15] It has also been sold for its antidepressant and anxiolytic effects and for its cholesterol-lowering effects. It has also been used in bodybuilding, as it has been thought to release growth hormone; however, its anabolic effects are unproven.[16] GHB has been implicated as a facilitator in 'date rape', although a systematic review of the international evidence suggests that it is rarely identified in cases of drug-facilitated sexual assaults.[17]

* See http://www.medicinescomplete.com/mc/bnf/current/PHP2146-sodium-oxybate.htm; http://www.medicines.org.uk/emc/medicine/17364/SPC/Xyrem+500+mg+ml+oral+solution; http://www.ukmi.nhs.uk/NewMaterial/html/docs/SodiumOxybateNMP0603.pdf; as well as the manufacturer's website, http://www.xyrem.com/images/Xyrem_Med_Guide.pdf.

GBL and 1,4-BD are used extensively by the chemical industry as precursors for the synthesis of plastics and industrial solvents. They are found in floor-cleaning products, nail polish (previously nail polish removers) and superglue removers.

3.6. Prevalence and patterns of use

At a population level, the use of GHB/GBL in the UK is low and appears to be concentrated among some sub-groups, often in specific contexts. Despite low levels of use, its health costs are relatively high compared with other drugs,[18] and other club drugs in particular, because of its intrinsic toxicity and potentially life-threatening withdrawal syndrome as discussed in section 3.12.2.

Questions regarding GHB/GBL use were added to the Crime Survey for England and Wales (CSEW; formerly the British Crime Survey) in October 2009 in response to concerns about its use. Overall, data from the CSEW show that the use of GHB/GBL in England and Wales remains low, although there was a statistically significant increase in its use by adults aged between 16 and 59 years, from 0.0% in 2010/11 to 0.1% in 2011/12. The 2010/11 survey showed that GHB/GBL was more likely to have been used in the past year by the 16–24-year age group (0.1%) than in the age group 25–59 years (0.0%).[19] Questions about the use of GHB/GBL were not included in the 2012/13 or 2013/14 surveys. No data on GHB/GBL use in Scotland are available, but it is believed that the prevalence is low, as suggested by police seizure data for Scotland 2010–11.[20]

There is evidence that GHB/GBL is often used as part of a wider poly-drug repertoire (see section 3.10.2). An internet survey of 189 GHB/GBL users reported that a third had taken GHB/GBL during the last month and two-thirds reported mixing GHB/GBL with other drugs.[21] Available data suggest that GHB/GBL users tend to be a well educated and well functioning group.[22,23]

GHB/GBL use is concentrated among some sub-groups and in particular settings and geographical areas. A number of European surveys conducted in dance music venues and other targeted settings suggest that the lifetime prevalence of use of GHB/GBL ranges from 3% to 19%.[18]

The Global Drug Survey 2012 reported that among UK respondents (69.7% male and 82.7% heterosexual) 'regular clubbers' used GBL and GHB more than other respondents (Table 3.1).[24]

Table 3.1. *Use of GBL and GHB among UK respondents in the 2012 Global Drug Survey*

	Lifetime use	Use in past 12 months	Use in the past 12 months by regular clubbers
GBL	7.7%	1.6%	2.5%
GHB	3.8%	1.5%	2.0%

In the UK, mainland Europe, the US and Australia, GHB/GBL use is particularly concentrated among gay men and other MSM, particularly those who frequent night clubs.[18,21,22,25–28] The 2007 UK Gay Men's Survey of 6155 men suggested that almost 13% had ever used GHB or GBL and 7% have used it in the last year.[29] GHB/GBL use is highest among attenders of gay clubs.[29] A survey carried out in 2010 in London gay nightclubs suggested there were higher levels of use of GHB/GBL than the study mentioned above, with 34% reporting lifetime GHB use (22% past-year use and 14% past-month use) and 27% reporting GBL lifetime use (24% past-year use and 19% past-month use). On the night of the survey, 7% reported having taken or planning to use GHB, and 14% reported already having taken or planning to take GBL on the night.[27]

Although its use has been mainly reported in cities, there is one report of a GHB-related hospital acute presentation in rural Wales.[30]

Due to its pro-sexual effects and muscle relaxant properties, GHB/GBL is often used by MSM in a sexual context. It is one of the drugs commonly implicated in 'chemsex' (see section 1.6.4.2.) and may be associated with high-risk sexual behaviour and thus with an increased risk of sexually transmitted infections. Studies in both the US and the UK have shown that GHB/GBL use is associated with increased sexual risk, with HIV-positive men more likely to use GHB/GBL and more likely to use it in a sexual context,[28,31,32] than those not known to be infected.[29]

GHB/GBL is often taken with other drugs, including alcohol, cannabis, ecstasy, stimulants and sildenafil (Viagra).[22,23] The setting for GHB/GBL use is typically nightclubs, circuit parties, sex parties, saunas and sex clubs,[28] although some evidence suggests that GHB/GBL is used in private settings as well.[21] The setting in which the drug is consumed may be linked to risk, as one study has shown that people who commonly use GHB/GBL in club settings are more likely to report problems than those who usually use it at home.[21]

3.7. Routes of ingestion and frequency of dosing

The routes of administration of GHB/GBL include:

- oral use (this route is the most common, when it is typically diluted in a beverage);
- insufflation;
- injection (though this is rare);
- mucosal (e.g. previously from absorption of nail polish removal pads).

GHB/GBL used for recreational purposes is most usually sold in the form of a liquid formulation, often in bottles or vials. Its taste is described as unpleasant and salty and is it therefore typically diluted in a beverage. It is more rarely used as powder, usually GHB sodium salt (capsules or loose) or a waxy substance to which water can be added.[18] The 'irritant' nature of GHB/GBL has been described, with a case report of a user syringing the liquid into capsules to make it easier to swallow.[33]

GBL for recreational use in the UK is usually bought from street dealers or via the internet in amounts ranging from 125 ml to 10 litres. The price of the substance differs by locality and over time, but a 2006 report by the Advisory Council on the Misuse of Drugs (ACMD) published in suggested that a 250 ml bottle of 99% pure GBL could be bought for £20, which amounts to 8p per recreational dose.[1] According to anecdotal reports from users at the time of writing (2014), a litre costs £80–£100.

Usually, 1 ml of liquid contains 1 g of GHB, although purity and concentration may vary;[18,34–36] data for 1,4-BD are limited. Miotto et al. suggest that single doses of GHB can range from 0.5 g to 5 g and those who develop tolerance and dependence will use in the range of more than 25 g per day.[34] GBL is far more lipophilic than GHB; hence, typical ingested dosages of GBL (1.5 in a single dose) are lower than those of GHB (with an average single dose ranging from 1 g to 5 g).[37,38]

GHB/GBL dose is often measured by users in imprecise 'capfuls', teaspoons, eye droppers or vials. This imprecise dose measurement is one of the main suggested causes of the acute GHB/GBL-related harms, as users risk overdose because of its steep dose–response curve.

Recreational users will typically use small doses frequently, in the context of binges, or sometimes at night to assist with sleep. Dependent users will ingest GHB/GBL frequently and at regular intervals over prolonged periods. They will generally use multiple daily doses, including at night.[34] The mean frequency of dosing in cases of dependence was reported by McDonough et al. to be every 4.4 hours,[39] although with case reports and series showing a wide range, from hourly to daily.[35,40,41]

3.8. Desired effects of GHB/ GBL for recreational use

GHB/GBL affects people in different ways and a euphoric dose for one person may be a sedative dose for another.[42] GHB/GBL tends to produce euphoric and pleasurable effects[43] without hangover or other subacute adverse effects, which helps popularise it as a 'club drug'.[1]

The desired effects of GHB/GBL include euphoria, relaxation, increased sociability, disinhibition, confidence boost, social and sexual disinhibition, enhanced libido, increased sexual arousal and enhancement of sexual encounters, with effects being dose-dependent.[8,18,44–46] The use of GHB/GBL for its stimulant, dissociative and sedating effects have also been reported.[34,47,48] In addition, some individuals use GHB/GBL after using other drugs (generally stimulants), to help 'come down'[22] or to enhance and modify the effects of drugs[34] such as stimulants.

GHB/GBL is also used as self-medication for sleep problems and anxiety. There are reports of people using GHB/GBL in the hope that it will improve cognitive ability, reduce the effects of ageing, reduce depression and anxiety, or make them feel more energised and dance more joyously.[49]

3.9. Mortality

Acute GHB/GBL toxicity and a severe withdrawal syndrome have been associated with fatalities. According to the Office for National Statistics, there were 20 deaths in England and Wales in 2011 where GHB/GBL was mentioned on the death certificate, 13 such deaths in 2012, and 18 in 2013.[50]

The National Programme on Substance Abuse Deaths (NPSAD) database from 1995 to 2006 identified 47 cases in the UK where GHB or GBL was found post-mortem and/or implicated in death.[1] In 2012, NPSAD reported a total of 17 such deaths for the whole of the UK. There was a slight increase from the previous years in the number of GHB/GBL-related deaths in England, with 6 deaths where no substance other than GHB/GBL was implicated, and 11 deaths where GHB/GBL was detected with or without another substance.[51]

In Scotland, 3 GHB/GBL-related deaths were reported with no other substances implicated and a total of 5 where GHB or GBL was found either on its own or with other drugs. The co-use of alcohol was implicated in many of these deaths.[52]

3.10. Acute harms

3.10.1. Acute GHB/GBL toxicity

There are potential acute harms relating to any use of GHB/GBL, as well as dependent use. All GHB/GBL users risk acute toxicity and overdose; tolerance is not fully protective of overdose and people dependent on GHB/GBL are also at risk of acute toxicity. In terms of acute single-dose systemic toxicity, GHB/GBL appears to be the most physiologically toxic club drug, with a safety ratio of 10[53] and overdoses typically occurring as a concequence of using large concentrations over a short period, or when GHB/GBL is used in combination of other CNS depressants, such as alcohol or benzodiazepines.[9]

The hazard profile of GHB has been described as less favourable than that of many other psychoactive substances. One study concluded that GHB is the most physiologically hazardous drug, partly because the dosage range is narrow[53] and varies between individuals and with whether other substances have also been used. The authors commented on particular harm resulting from imprecise dosing of illicit GHB or GBL, which cannot be easily measured.[53]

As mentioned above, GHB/GBL affects people in different ways and a euphoric dose for one person could be a sedative dose for another.[42] It has been reported that adverse effects of GHB/GBL happen at a variety of doses, indicating the variable individual responses to the drug.[54] GHB/GBL intoxication exists within a spectrum of severity and that is influenced by: dose ingested, individual variation and other substances ingested (discussed in more detail below).

