Review

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Acute toxicity and withdrawal syndromes related to gamma-hydroxybutyrate (GHB) and its analogues gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD)[1]

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Gamma-hydroxybutyrate (GHB) has been used as a recreational drug since the 1990s and over the last few years there has been increasing use of its analogues gamma-butyrolactone (GBL) and to a lesser extent 1,4-butanediol (1,4BD). This review will summarize the literature on the pharmacology of these compounds; the patterns and management of acute toxicity associated with their use; and the clinical patterns of presentation and management of chronic dependency associated with GHB and its analogues.

Keywords: gamma-hydroxybutyrate; gamma-butyrolactone; 1,4-butanediol; poisoning; recreational drugs; drugs of abuse; dependency; withdrawal

Introduction

Gamma-hydroxybutyrate (GHB) (Figure 1) is structurally related to the neurotransmitter gamma-aminobutyric acid (GABA) and is present in the human brain as a metabolite of GABA. GHB was first synthesized for use as an anaesthetic agent in 1964.[1] During early clinical trials, however, there was a high incidence of adverse effects, in particular seizures and vomiting, and so it was not further developed for this indication. During the 1970s and 1980s, GHB was abused by body builders due to its neuroendocrine effects, particularly its ability to increase growth hormone.[2] Subsequently, in the 1980s and 1990s, there were reports of use of GHB for stimulant and pro-sexual effects in the recreational drug scene, particularly amongst clubbers.[3,4] However, alongside this there were increasing reports during the 1990s of significant acute toxicity associated with the recreational use of GHB which led to its classification in many countries; GHB was listed as a DEA Schedule I drug in the USA in 2000 and classified as a Class C drug under the Misuse of Drugs Act (1971) in the UK in 2003; it is now controlled across all EU member states.

Gamma-butryolactone (GBL) (Figure 2) and 1,4-butanediol (1,4-BD) (Figure 3) are precursors and analogues of GHB that are not present as endogenous compounds. However, if they are ingested, they are metabolized to GHB and therefore cause similar clinical features. There have been reports of recreational use and of acute toxicity and deaths associated with the use of both of these analogues. Both GBL and 1,4-BD were classified as Class C drugs under the Misuse of Drugs Act (1971) in the UK in December 2009 in relation to human use; however, this classification still allows the use of these compounds in products in the chemical industry.

GHB and its analogues are usually sold to individuals for recreational use as liquid preparations. Although GHB can form salts and is therefore also available in powder form, there have been no reports to date of nasal insufflation of GHB powder, and where the powder is purchased by/supplied to users, this is usually dissolved in water or other drinks prior to use.[5] GBL and 1,4-BD are used in the chemical industry and are available in some cleaning and cosmetic products, in particular some nail varnish remover solutions and pads contain GBL; these have become a common source of GBL for recreational use.[5] Typically, GHB and its analogues are used orally, although there have been some rare reports of IV use.[5]

This review will summarize the available literature on the prevalence of use of GHB and its analogues, and discuss the pharmacology of these compounds and the patterns of acute toxicity and chronic dependence associated with their use.

Prevalence of Use

Data are not routinely collected on the use of GHB and its analogues GBL and 1,4BD within national surveys that report to European (European Monitoring Centre for Drugs and Drug Addiction, EMCDDA) and International (United Nations Office on Drug and Crime, UNODC) bodies that produce and publish annual reports on the prevalence of recreational drug use. Therefore, the data that are available on the prevalence of use of GHB and its analogues are based on small surveys conducted within

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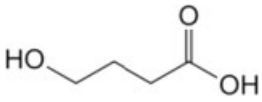

Figure 1. Chemical structure of gamma-hydroxybutyrate (GHB).

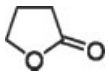

Figure 2. Chemical structure of gamma-butyrolactone (GBL).

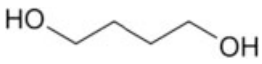

Figure 3. Chemical structure of 1,4-butanediol (1,4-BD).

smaller geographical areas or within sub-populations, such as schoolchildren or individuals who attend nightclubs.

In a European Schools Survey conducted in 25 European countries in 2003, only 0.5–1.4% of 15–16-year-olds reported that they had ever used GHB/GBL; although one finding of concern in this study was that the majority of students felt that use of GHB/GBL was lower risk when compared to the use of cannabis.[6]

The Independent Drug Monitoring Unit (IMDU) in the UK, which carries out online surveys of 1000 drug users each year reported that less than 3% of those surveyed in 1999 and 2000 reported every having used GHB.[7]

A survey of 408 individuals in bars in Amsterdam reported an overall lifetime prevalence of GHB/GBL use of 10%; however, use was up to 17