The effects of GHB are dose-dependent, as summarised in a recent review (Table 3.2).[8]

Table 3.2. *Dose-dependent effects of GHB*

Dose	Effects
Below 10 mg/kg	Mild clinical effects: short term anterograde amnesia, hypotonia (relaxed muscles) and euphoria[55]
20–30 mg/kg	Drowsiness, sleep and myoclonus (jerking of muscles) can happen[55,56]
50 mg/kg	May cause coma[57–59]
Over 50 mg/kg	May lead to the onset of coma, bradycardia (slowed hear rate) and/or respiratory depression and death.[55,57,59]

GHB/GBL has a steep dose–response curve, whereby even a small increase in dose can cause serious toxic effects, such as impaired consciousness and coma. This steep dose–response relationship differentiates GHB/GBL from other drugs.

The usual clinical course after overdose – if other sedative hypnotics (most commonly alcohol) have not been used – is rapid, spontaneous awakening from drug-induced loss of consciousness or coma and uneventful recovery. CNS depression usually persists for 1 to 3 hours, with patients typically making a full recovery within 4–8 hours.[54,60–62]

Thus, patients with acute intoxication typically: develop signs of intoxication rapidly but then improve quickly.

Overdoses are common among all users – dependent users as well inexperienced, intermittent and regular users (tolerance and dependence do not protect against overdose).[22] In an Australian study of 76 GHB users, half reported a history of overdose during which they had lost consciousness.[22] In another study, 66% reported some degree of loss of consciousness.[34] Similarly, a study of 505 consecutive GHB cases in emergency departments in Barcelona showed that the motive for seeking medical treatment in all cases was reduced consciousness.[44]

The use of other drugs and alcohol can increase the toxic effects of GHB and is discussed in section 3.10.2. In addition to the GHB-related adverse effects, the adulterant compounds may also have serious toxic effects.[18] As with alcohol, and unlike with benzodiazepines, there is no antagonist or antidote.

Because of GHB's short elimination half-life, people can progress from deep coma to wakefulness over about 30 minutes. A 30-month review of an Australian emergency department reported that if ventilation was not required, the great majority improved rapidly and were discharged straight from the emergency department, without a need for further medical treatment.[63,64]

In European cities, accidental GHB/GBL overdoses in night clubs account for a substantial proportion of drug-related emergencies that require ambulance, emergency or hospital services.[18] A similar picture may exist in the UK, as suggested by a retrospective review of a clinical toxicology database of a large London inner-city emergency department which showed that 38% of all poisonings with drugs of misuse in 2006 were GHB/GBL-related. The total number of presentations was 420 and 158 (37.6%) included the use of GHB or GBL.[65]

3.10.1.1. The features of acute GHB/GBL toxicity

The reported effects of acute GHB/GBL toxicity are summarised as follows:

- **Mild/moderate effects** include nausea, hypersalivation, vomiting, diarrhoea, drowsiness, headache, ataxia, dizziness, confusion, amnesia, urinary incontinence, tremor, myoclonus, hypotonia, agitation, euphoria and hypothermia.
- **Severe effects** include coma, convulsions, bradycardia, ECG abnormalities (e.g. U waves), hypotension (or rarely hypertension after intravenous use), Cheyne-Stokes respiration and respiratory depression leading to respiratory arrest. Metabolic acidosis has been reported.

Laboratory investigations may also indicate hypernatraemia, hypokalaemia, hyperglycaemia and metabolic acidosis.

GHB/GBL produces CNS and respiratory depression of relatively short duration. Psychotic episodes may occur. It has also been suggested that GHB/GBL intoxication should be considered a differential diagnosis for patients presenting to an ED with acute agitation.[47]

Box 3.1. *Reported neurological and psychiatric features of GHB/GBL intoxication*

CNS symptoms: dose-related. Patients may therefore present with CNS symptoms ranging from sudden drowsiness through to unresponsive coma, depending on dose[44,54–56,60,61,63–76] **Common**
Amnesia[77,78] **Common**
Ataxia[45,47,57,61,71,77–113] **Common**
Hypotonia[57,66,74,79,114] **Common**
Disorientation[44,61, 78,84,110] **Common**
Hyporeflexia[91,100,105,109] **Common**
Dizziness[45,68,77,92,93,94,110] **Common**
Tremor[57,80] **Common**
Confusion[68,78,79,93,94] **Common**
Myoclonus[54,57,58,60,77,90,115–117] **Common**
Hallucination[83,84,93,94] **Common**
Convulsions (seizures or seizure-like activity) have been reported,[34,57,60,61,63–65,68,69,72,74,78,87,89,93,94,97,108,113,114] but most studies have shown them to be uncommon. They may occur secondary to hypoxia or due to other substances used[8]
Somnolence[78,82,90,112] **Common**
Agitation,[47] bizarre behaviour and combativeness, either at presentation or when waking[44,47,55,56,60,61,63,66,68,71,75–78,80,81,84,85,88,92–94,96,98,101,106,108,110,114,115]
Slurred speech[80,83,84] **Common**
Miosis[44,68] **Common**
Dysarthria[44,77] **Common**
Less common neurological effects include bruxism,[98] vertigo,[57] delusion,[110] extrapyramidal side-effects,[83] dystonia,[83] athetoid posturing[98]
Confusion[68,84,66] **Common**
Mydriasis (wide pupils)[44,68,72,80,85,86,90,92,93]
Headache[44,85] **Common**
Horizontal and vertical gaze nystagmus[79,80,83–85]
Reduced coordination[80,93] **Common**
Pupils may be sluggish and non-reactive[66,72,94,107]
Euphoria **Common**
One report of paroxysmal sympathetic surge[118]

Box 3.2. *Reported medical features of GHB/GBL intoxication*

Cardiovascular effects

Bradycardia[44,57,60,61,65,68,72,76–78,80,84,89,92,93,95,96,98, 100,102,106–109,112,114,115] **Common**

Mild bradycardia without haemodynamic compromise is the most common cardiovascular effect and has been noted in recreational drug users[54]

Tachycardia and hypertension[61,63,72,77–79,81,93,106]

Hypotension[44,57,63,68,74,77,84,89,98,101,102,107,112,119] Rare when GHB/GBL used on its own; generally when GHB/GBL co-ingested with other substances[54,68]

ECG abnormalities occur occasionally[63]

Chest tightness[44,94]

Palpitations[44]

Respiratory effects

Dose-related respiratory depression[56,57,60,61,65,68,71,72,75,77,78,81,88,92,93,107] Respiratory failure is normally the cause of death from GHB/GBL

Tachypnoea[63]

Bradypnea[44,63,64,66,77,84,91,92,98,100,101,104,107] **Common**

Pneumothorax[109]

Periodic (Cheyne-Stokes) respirations[114,120,121]

Cyanosis[66,72]

Pulmonary aspiration[61,66–68,70,73,107]

Pulmonary oedema[77,88,105,122,123]

Apnoea and respiratory failure[54,56,93]

Hypothermia

Hypothermia[44,54,60,63,68,71,74,78,98,100,107,109,110] **Common**

Metabolic features

Hyperglycaemia[61, 88, 106]

Elevated creatine activity/rhabdomyolysis[60, 68, 85, 112, 114,124]

Gastrointestinal symptoms

Nausea and vomiting[57,61,59,60,63,65,66,68,71,74,77,78,82,84,89,9–94,97,109,110,115,123] **Common**

Incontinence (urine and stools)[68,77,78,93,94,98,109,112,113]

Salivation[114,125]

Diarrhoea[126127]

Abdominal pain[110]

Diaphoresis[56,71,77,78,81,84,112,128]

Reported features of GHB/GBL intoxication are listed in Boxes 3.1 and 3.2. It is important to note that other additional symptoms or features may occur due to co-used ethanol or other recreational drugs.

The CNS symptoms of acute toxicity can vary, depending on ingested dose, from sudden drowsiness to unresponsiveness and profound coma. CNS depression typically persists for 1–3 hours, with patients making a complete recovery typically within 4–8 hours.

Coma accounts for a significant proportion of GHB/GBL-related presentations to EDs, with a reported range of 16–33%.[68] For example, a third of cases in a Swiss study[68] presented to hospital with coma, 28% of cases of a US study[54] and 16% of cases in a study conducted in Spain.[60] In a case series of presentations to a London ED, approximately 16% of cases had severe coma at presentation, with a score on the Glasgow Coma Scale (GCS) of 3. In this study, 47% of patients had a GCS score ≤8, which is

the usual cut-off for intubation.[65] A case series of 88 patients presenting to medical services after taking GHB reported a GCS score of 3 and 33% had a score of 4–8.[54]

Vomiting in acute intoxication is common. The London-based study mentioned above reported that vomiting occurred in 17% of presentations,[65] while Garrison et al. reported vomiting in 22% of presentations.[128] Other studies have reported higher rates: 30% of the presentations in a US ED study[54] and more than half of cases of overdose in an Australian study.[22] Vomiting in individuals with reduced consciousness (especially when the GCS score is less than 8 out of 15) is believed to increase the risk of aspiration due to the lack of protective airway reflexes in people with neurological depression.[129] Indeed, aspiration in patients intoxicated with GHB/GBL needs to be considered a significant risk, particularly in those with reduced consciousness. Local clinical protocols should include steps to assess and reduce the likelihood of vomiting and subsequent aspiration.

Convulsions – or seizures or seizure-like activity – associated with GHB/GBL have been reported,[34,60,63,65,68,72,87,93,113,130] especially in severe cases of acute intoxication, although studies suggest that they are uncommon.[8] It has been argued that it is difficult to determine the true frequency of 'seizures', as GHB and its analogues have been shown to cause myoclonic jerks, which – in pre-hospital settings in particular – may be misinterpreted as a seizure.[129]

Hypothermia is usually not severe, but can be common. For example, in a series of 88 cases of GHB/GBL overdose, 55% were assessed to have an initial temperature of 36°C or less and 25% an initial temperature of 35° C or less.[54] Bradycardia is also common. In the same case series of 88 GHB overdose patients, over a third (36%) developed bradycardia, although only one case was severe enough to require atropine.[54]

Acute GHB/GBL toxicity can cause amnesia, which increases the risk of relapse because users do not remember the experience of acute intoxication and overdose.[131] As mentioned above, GHB can cause profound unconsciousness and the steep dose–response curve puts the user at risk of death. The co-ingestion of alcohol is a significant added risk factor, but GHB/GBL intoxication alone can cause death.[1]

Other reported effects of GHB/GBL use include one observational case report of acute central serous chorioretinopathy.[132]

3.10.1.2. Acute withdrawal

People who use at least daily may commonly develop tolerance and dependence. Withdrawal syndrome following abstinence or dose reduction after prolonged use can be severe and must be treated as a medical emergency.

For more details on withdrawal see section 3.12.2.

3.10.2. Poly-drug use and drug interactions

The co-ingestion of alcohol (ethanol) and/or other recreational drugs may contribute to some of the other clinical features seen in patients presenting with GHB/GBL and or GHB/GBL toxicity.[133] A number of authors have suggested that GHB users who

co-ingest alcohol are more likely to develop severe complications related to GHB use. A double-blind, placebo-controlled, cross-over volunteer study that investigated the potential for toxicity associated with GHB alone compared with GHB and alcohol co-ingestion showed that GHB plus ethanol was associated with more adverse effects, in particular hypotension and hypoxia; there were no differences in GHB/GBL concentrations between the groups.[134]

Co-ingestion of GHB/GBL and alcohol has been associated with increased agitation[68] and aggressive behaviour. Patients who used alcohol were also more likely to vomit.[68] There is evidence that when GHB/GBL is taken in combination with other drugs (including alcohol or stimulants), the duration and depth of coma are greater than when it is taken alone, and recovery times are longer. [44,135,68]

GHB is rapidly eliminated by metabolism to succinic semialdehyde (SSA) via the GHB-dehydrogenase enzyme, and then to succinic acid via the SSA-dehydrogenase enzyme. Several drugs (i.e. valproate, ethosuximide, salicylate, amobarbital, phenytoin, disulfiram, cyanide) have been shown to inhibit GHB-dehydrogenase. However, the clinical significance of the co-administration of such agents and GHB remains unknown.[136,137]

3.10.3. GHB and HIV antiretroviral therapy

While clearance of GHB from the systemic circulation occurs rapidly by oxidation to succinic acid,[138] [136] animal data suggest that GHB is also a substrate of first-pass metabolism (while not proven, this may involve the enzymes CYP2D6 and CYP3A4). Therefore, co-administration of GHB with CYP2D6 inhibitors (i.e. cobicistat) or CYP3A4 inhibitors (i.e. ritonavir, cobicistat) may lead to raised systemic exposures of GHB and increased toxicity.

It has been recommended that GHB/GBL should be used with caution by HIV-sero-positive patients with predisposing seizure disorders or with opportunistic infections that may lower seizure threshold (i.e. toxoplasmosis, cryptococcal meningitis), as GHB/GBL may precipitate seizure-like activity. GHB/GBL use may also cause severe nausea, vomiting and gastrointestinal tract irritation, and adversely effect absorption of antiretroviral therapy.[139] There are also concerns about compliance with HIV medication while intoxicated, especially during prolonged binges, which may complicate antiretroviral therapy and affect adherence.[139]

3.11. Clinical management of acute toxicity

3.11.1. Identification and assessment

Diagnosis of acute GHB/GBL toxicity should be made on clinical assessment. There are no rapid urine or serum field tests, so analytical assessment should not be considered a component of routine diagnosis. It has been suggested by Wood et al. that the diagnosis of acute GHB/GBL toxicity be based on the recognition of the clinical toxidrome associated with the overdose of GHB/GBL.[129]

Standard medical assessment is always indicated, so that other causes of the presentation can be excluded. The ease of making a clinical diagnosis often depends on understanding the circumstances in which an individual was found and the frequency of managing patients with acute GHB/GBL intoxication.

Problems relating to the identification of GHB/GBL intoxication are linked to the similarities in clinical features to alcohol, opiate and/or benzodiazepine intoxication, [140,8] or similarities to other clinical presentations, such as hypoglycaemia. Given the similarity to acute opioid toxicity, it is recommended by TOXBASE® that, where there is clinical uncertainty, it may be worth considering a trial of the opioid antagonist naloxone, although it is not effective in managing acute GHB/GBL intoxication.

Diagnosis is also complicated by frequency of other co-intoxicants[141] and by the diversity of clinical presentation.[47] That is, some or all of clinical features of acute GHB/GBL toxicity may be 'masked' by other co-ingested substances (e.g. an individual may present with drowsiness and normal heart rate due to co-ingestion of GHB/GBL and a stimulant such as cocaine or amphetamine).

3.11.2. Clinical management of overdose and acute toxicity

No randomised controlled trials have looked at the management of acute GHB/GBL toxicity but there is consistency in the evidence reviewed that the treatment of GHB/GBL acute toxicity should consist of symptom-directed supportive care with an emphasis on respiratory support. Wood et al. suggest that the duration of reduced consciousness (particularly non-responsive coma) is generally short-lived, with the majority of patients recovering fully within 2–3 hours of the onset of coma.[129]

Overall, the evidence suggests the following:

The protection of airways and proper airway management is recommended because vomiting is common.[61,75,109,121,142] However, it has also been suggested that 'prophylactic' intubation in cases of vomiting is not indicated[54] and it has been argued that routine intubation of patients with acute GHB/GBL toxicity is not recommended unless patients exhibit vomiting, seizures or other clinical indications for intubation.[129] Clinical consensus suggests that there does not appear to be a need to intubate purely on the basis of GCS score, as in other medical and trauma patients.

For up-to-date guidance on the management of GHB/GBL acute toxicity, it is recommended that information be sought from the National Poisons Information Service (NPIS), specifically the NPIS 24-hour telephone service and the poisons information database TOXBASE®:

http://www.TOXBASE.org/Chemicals/Management-Pages/GHB-overdose---features-and-management

It is recommended that relevant clinicians and departments are registered to receive these facilities.

Non-UK readers should consult their local or national guidelines.

Reports in the literature indicate that intubation is needed in 3–13% of cases.[54,60,63,68,124] One study found a greater requirement for mechanical ventilation for patients who had ingested GHB/GBL with other drugs or alcohol, as the duration and depth of coma were greater than when it was taken alone.[44]

Gastric decontamination (e.g. activated charcoal) is not recommended, as its effects are uncertain. There are no antidotes for GHB/GBL poisoning.[8] It may be worth giving naloxone to treat possible opiate poisoning where there is an uncertain presentation or opiate use is suspected. Pharmacological intervention is rarely required for bradycardia.

Case series have shown that where mechanical ventilation has not been required, consciousness was recovered within 5 hours.[1] Expert consensus has highlighted the need to fully investigate unconscious patients, particularly when the diagnosis is unclear. CT scanning may be indicted, particularly when convulsions occur, although there is no robust evidence on the routine use of CT scanning specifically for GHB/GBL overdoses.

Some patients may have a fluctuating course on recovery, where they have periods of agitation alongside periods of drowsiness or coma. These patients can sometimes be difficult to manage, since they require appropriate sedation for their periods of agitation, which may worsen the degree of sedation when it occurs. Should this occur, there may be a need for appropriate respiratory support until the patient has fully recovered. Dependent users may begin to go into withdrawal on recovery from the overdose – see section 3.12.2.

Outside clinical settings, in night clubs for example, harm reduction information should stress the need to put people in the recovery position and call for an ambulance. GHB/GBL users should similarly be told to put people with signs of acute intoxication in the recovery position.

3.11.3. Treatment outcome

Patients with GHB/GBL acute toxicity will typically develop symptoms quickly, but will also improve rapidly. Even in more severe cases, patients will usually make a full recovery, provided they are hospitalised and receive appropriate supportive care.[8] Studies have shown that patients will regain a GCS score of 15 in a short time after presentation (a median of 76 minutes in one study), albeit this is longer for those with severely reduced consciousness, typically resulting from poly-substance use.[44,63] They also show a rapid rate of discharge from hospital,[44,63] although people presenting to hospital with a low GCS may have a longer recovery period.[65]

A retrospective study of patients presenting to a large London inner-city ED with acute poisoning with self-reported GHB/GBL toxicity reported on the disposition of patients with acute GHB/GBL intoxication. The majority (92.2%) were discharged directly or self-discharged from ED or required only a short period of observation in the ED observation ward. Fewer than 1 in 10 (7.8%) required admission to hospital. Among those, the majority were admitted to critical care facilities, usually because

of significant neurological or respiratory compromise and the need for airway protection and intubation. The study also looked at length of stay and reported an overall median stay of 2.8 hours: discharged or self-discharged directly from ED 2.4 hours (range 1.7–3); admitted to ED observation ward 5.6 hours (range 3.6–8.6); admitted to general medical ward 15.6 hours; admitted to a critical care facility 18.7 hours (range 10.1–39.2).[65]

As amnesia is a direct effect of GHB/GBL, patients may recover with no recall of GHB/GBL intoxication or overdose.[34] In a study of 42 users, 13% had amnesia during GHB use and 45% after GBL use.[34] As noted above, patients may be at risk of relapse or may delay treatment because they do not remember their experience of overdose or severe withdrawal.[131]

3.11.4. Acute withdrawal following detoxification

In GBL/GHB-dependent people, rapid improvement from acute toxicity may be followed by deterioration as withdrawal symptoms develop if they are dependent on GHB/GBL (for details on withdrawal see section 3.12.2). Withdrawal symptoms may manifest quickly, or up to 24–48 hours later, and the delayed onset of withdrawal symptoms must be considered in the management of acute toxicity.[143] A vital part of discharge instructions to patients, friends and carers is to inform them about the potential for these symptoms to recur after discharge.[143]

In the majority of published cases of GHB/GBL withdrawal, detoxification was unplanned and treatment started after the patient presented in crisis, usually to an ED.[39] Acute withdrawal is potentially life threatening and it is recommended that cases are considered a medical emergency. It is also recommended that all dependent users of GHB/GBL are advised not to stop use abruptly or to attempt self-detoxification. Medical assistance should always be sought.

3.12. Harms associated with chronic use

3.12.1. Dependence

The regular, prolonged use of GHB/GBL and its analogues can lead to physiological dependence.[8] Its typical features include difficulty controlling the amount used, neglect of other activities and withdrawal. Part of the dependence syndrome is tolerance, in which larger doses are needed over time to produce the same psychoactive effects. Long-term users therefore typically use higher doses than naïve users.[18] Users have reported taking larger doses in order to achieve previous effects or use just *'to normalise' themselves* rather than to get high.[40] Cross-tolerance between GHB/GBL and alcohol may exist.

At a social level, dependence has been described by patients to be the opposite to why they chose to use GHB/GBL in the first place: rather than enhancing sociability, GHB/GBL dependence leads to introversion, lack of motivation and failing to maintain contact with family and non-using friends; other concerns included loss of employment and absenteeism.[23]

3.12.2. The GHB/GBL withdrawal syndrome

The potential of GHB/GBL to produce dependence is well recognised. Dependent users will consume GHB/GBL at regular intervals during the day and at night, sometimes as often as every 1–3 hours,[9] in order to avoid withdrawal.

GHB/GBL withdrawal can appear clinically similar to withdrawal from opioids, benzodiazepines and alcohol,[8] and problems relating to the identification of GHB/GBL intoxication and withdrawal are linked to the similarities in clinical features.[140] However, although the autonomic features of GHB/GBL withdrawal are less prominent than for alcohol withdrawal, symptoms are often more prolonged (up to 2 weeks, occasionally longer) and are typically more resistant to treatment with benzodiazepines.

GHB/GBL withdrawal can also have similarities to clinical presentations such hypoglycaemia or sympathomimetic toxicity, typically associated with stimulant use.

3.12.2.1. Predictors of withdrawal

Dependent users will develop withdrawal symptoms on reduction or cessation of use, which can be severe and life threatening.[39,126,144,145] GHB/GBL withdrawal is on a spectrum that varies in clinical severity.

There is increasing evidence that daily use of GHB/GBL is a predictor of withdrawal. In their review, McDonough et al. report a minimum daily dose associated with withdrawal is approximately 18 g for GHB and 10 g for GBL,[39] but it is possible that it occurs at lower daily doses. Withdrawal can be seen after as little as 2–3 months of use,[39] or even a shorter time after high-frequency use.

3.12.2.2. Rapid onset and duration of withdrawal syndrome

One distinctive feature of GHB/GBL is the quick onset of withdrawal. It can happen 30 minutes after the last dose, but more typically it is a few hours. GHB/GBL withdrawal symptoms have been reported to last from 3 to 21 days,[8,39] with one review reporting a mean of 9 days.[39]

Wood et al. report that in their clinical experience, 50% of those who present to hospital with acute GHB/GBL withdrawal will require barbiturates and admission to intensive care, as they typically present with delirium.[146]

3.12.2.3. Individual variations and unpredictability of the withdrawal syndrome

Although there are similarities between cases of withdrawal reported in the literature, there are also wide variations in both the withdrawal symptoms and the clinical responses between and within patients.[147] Withdrawal symptoms can be self-limiting in some patients, but others can present with more severe withdrawal that can progress to delirium.[9]

3.12.2.4. GHB/GBL withdrawal symptoms

The early symptoms of GHB/GBL withdrawal typically include insomnia, tremor, confusion, nausea and vomiting. Over the next 12–48 hours, tachycardia, hypertension, agitation, seizures and/or myoclonic jerks and hallucinations may develop.

Withdrawal symptoms reported in the literature are summarised in Box 3.3.

It is not possible to determine accurately how common these symptoms are.

A review of 36 ED presentations reported that the early symptoms of withdrawal were tremor (67%), hallucinations (63%), tachycardia (63%), insomnia (58%), seizures (7%) and rhabdomyolysis (7%).[145]

McDonough et al. in their review reported that an 8-hourly dosing was the minimum frequency associated with withdrawal delirium.[39] There are indications that heavy, frequent users are most likely to progress to severe delirium. It has been proposed that withdrawal in cases of co-dependence on GHB/GBL and another CNS depressant

Box 3.3. *GHB withdrawal symptoms*

Commonly reported symptoms
Hallucinations – visual and auditory[9,15,41,126,145,148–162]
Anxiety[15,23,34,40,41,59,126,149,150,156,163–165]
Tremors[23,36,40,41,59,140,148–151,154,156,157,159–164]
Paranoia[9,15,40,41,126,153–156,159,162]
Tachycardia[15,34,41,126,145,148–151,153,156–159,163,164]
Insomnia[15,23,36,41,59,148,149,151,153,156,158,162]
Hypertension[41,126,148,149,158,159,164]
Disorientation[15,126,145,149,150,153,156,158,162]
Sweating[36,40,41,126,148,149,151,154–157,159,163]
Confusion[15,126,140,149,153,156,160]
Agitation[34,126,140,145,153,155,157,158,160,166]
Aggression/combativeness[40,126,150,152,159]

Other reported symptoms
Depression[36,41,156]
Tachypnoea[154]
Miosis[153]
Nausea and vomiting[126,163]
Nystagmus[15,157,162,164,]
Diarrhoea[126,165]
Cardiac palpitations[35,160,164]
Abdominal pain (less common)[164]
Dyspnoea[160]

Severe withdrawal
Delirium[23,34,41,140,145,148,157,158,160]
Seizures[40,126,140,145,153] – may become life-threatening
Psychosis[67,151,153,156, 159,160,161]
Withdrawal mimicking schizophrenia[167]
Rhabdomyolysis[145, 149, 161]
Medical complications reported during withdrawal include sepsis, myoglobinuria, Wernicke's encephalopathy without alcohol dependence

(opiates or other sedatives) or a stimulant are likely to be more severe, but such cases have not been described in the literature.[39]

Seizures associated with GHB/GBL withdrawal appear to be less common than with alcohol and are reported in fewer than 10% of cases.[129]

3.13. Management of harms from chronic use

GBL has been described as a mild skin irritant and a strong mucous membrane irritant. It can penetrate the epidermis and cause rashes or eczema.[1]

Little is known about the long-term harms of GHB/GBL that are secondary to acute harms or dependence. It is recommended that more research be carried out on the long-term effects of GHB/GBL, including psychiatric (and cognitive), physical and teratogenicity-related harms. This includes the recommendation by Mitto et al. to study the possibility of persistent problems with memory acquisition as a result of GHB/GBL use.[168]

Among MSM in particular, GHB/GBL is often used in a sexual context and in a context of potential high-risk sexual behaviour. Studies have shown that GHB/GBL use is associated with increased sexual risk and potential transmission of HIV, as well as other sexually transmitted and blood-borne infections[169–171] (see section 3.10.3).

3.13.1. Clinical management of dependence

3.13.1.1. Identification and assessment of GHB/GBL dependence and withdrawal

The NEPTUNE group consensus was that the warning signs of dependence might be the use of GHB/GBL during the week when not out clubbing or engaging in similar social activities. Alert signs for dependence are the following:

- daily use on multiple times throughout the day;
- waking at night to use;
- using other drugs to prevent symptoms overnight;
- symptoms on days not using;
- not able to go a day without use.

There are no validated GHB/GBL withdrawal scales, but it may be reasonable to use alcohol or benzodiazepine withdrawal scales.[9] However, in cases of emergency acute withdrawal, many would recommend not using scales and instead treating on the basis of symptomatic control, since non-GHB-specific scales do not always pick up the degree of neuropsychiatric symptoms, which could lead to underdosing and then escalation of delirium.

In specialist drug treatment clinical practice, the Clinical Institute Withdrawal Assessment of Alcohol Scale (CIWA-Ar) has been used, as well as the Alcohol Withdrawal Scale (AWS). Other scales used include: the Subjective Withdrawal

Scale (SWS), which is based on the Subjective Opiate Withdrawal Scale, where all subjective criteria of the DSM-IV-TR withdrawal syndromes were added to SWS;and the Objective Withdrawal Scale, which is based on the Objective Opiate Withdrawal Scale, where nursing staff record their observations.[172]

There are no validated tools for the identification of or screening for harmful GHB/GBL use in non-drug specific settings. Winstock and Mitcheson have provided helpful guidance for addressing substance misuse issues in general practice.[173]

It is worth noting that some individuals self-medicate with baclofen or ethanol or benzodiazepines to prevent GHB/GBL withdrawal. This can also be harmful and must be discouraged. Self-detoxification from GHB/GBL can be dangerous and should be avoided, as withdrawal symptoms can be severe and potentially life threatening. GHB/GBL users who wish to stop should be encouraged to seek medical assistance. If they want to reduce GHB/GBL use on their own, they should do so in very small increments and with the support of health professionals. Consumption diaries may be useful.

Attempts at self-detoxification from GHB/GBL can be ineffective. In one study of 56 users recruited via the internet, respondents had unsuccessfully attempted to quit on average 4.07 times and 30% had been previously treated for GHB/GBL misuse.[49]

3.13.1.2. Psychosocial and pharmacological support

Chapter 2 discusses in general terms the psychosocial interventions for the use of club drugs. These are applicable to the management of the chronic harms of GHB use, as well as aftercare and support, and so are not discussed further here. The pharmacological interventions are discussed below.

3.13.2. Clinical management of withdrawal

No randomised controlled trials or robust prospective clinical trials have investigated GHB/GBL withdrawal. The research evidence on the management of GHB/GBL withdrawal is instead based mainly on case reports and series and it is therefore not possible to draw robust recommendations.

For up-to-date guidance on the management of GHB/GBL withdrawal, it is recommended that information be sought from the National Poisons Information Service (NPIS), specifically the NPIS 24-hour telephone service and the poisons information database TOXBASE®:

http://www.toxbase.org/Chemicals/Management-Pages/GHB-withdrawal---features-and-management1

It is recommended that relevant clinicians and departments are registered to receive these facilities.

Non-UK readers should consult their local or national guidelines.

It is, though, consistently suggested that symptomatic treatment is indicated for GHB/GBL withdrawal syndrome. The review of the evidence shows that benzodiazepines are most typically used for this purpose.[15,126,149,153,154,158,163,165] Combined evidence suggests that benzodiazepines are the first line of treatment, but adjuncts may be helpful to control symptoms.[149] Baclofen and barbiturates have been described as second-line adjuncts.[39,41,55,126,129,145] TOXBASE® recommends that withdrawal symptoms can be effectively treated with a combination of diazepam and baclofen and this has been used successfully in clinical practice, as part of medically assisted detoxification.[23] However, clinicians must be aware of the risks of patients taking the baclofen on top of their use of GHB/GBL and this leading to coma and respiratory distress.[174] There is anecdotal evidence that some GHB/GBL users are also buying baclofen online.

A wide range of medications have been used and described as potentially helpful in GHB/GBL withdrawal management. However, supporting evidence for any of these medications is mainly based on a small number of case reports and case series. The decision on which additional agent to use depends on the clinical presentation. Anti-psychotics should be used with caution due to the risk of neuroleptic malignant syndrome and seizure.

Medications which have been used to manage acute withdrawal are listed in Box 3.4.

Box 3.4. *Medications used to manage acute GHB/GBL withdrawal*

Diazepam[126,143,165,175]
Baclofen[23,140,156]
Barbiturates[41, 59, 157, 159, 161]
Benzodiazepines are safe and effective in managing most cases
Barbiturates can be used in benzodiazepine refractory cases[39]
Carbamazepine[156]
Gabapentin[156]
Chloral hydrate[151,156]
Clonidine[35,156]
Paroxetine[35]
Beta blockers[35,127]
Bromocriptine[145]
Trazadone[41,150,156]
Fentanyl[148]
Propofol[77, 48,161]
Antipsychotics[15,126,150,151,153,155,159,160,161,162,166]
Antipsychotics, including haloperidol, should be administered with caution[151,157,160,176]
Typical antipsychotics should be avoided due to the risk of developing NMS type syndromes[156]
Intramuscular typical antipsychotics in GHB withdrawal should be used with caution[161]
Antipsychotic not indicated unless delirium is present[167]
Lorazepam and/or droperiol for the management of agitation[47]
Olanzapine[160]
Pentobarbital in an inpatient setting. [41]
Propranol[35]

Pharmaceutical GHB.[35] Gradual dose tapering can be an effective way to achieve withdrawal from dependent GHB use. However, this requires high motivation and careful monitoring in an in-patient setting

3.13.2.1 Medical complications reported during withdrawal

A 2004 review by Mc Donough et al.[39] of 38 cases reported the following complications during withdrawal: sepsis, rhabdomyolysis and Wernicke's encephalopathy – without alcohol dependence. No frank withdrawal seizures were Seen. Rosenberg et al. suggest that all cases of GHB withdrawal delirium be considered medical emergencies and be managed in critical care settings, rather than psychiatric settings. The involvement of both disciplines, however, may be required.[161]

3.13.3. Medically assisted elective or planned withdrawal and detoxification

There is limited evidence on the provision of medically assisted withdrawal, as most case reports and series are concerned with acute withdrawal. There are, though, a few reports of elective medically-assisted withdrawal[23] and it has been argued that it is best if detoxification is carried out on a elective basis,[23] planned in advance so that withdrawal symptoms can be identified and treated early, as most patients presenting symptomatically following enforced abstinence have presented with more severe symptoms and increased risk of delirium.[41] This approach also enables planning of post-withdrawal support and recovery.

There seems to be no consensus on the best clinical settings for the detoxification of patients with GHB/GBL dependence. Intensive care, hospital inpatient basis or in outpatient specialist drug treatment centres have all been suggested. Some have recommended that withdrawal be monitored in an intensive care unit (ICU) along with continuous monitoring of vital parameters because of the severity of associated symptoms.[8,177,178] Others have described successful outpatient detoxification.[23]

There have been some attempts to identify the parameters and to develop algorithms for the management of GHB/GBL detoxification in specialist drug treatment or acute centres on an inpatient or outpatient basis,[39] as well as to define the medication and monitoring required.[23,39]

3.13.4. Aftercare and supporting recovery

There are few studies of the longer-term outcomes of detoxification. It is recommended that research be funded and carried out. Relapse to further use following GHB/GBL detoxification may be high, as suggested by some case series and case reports.[30,156]

In elective, medically assisted detoxification, aftercare is an integral part of treatment and should be planned at the onset of the intervention. The risk of relapse is addressed through psychological interventions, as well as through peer support groups such as Narcotics Anonymous or Alcoholics Anonymous (for more information see Chapter 2).

3.14. Public health and safety

GHB/GBL use can have a negative impact on public health and safety. Studies have shown that it is associated with increased sexual risk and potential transmission of HIV, as well as other sexually transmitted infections and blood-borne infections.[169,170,171] The links between GHB/GBL use and increased aggression (especially in combination with alcohol) should also be kept in mind, as should the possibility that GHB/GBL is used in drug-facilitated sexual assaults.

GHB/GBL is associated with the abrupt onset of sleep, which can have dangerous consequences if driving or operating heavy machinery.[9] However, the lack of hangover or sub-acute effects may encourage some to drive under the influence.

One study also noted that re-arrests for driving under the influence of GHB/GBL were not uncommon.[179]

3.15. Harm reduction

3.15.1. Supporting patients undergoing outpatient medically assisted GHB/GBL withdrawal

Patients undergoing outpatient medically assisted GHB/GBL withdrawal should be provided with a pro-forma letter describing their detoxification and medication regime, to be presented to ED in case of severe withdrawal.

3.15.2. Advice for users S-T-A-Y-I-N-G S-A-F-E on GHB/GBL

S Seek medical attention immediately if you have taken too much GHB/GBL. Do not use other drugs in the hope of reversing the effects.

T Two or more substances used at the same time increase the risk of overdose significantly (especially sedatives e.g. alcohol, ketamine).

A Always measure GHB/GBL doses accurately (use for example syringes or pipettes). Wait until the effects are felt and do not re-dose for at least 2 hours.

Y You should avoid using GBL on your own and always use in a safe place and with someone who has not taken it, as it is common to become unconscious.

I If you have used and are going to sleep, sleep on your side in case you are sick. Place sleeping or unconscious friends in the recovery position.

N Never drink GHB/GBL straight out of a bottle or pour a dose straight out of a bottle. Always dilute in water and add food colouring to avoid accidental drinking. *Never* keep GBL in drinks bottles, especially in public venues, where it might be drunk by others not aware of the content.

G GHB/GBL is physically addictive and dependence can happen quickly. Avoid frequent use, especially daily use.

S Severe and potentially serious GHB/GBL withdrawal symptoms occur if you are dependent and you miss a dose or reduce amounts taken abruptly.

A Acute withdrawal symptoms and have no GHB/GBL? Seek medical help immediately in an emergency department. It can be a very serious medical emergency.

F Find a medical support for planned GHB/GBL detoxification. Do not attempt to stop abruptly on your own. If you want to reduce your dose, do so in *very* small doses until you find medical support.

E Employ methods to stabilise your use; consumption diaries can be very helpful. Keep a GHB/GBL diary and record of your doses and times you use.

Users should also be reminded of safe sexual practices, given the association between GHB/GBL and chemsex and other forms of high-risk sexual behaviour.

References

1 Advisory Council on the Misuse of Drugs (ACMD). *GBL and 1,4-BD: Assessment of Risk to the Individual and Communities in the UK*. 2008.

2 Palatini P, Tedeschi L, Frison G, Padrini R, Zordan R, Orlando R, et al. Dose-dependent absorption and elimination of gammahydroxybutyric acid in healthy volunteers. *Eur J Clin Pharmacol.* 1993;45:353–6.

3 Borgen LA, Okerholm R, Morrison D, Lai A. The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. *J Clin Pharmacol.* 2003;43:59– 65.

4 Brenneisen R, Elsohly MA, Murphy TP, Passarelli J, Russmann S, Salamone SJ, Watson DE. Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J Anal Toxicol.* 2004;28:625–30.

5 Helrich M, Mcaslan TC, Skolnik S, Bessman SP. Correlation of blood levels of 4-hydroxybutyrate with state of consciousness. *Anesthesiology.* 1964 ;25:771–5.

6 Abanades S, Farre M, Segura M, Pichini S, Barral D, Pacifici R, et al. Gamma-hydroxybutyrate (GHB) in humans: pharamacodynamics and pharmacokinetics. *Ann NY Acad Sci.* 2006;1074:559–76.

7 Brailsford AD, Cowan DA, Kicman AT. Pharmacokinetic properties of g-hydroxybutyrate (GHB) in whole blood, serum, and urine. *J Anal Toxicol.* 2012 Mar;36(2):88–95. doi: 10.1093/jat/bkr023.

8 Schep LJ, Knudsen K, Slaughter RJ, Vale JA, Mégarbane B. The clinical toxicology of γ-hydroxybutyrate, γ-butyrolactone and 1,4-butanediol. *Clin Toxicol (Phila).* 2012 Jul;50(6):458–70. doi: 10.3109/15563650.2012.702218.

9 González A, Nutt D. Gamma hydroxy butyrate abuse and dependency. *J Psychopharmacol.* 200;519(2):195–204.

10 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *Report on the Risk Assessment of GHB in the Framework of the Joint Action on New Synthetic Drugs*. 2002.

11 Bessman SP, Fishbein WN. Gamma-hydroxybutyrate, a normal brain metabolite. *Nature*. 1963 Dec 21;200:1207–8.

12 Poldrugo F, Snead OC. 1,4-butanediol and ethanol compete for degradation in rat brain and liver in vitro. *Alcohol*. 1986 Nov–Dec;3(6):367–70.

13 Poldrugo F, Snead OC. 1,4-butanediol, gamma-hydroxybutyric acid and ethanol: relationships and interactions. *Neuropharmacology*. 1984 Jan;23(1):109–13.

14 Quang LS, Desai MC, Shannon MW, Woolf AD, Maher TJ. 4-methylpyrazole decreases 1,4-butanediol toxicity by blocking its in vivo biotransformation to gamma-hydroxybutyric acid. *Ann NY Acad Sci.* 2004 Oct;1025:528–37.

15 Craig K, Gomez HF McManus JL, Bania TC. Severe gammahydroxybutyrate withdrawal: a case report and literature review. *J Emerg Med.* 2000;18:65–70.

16 Nicholson KL, Balster RL. GHB: a new and novel drug of abuse. *Drug Alcohol Depend.* 2001;63:1–22.

17 Németh Z, Kun B, Demetrovics Z. The involvement of gammahydroxybutyrate in reported sexual assaults: a systematic review. *J Psychopharmacol.* 2010;24 :1281– 7.

18 European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). *GHB and Its Precursor GBL: An Emerging Trend Case Study* (Thematic Paper). 2008. http://www.emcdda.europa.eu/publications/thematic-papers/ghb (accessed 11 March 2013).

19 Smith K, Flatley J, eds. *Drug Misuse Declared: Findings from the 2010/11 British Crime Survey England and Wales* (Statistical Bulletin). Home Office, July 2011.

20 Scottish Government. *Drug Seizures by Scottish Police Forces, 2011–12* (Statistical Bulletin, Crime and Justice Series). 23 April 2013.

21 Sumnall H, Woolfalla K, Edward S, Cole J, Beynon C. Use, function, and subjective experiences of gammahydroxybutyrate (GHB). *Drug Alcohol Depend*. 2008;92(1–3):286–90.

22 Degenhardt L, Darke S, Dillon P. GHB use among Australians: characteristics, use patterns and associated harm. *Drug Alcohol Depend.* 2002 Jun 1;67(1):89–94.

23 Bell J, Collins R. Gamma-butyrolactone (GBL) dependence and withdrawal. *Addiction*. 2011 Feb;106(2):442–7. doi: 10.1111/j.1360-0443.2010.03145.x.

24 Mixmag's Global Drug Survey: The Results. http://www.mixmag.net/words/features/mixmags-global-drug-survey-the-results.

25 Guasp A. *Gay and Bisexual Men's Health Survey*. Stonewall 2012. http://www.healthylives.stonewall.org.uk/lgb-health/gay-and-bisexual-men/default.aspx#main (accessed 1 May 2012).

26 Wood DM, Measham F, Dargan PI. 'Our favourite drug': prevalence of use and preference for mephedrone in the London night-time economy 1 year after control. *J Substance Use.* 2012;17(2):91–7. DOI: 10.3109/14659891.2012.661025.

27 Measham F, Wood DM, Dargan PI, Moore KA. The rise of legal highs: prevalence and patterns in the use of illegal drugs and first- and second-generation 'legal highs' in south London gay dance clubs. *Journal Substance Use.* 2011;16(40):263–72.

28 Halkitis PN, Palamar JJ. GHB use among gay and bisexual men. *Addictive Behaviors.* 2006;31:2135–9.

29 Keogh P, Reid D, Bourne A, Weatherburn P, Hickson F, Jessup K, Hammond G. *Wasted Opportunities: Problematic Alcohol and Drug Use Among Gay Men and Bisexual Men*. Sigma Research, 2009. http://sigmaresearch.org.uk/files/report2009c.pdf.

30 O'Toole JG, Kristian MR, Devereaux L, Kurien S. Gamma-hydroxybutarate dependence in a rural setting in Wales. *J Substance Use.* Feb 2009;14(1):70–4.

31 Colfax GN, Mansergh G, Guzman R, Vittinghoff E, Marks G, Rader M, Buchbinder S. Drug use and sexual risk behavaiour among gay and bisexual men who attend circuit parties: a venue-based comparison. *J Acquir Immune Defic Syndr*. 2001 Dec 1;28(4):373–9.

32 Mattison AM, Ross MW, Wolfson T, Franklin D; San Diego HIV Neurobehavioral Research Center Group. Circuit party attendance, clun drug use and unsafe sex in gay men. *J Subst Abuse.* 2001;13(1–2):119–26.

33 Evans R, Sayal K. Gammabutyrolactone: withdrawal syndrome resembling delirium tremens. *J Substance Use.* 2012;17(4):384–7.

34 Miotto K, Darakjian J, Basch J, Murray S, Zogg J, Rawson R. Gamma-hydroxybutyric acid: patterns of use, effects and withdrawal. *Am J Addict.* 2001 Summer;10(3):232–41.

35 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. doi: 10.1159/000333022.

36 Herold AH, Sneed KB. Treatment of a young adult taking gamma-butyrolactone (GBL) in a primary care clinic. *J Am Board Fam Pract.* 2002 Mar–Apr;15(2):161–3.

37 Drug Enforcement Agency. http://www.getsmartaboutdrugs.com/drugs/ghb.html (accessed 9 June 2014).

38 Couper FJ, Marinetti LJ. Gamma-hydroxybutyrate(GHB) – effects on human performance and behavior. *Forensic Sci Rev.* 2002;14(1):101–21.

39 McDonough M, Kennedy N, Glasper A, Bearn J. Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. *Drug Alcohol Depend.* 2004 ;75:3– 9.

40 Chew G, Fernando A. Epileptic seizure in GHB withdrawal. *Australas Psychiatry.* 2004;12:410–11.

41 Sivilotti MLA, Burns MJ, Aaron CK, Greenberg MJ. Pentobarbital for severe gamma-butyrolactone withdrawal. *Ann Emerg Med.* 2001;38:660–5.

42 Kam P, Yoong F. Gamma-hydroxybutyric acid: an emerging recreational drug. *Anaesthesia.* 1998;53:1195–8.

43 Abanades S, Farré M, Barral D, Torrens M, Closas N, Langohr K, Pastor A, de la Torre R. Relative abuse liability of [gamma]-hydroxybutyric acid, flunitrazepam, and ethanol in club drug users. *J Clin Psychopharmacol.* 2007 Dec;27(6):625–38.

44 Galicia M, Nogue S, Miro O. Liquid ecstasy intoxication: clinical features of 505 consecutive emergency department patients. *Emerg Med J.* 2011 Jun;28(6):462–6. doi: 10.1136/emj.2008.068403.

45 Luby S, Jones J, Zalewski A. GHB use in South Carolina. *Am J Public Health.* 1992 Jan;82(1):128.

46 Henderson DL, Ginsberg JP. Withdrawal, recovery, and long-term sequelae of gamma-butyrolactone dependence: a case report. *Am J Addict.* 2008 Sep–Oct;17(5):456–7. doi: 10.1080/10550490802266193.

47 Zvosec DL, Smith SW. Agitation is common in gamma-hydroxybutyrate toxicity. *Am J Emerg Med.* 2005 May;23(3):316–20.

48 Oliveto A, Gentry WB, Pruzinsky R, Gonsai K, Kosten TR, Martell B, Poling J. Behavioral effects of gamma-hydroxybutyrate in humans. *Behav Pharmacol.* 2010 Jul;21(4):332–42. doi: 10.1097/FBP.0b013e32833b3397.

49 Stein LA, Lebeau R, Clair M, Martin R, Bryant M, Storti S, Monti P. A web-based study of gamma hydroxybutyrate (GHB): patterns, experiences, and functions of use. *Am J Addict.* 2011 Jan–Feb;20(1):30–9. doi: 10.1111/j.1521-0391.2010.00099.x.

50 Office for National Statistics. *Deaths Related to Drug Poisoning in England and Wales, 2013* (Statistical Bulletin). Home Office, September 2014.

51 Corkery J, Claridge H, Loi B, Goodair C, Schifano F. *Drug-Related Deaths in the UK: January–December 2012 Annual Report*. National Programme on Substance Abuse Deaths (NPSAD), 2013.

52 National Programme on Substance Abuse Deaths (NPSAD). *Drug-Related Deaths Reported by Coroners in England, Wales, Northern Ireland, Guernsey, Jersey and the Isle of Man; Police Forces in Scotland; and the Northern Ireland Statistics and Research Agency Annual Annual Report 2013 on Deaths Between January–December 2012*.

53 Gable RS. Acute toxic effects of club drugs. *J Psychoactive Drugs.* 2004 Sep;36(3):303–13.

54 Chin RL, Sporer KA, Cullison B, Dyer JE, Wu TD. Clinical course of gamma-hydroxybutyrate overdose. *Ann Emerg Med.* 1998 Jun;31(6):716–22.

55 Snead OC, Gibson KM. Gamma-hydroxybutyric acid. *N Engl J Med*. 2005 Jun 30;352(26):2721–32. Review. No abstract available. Erratum in: *N Engl J Med.* 2006 Feb 2;354(5):537.

56 Li J, Stokes SA, Woeckener A. A tale of novel intoxication: a review of the effects of gamma-hydroxybutyric acid with recommendations for management. *Ann Emerg Med.* 1998;31:729–736.

57 Centers for Disease Control (CDC). Multistate outbreak of poisonings associated with illicit use of gamma hydroxy butyrate. *MMWR Morb Mortal Wkly Rep.* 1990;39:861–63.

58 Vickers MD. Gammahydroxybutyric acid. *Int Anesthesiol Clin.* 1969;7:75–89.

59 Galloway GP, Frederick SL, Staggers FE, Gonzales M, Stalcup SA, Smith DE. Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. *Addiction.* 1997;92:89–96.

60 Miró O, Nogué S, Espinosa G, To-Figueras J, Sánchez M. Trends in illicit drug emergencies: the emerging role of gamma-hydroxybutyrate. *J Toxicol Clin Toxicol*. 2002;40(2):129–35.

61 Louagie HK, Verstraete AG, DeSoete CJ, Baetens DG, Calle PA. A sudden awakening from a near coma after combined intake of gamma-hydroxybutyric acid (GHB) and ethanol. *J Toxicol Clin Toxicol.* 1997;35:591–4.

62 Ingels M, Rangan C, Bellezzo J, Clark RF. Coma and respiratory depression following the ingestion of GHB and its precursors: three cases. *J Emerg Med.* 2000;9(1):47–50.

63 Munir VL, Hutton JE, Harney JP, Buykx P, Weiland TJ, Dent AW. Gamma-hydroxybutyrate: a 30 month emergency department review. *Emerg Med Australas.* 2008 Dec;20(6):521–30. doi: 10.1111/j.1742-6723.2008.01140.x.

64 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;45:533–8.

65 Wood DM, Warren-Gash C, Ashraf T, Greene SL, Shather Z, Trivedy C, et al. Medical and legal confusion surrounding gammahydroxybutyrate (GHB) and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD). *QJM.* 2008;101:23–9.

66 Rambourg-Schepens MO, Buffet M, Durak C, Mathieu-Nolf M. Gamma-butyrolactone poisoning and its similarities to gammahydroxybutyric acid: two case reports. *Vet Hum Toxicol.* 1997 Aug;39(4):234–5.

67 Knudsen K, Greter J, Verdicchio M. High mortality rates among GHB abusers in Western Sweden. *Clin Toxicol (Phila).* 2008;46:187–92.

68 Liechti ME, Kunz I, Greminger P, Speich R, Kupferschmidt H. Clinical features of gamma-hydroxybutyrate and gamma-butyrolactone toxicity and concomitant drug and alcohol use. *Drug Alcohol Depend.* 2006;81:323–6.

69 Dietze PM, Cvetkovski S, Barratt MJ, Clemens S. Patterns and incidence of gamma-hydroxybutyrate (GHB)-related ambulance attendances in Melbourne, Victoria. *Med J Aust*. 2008;188:709–11.

70 Theron L, Jansen K, Skinner A. New Zealand's first fatality linked to use of 1,4-butanediol (1,4-B, Fantasy): no evidence of coingestion or comorbidity. *N Z Med J.* 2003;116:U650.

71 Couper FJ, Thatcher JE, Logan BK. Suspected GHB overdoses in the emergency department. *J Anal Toxicol.* 2004;28:481–4.

72 Roberts DM, Smith MW, Gopalakrishnan M, Whittaker G, Day RO. Extreme gamma-butyrolactone overdose with severe metabolic acidosis requiring hemodialysis. *Ann Emerg Med*. 2011;58:83–5.

73 Anderson IB, Kim SY, Dyer JE, Burkhardt CB, Iknoian JC, Walsh MJ, Blanc PD. Trends in gamma-hydroxybutyrate (GHB) and related drug intoxication: 1999 to 2003. *Ann Emerg Med.* 2006;47:177–83.

74 Ryan JM, Stell I. Gamma hydroxybutyrate – a coma inducing recreational drug. *J Accid Emerg Med.* 1997;14:259–91.

75 Centers for Disease Control and Prevention (CDC). Gamma hydroxy butyrate use – New York and Texas, 1995–1996. *MMWR Morb Mortal Wkly Rep.* 1997;46:281–3.

76 Schneidereit T, Burkhart K, Donovan JW. Butanediol toxicity delayed by preingestion of ethanol. *Int J Med Toxicol.* 2000;3:1.

77 Zvosec DL, Smith SW, McCutcheon JR, Spillane J, Hall BJ, Peacock EA. Adverse events, including death, associated with the use of 1,4-butanediol. *N Engl J Med*. 2001;344:87–94.

78 Centers for Disease Control and Prevention (CDC). Adverse events associated with ingestion of gamma-butyrolactone – Minnesota, New Mexico, and Texas, 1998–1999. *MMWR Morb Mortal Wkly Rep.* 1999;48:137–40.

79 Stephens BG, Baselt RC. Driving under the influence of GHB? *J Anal Toxicol.* 1994;18:357–8.

80 Al-Samarraie MS, Karinen R, Morland J, Opdal MS. Blood GHB concentrations and results of medical examinations in 25 car drivers in Norway. *Eur J Clin Pharmacol.* 2010;66:987–98.

81 Ross TM. Gamma hydroxybutyrate overdose: two cases illustrate the unique aspects of this dangerous recreational drug. *J Emerg Nurs.* 1995;21:374–6.

82 Ortmann LA, Jaeger MW, James LP, Schexnayder SM. Coma in a 20-month-old child from an ingestion of a toy containing 1,4-butanediol, a precursor of gamma-hydroxybutyrate. *Pediatr Emerg Care.* 2009;25:758–60.

83 Price PA, Schachter M, Smith S, Baxter RC, Parkes JD. Gamma-hydroxybutyrate in narcolepsy. *Ann Neurol.* 1981;9:198.

84 Couper FJ, Logan BK. Determination of gamma-hydroxybutyrate (GHB) in biological specimens by gas chromatography–mass spectrometry. *J Anal Toxicol.* 2000;24:1–7.

85 Eckstein M, Henderson SO, DelaCruz P, Newton E. Gamma hydroxybutyrate (GHB): report of a mass intoxication and review of the literature. *Prehosp Emerg Care.* 1999;3:357–61.

86 Bosman IJ, Lusthof KJ. Forensic cases involving the use of GHB in the Netherlands. *Forensic Sci Int.* 2003;133:17–21.

87 Mégarbane B, Fompeydie D, Garnier R, Baud FJ. Treatment of a 4-butanediol poisoning with fomepizole. *J Toxicol Clin Toxicol.* 2002;40:77–80.

88 Piastra M, Tempera A, Caresta E, Chiaretti A, Genovese O, Zorzi G, et al. Lung injury from 'liquid ecstasy': a role for coagulation activation? *Pediatr Emerg Care.* 2006;22:358–60.

89 Gunja N, Doyle E, Carpenter K, Chan OT, Gilmore S, Browne G, Graudins A. Gamma-hydroxybutyrate poisoning from toy beads. *Med J Aust.* 2008;188:54–5.

90 Hefele B, Naumann N, Trollmann R, Dittrich K, Rascher W. Fast-in, fast-out. *Lancet*. 2009;373:1398.

91 Ragg M. Gamma hydroxy butyrate overdose. *Emerg Med (Fremantle).* 1997;9:29–31.

92 Williams H, Taylor R, Roberts M. Gamma-hydroxybutyrate (GHB): a new drug of misuse. *Ir Med J.* 1998;91:56–7.

93 Dyer JE. Gamma-hydroxybutyrate: a health-food product producing coma and seizurelike activity. *Am J Emerg Med.* 1991;9:321–4.

94 Chin MY, Kreutzer RA, Dyer JE. Acute poisoning from gammahydroxybutyrate in California. *West J Med.* 1992;156:380–4.

95 Viswanathan S, Chen C, Kolecki P. Revivarant (gamma-butyrolactone) poisoning. *Am J Emerg Med.* 2000;18:358–9.

96 Osterhoudt KC, Henretig FM. Comatose teenagers at a party: what a tangled ' Web' we weave. *Pediatr Case Rev.* 2003;3:171–3.

97 Shannon M, Quang LS. Gamma-hydroxybutyrate, gammabutyrolactone, and 1,4-butanediol: a case report and review of the literature. *Pediatr Emerg Care.* 2000;16:435–40.

98 Caldicott DG, Kuhn M. Gamma-hydroxybutyrate overdose and physostigmine: teaching new tricks to an old drug? *Ann Emerg Med.* 2001;37:99–102.

99 Runnacles JL, Stroobant J. Gamma-hydroxybutyrate poisoning: poisoning from toy beads. *BMJ.* 2008;336:110.

100 Yates SW, Viera AJ. Physostigmine in the treatment of gammahydroxybutyricacid overdose. *Mayo Clin Proc.* 2000;75:401–2.

101 Libetta C. Gamma hydroxybutyrate poisoning. *J Accid Emerg Med.* 1997;14:411.

102 Savage T, Khan A, Loftus BG. Acetone-free nail polish remover pads: toxicity in a 9-month old. *Arch Dis Child.* 2007;92:371.

103 Robert R, Eugène M, Frat JP, Rouffineau J. Diagnosis of unsuspected gamma hydroxy-butyrate poisoning by proton NMR. *J Toxicol Clin Toxicol.* 2001;39:653–4.

104 Winickoff JP, Houck CS, Rothman EL, Bauchner H. Verve and jolt: deadly new Internet drugs. *Pediatrics.* 2000;106:829–31.

105 Lenz D, Rothschild MA, Kroner L. Intoxications due to ingestion of gamma-butyrolactone: organ distribution of gamma-hydroxybutyric acid and gamma-butyrolactone. *Ther Drug Monit.* 2008;30:755–61.

106 Lora-Tamayo C, Tena T, Rodriguez A, Sancho JR, Molina E. Intoxication due to 1,4-butanediol. *Forensic Sci Int.* 2003;133:256–9.

107 Higgins TFJ, Borron SW. Coma and respiratory arrest after exposure to butyrolactone. *J Emerg Med.* 1996;14:435–57.

108 Yambo CM, McFee RB, Caraccio TR, McGuigan M. The inkjet cleaner 'Hurricane' – another GHB recipe. *Vet Hum Toxicol.* 2004;46:329–30.

109 Suner S, Szlatenyi CS, W ang RY. Pediatric gamma hydroxybutyrate intoxication. *Acad Emerg Med.* 1997;4:1041–5.

110 Krul J, Girbes AR. Gamma-hydroxybutyrate: experience of 9 years of gamma-hydroxybutyrate (GHB)-related incidents during rave parties in the Netherlands. *Clin Toxicol (Phila).* 2011;49:311–15.

111 Elliott S. Nonfatal instances of intoxication with gammahydroxybutyrate in the United Kingdom. *Ther Drug Monit.* 2004;26:432–40.

112 Tancredi DN, Shannon MW. Case records of the Massachusetts General Hospital. Weekly clinico-pathological exercises. Case 30-2003. A 21-year-old man with sudden alteration of mental status. *N Engl J Med.* 2003;349:1267–75.

113 Cisek J. Seziure associated with butanediol ingestion. *Int J Med Toxicol.* 2001;4:12.

114 Harraway T, Stephenson L. Gamma hydroxybutyrate intoxication: the Gold Coast experience. *Emerg Med (Fremantle).* 1999;11:45–8.

115 Hardy CJ, Slifman NR, Klontz KC, Dyer JE, Coody GL, Love LA. Adverse events reported with the use of gamma butyrolactone products marketed as dietary supplements. *Clin Toxicol (Phila).* 1999;37:649–50.

116 Mahon KD, Tomaszewski CA, Tayal VS. Emergency department presentation of serum confirmed GHB ingestions. *Acad Emerg Med.* 1999;6:395–6.

117 Vickers MD. Gamma hydroxybutyric acid. *Proc R Soc Med.* 1968; 61:821–4.

118 Reed MJ, Clegg GR. Paroxysmal sympathetic surge associated with gamma hydroxybutyrate. *Eur J Emerg Med*. 2006 Feb;13(1):41–2.

119 Geldenhuys FG, Sonnendecker EW, De Kirk MC. Experience with sodium-gamma-4-hydroxybutyric acid (gamma-OH) in obstetrics. *J Obstet Gynaecol Br Commonw.* 1968 Apr;75(4):405–13.

120 Tunstall ME. Gamma-OH in anesthesia for caesarean section. *Proc R Soc Med. 1968;61:827–30.*

121 Laborit H. Soduim 4-hydroxybutyrate. *Int J Neuropharmacol.* 1964;3:433–45.

122 Piastra M, Barbaro R, Chiaretti A, Tempera A, Pulitanò S, Polidori G. Pulmonary oedema caused by 'liquid ecstasy' ingestion. *Arch Dis Child*. *2002;86:302–3.*

123 Jones C. Suspicious death related to gamma-hydroxybutyrate (GHB) toxicity. *J Clin Forensic Med.* 2001;8:74–6.

124 Liechti ME, Kupferschmidt H. Gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL): analysis of overdose cases reported to the Swiss Toxicological Information Centre. *Swiss Med Wkly.* 2004;134:534–7.

125 Brown TC. Gamma-hydroxybutyrate in paediatric anaesthesia. *Aust N Z J Surg.* 1970;40:94–9.

126 Dyer JE, Roth B, Hyma BA. Gamma-hydroxybutyrate withdrawal syndrome. *Ann Emerg Med. 2001;37:147–53.*

127 Dyer JE, Andrews KM. Gamma hydroxybutyrate withdrawal. *J Toxicol Clin Toxicol.* 1997;35:553–4.

128 Garrison G, Mueller P. Clinical features and outcomes after unintentional gamma hydroxybutyrate (GHB) overdose [abstract]. J Toxicol Clin *Toxicol.* 1998;35:503–4.

129 Wood DM, Brailsford AD, Dargan PI. Acute toxicity and withdrawal syndromes related to gamma-hydroxybutyrate (GHB) and its analogues gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD). *Drug Test Anal.* 2011 Jul–Aug;3(7–8):417–25. doi: 10.1002/dta.292.

130 Entholzner E, Mielke L, Pichlmeier R, Weber F, Schneck H. EEG changes during sedation with gamma-hydroxybutyric acid. *Anaesthesist.* 1995;44:345–50.

131 Doyon S. The many faces of ecstasy. *Curr Opin Pediatr.* 2001;13(6):170–6.

132 Bamonte G, de Hoog J, Van Den Biesen PR. A case of central serous chorioretinopathy occurring after γ-hydroxybutyric acid (liquid ecstasy) ingestion. *Retin Cases Brief Rep.* 2013 Fall;7(4):313–14. doi: 10.1097/ICB.0b013e31828ef073.

133 Okun MS, Boothby LA, Bartfield RB, Doering PL. GHB: an important pharmacological and clinical update. *J Pharm Pharm Sci*. 2001 May–Aug;4(2):167–75.

134 Thai D, Dyer JE, Benowitz NL, Haller CA. Gamma-hydroxybutyrate and ethanol effects and interactions in humans. *J Clin Psychopharmacol.* 2006 Oct;26(5):524–9.

135 Department of Health. *A Summary of the Health Harms of Drugs*. August 2011.

136 Lettieri J, Fung HL. Absorption and first-pass metabolism of 14C-gamma-hydroxybutyric acid. *Res Commun Chem Pathol Pharmacol.* 1976,13:425–37.

137 Drugs and human performance fact sheet. http://www.nhtsa.gov.

138 Harrington RD, Woodward JA, Hooton TM, Horn JR. Life-threatening interactions between HIV-1 protease inhibitors and the illicit drugs MDMA and gamma-hydroxybutyrate. *Arch Intern Med.* 1999 Oct 11;159(18):2221–4.

139 Romanelli F, Smith KM, Pomeroy C. Use of club drugs by HIV-seropositive and HIV-seronegative gay and bisexual men. *Top HIV Med.* 2003 Jan–Feb;11(1):25–32.

140 LeTourneau JL, Hagg DS, Smith SM. Baclofen and gamma-hydroxybutyrate withdrawal. *Neurocrit Care.* 2008;8(3):430–3. doi: 10.1007/s12028-008-9062-2.

141 Mason PE, Kerns WP 2nd.Gamma hydroxybutyric acid (GHB) intoxication. *Acad Emerg Med.* 2002 Jul;9(7):730–9.

142 Thomas G, Bonner S, Gascoigne A. Coma induced by abuse of gamma-hydroxybutyrate (GHB or liquid ecstasy): a case report. *BMJ*. 1997;314:35–6.

143 Reeves J, Duda R. GHB/GBl intoxication and withdrawal: a review and case presentation. *Addict Disord Treatment.* 2003;2:25–8.

144 Galloway GP, Frederick SL, Staggers F. Physical dependence on sodium oxybate. *Lancet.* 1994;343:57.

145 Wojtowicz JM, Yarema MC, Wax PM. Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *CJEM*. 2008 Jan;10(1):69–74.

146 Wood DM, Dargan PI. Development of a protocol for the management of acute gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL) withdrawal. *Clin Toxicol.* 2010;48:306.

147 Glasper A, McDonough M, Bearn J. Within-patient variability in clinical presentation of gamma-hydroxybutyrate withdrawal: a case report. *Eur Addict Res*. 2005;11(3):152–4.

148 Snead OC. Gamma-hydroxybutyrate. *Life Sci.* 1977;20:1935–44.

149 van Noorden MS, van Dongen L, Zitman FG, Vergouwen T. Gamma-hydroxybutyrate withdrawal syndrome: dangerous but not well-known. *Gen Hosp Psychiatry*. 2009 ;31:394–396.

150 Miglani JS, Kim KY, Chahil R. Gamma-hydroxy butyrate withdrawal delirium: a case report. *Gen Hosp Psychiatry.* 2000;22:213–15.

151 Hutto B, Fairchild A, Bright R. Gamma-hydroxybutyrate withdrawal and chloral hydrate. *Am J Psychiatry*. 2000;157:1706.

152 Hernandez M, McDaniel CH, Costanza CD, Hernandez OJ. GHB-induced delirium: a case report and review of the literature of gamma hydroxybutyric acid. *Am J Drug Alcohol Abuse.* 1998;24:179–83.

153 Catalano MC, Glass JM, Catalano G, Burrows S, Lynn W, Weitzner BS. Gamma butyrolactone (GBL) withdrawal syndromes. *Psychosomatics*. 2001;42:83–8.

154 Bowles TM, Sommi RW, Amiri M. Successful management of prolonged gamma-hydroxybutyrate and alcohol withdrawal. *Pharmacotherapy*. 2001;21:254–7.

155 Mahr G, Bishop CL, Orringer DJ. Prolonged withdrawal from extreme gamma-hydroxybutyrate (GHB) abuse. *Psychosomatics*. 2001;42:439–40.

156 McDaniel CH, Miotto KA. Gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) withdrawal: five case studies. *J Psychoactive Drugs.* 2001;33:143–9.

157 Schneir AB, Ly HT, Clark RF. A case of withdrawal from the GHB precursors gamma-butyrolactone and 1,4-butanediol. *J Emerg Med.* 2001;21:31–3.

158 Perez E, Chu J, Bania T. Seven days of gamma-hydroxybutyrate (GHB) use produces severe withdrawal. *Ann Emerg Med.* 2006;48:219–20.

159 Zepf FD, Holtmann M, Duketis E, Maier J, Radeloff D, Wagner A, et al. A 16-year-old boy with severe gamma-butyrolactone (GBL) withdrawal delirium. *Pharmacopsychiatry.* 2009;42:202–3.

160 Bennett WRM, Wilson LG, Roy-Byrne PP. Gamma-hydroxybutyric acid (GHB) withdrawal: a case report. *J Psychoactive Drugs*. 2007;39:293–6.

161 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;29:487–96.

162 Friedman J, Westlake R, Furman M. 'Grievous bodily harm': gamma hydroxybutyrate abuse leading to a Wernicke–Korsakoff syndrome. *Neurology*. 1996;46:469–71.

163 Addolorato G, Caputo F, Capristo E, Bernardi IM, Stefanini GF, Gasbarrini G. A case of gamma-hydroxybutyric acid withdrawal syndrome during alcohol addiction treatment: utility of diazepam administration. *Clin Neuropharmacol.* 1999;22:60–2.

164 Mycyk MB, Wilemon C, Aks SE. Two cases of withdrawal from 1,4-butanediol use. *Ann Emerg Med.* 2001;38:345–6.

165 Price G. In-patient detoxification after GHB dependence. *Br J Psychiatry.* 2000;177:181.

166 Mullins ME, Fitzmaurice SC. Lack of efficacy of benzodiazepines in treating gamma-hydroxybutyrate withdrawal. *J Emerg Med.* 2001;20:418–20.

167 Constantinides P, Vincent P. Chronic gamma-hydroxybutyric-acid use followed by gamma-hydroxybutyric-acid withdrawal mimic schizophrenia: a case report. *Cases J.* 2009 Jul 10;2:7520. doi: 10.4076/1757-1626-2-7520.

168 Miotto K, Darakjian J, Basch J, Murray S, Zogg J, Rawson R. (). Gamma-hydroxybutyric acid: patterns of use, effects and withdrawal. Am J Addictions. 2001;10(3):232–41.

169 Heiligenberg M, Wermeling PR, van Rooijen MS, Urbanus AT, Speksnijder AG, Heijman T, Prins M, Coutinho RA, van der Loeff MF. Recreational drug use during sex and sexually transmitted infections among clients of a city sexually transmitted infections clinic in Amsterdam, the Netherlands. *Sex Transm Dis.* 2012 Jul;39(7):518–27. doi: 10.1097/OLQ.0b013e3182515601.

170 Carey JW, Mejia R, Bingham T, Ciesielski C, Gelaude D, Herbst JH, Sinunu M, Sey E, Prachand N, Jenkins RA, Stall R. Drug use, high-risk sex behaviors, and increased risk for recent HIV infection among men who have sex with men in Chicago and Los Angeles. *AIDS Behav.* 2009 Dec;13(6):1084–96. doi: 10.1007/s10461-008-9403-3.

171 Grov C, Parsons JT, Bimbi DS; Sex and Love v3.0 Research Team. In the shadows of a prevention campaign: sexual risk behavior in the absence of crystal methamphetamine. *AIDS Educ Prev.* 2008 Feb;20(1):42–55. doi: 10.1521/aeap.2008.20.1.42.

172 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;13:293–308.

173 Winstock AR, Mitcheson L. New recreational drugs and the primary care approach to patients who use them. *BMJ*. 2012 Feb 15;344:e288. doi: 10.1136/bmj.e288.

174 Kamal RM, Qurishi R, De Jong CA. Baclofen and γ-hydroxybutyrate (GHB), a dangerous combination. *J Addict Med*. 2015 Jan–Feb;9(1):75–7. doi: 10.1097/ADM.0000000000000084.

175 Addolorato G, Caputo F, Capristo E, et al. Diazepam in the treatment of GHB dependence. *Br J Psychiatry*. 2001;178:183 (letter).

176 Eiden C, Capdevielle D, Deddouche C, Boulenger JP, Blayac JP, Peyrière H. Neuroleptic malignant syndrome-like reaction precipitated by antipsychotics in a patient with gamma-butyrolactone withdrawal. *J Addict Med*. 2011 Dec;5(4):302–3. doi: 10.1097/ADM.0b013e3182236730.

177 Project GHB. 2002. http://www.projectghb.org/addiction/addiction.htm; http://www.projectghb.org.addiction/addiction.htm.

178 Zepf FD, Holtmann M, Duketis E, Maier J, Radeloff D, Schirman S, Wagner A, Poustka F, Wöckel L. Withdrawal syndrome after abuse of GHB (gamma-hydroxybutyrate) and its physiological precursors – its relevance for child and adolescent psychiatrists. *Z Kinder Jugendpsychiatr Psychother*. 2009 Sep;37(5):413–20. doi: 10.1024/1422-4917.37.5.413.

179 Jones AW, Holmgren A, Kugelberg FC. Driving under the influence of gamma-hydroxybutyrate (GHB). *Forensic Sci Med Pathol*. 2008;4(4):205–11. doi: 10.1007/s12024-008-9040-1.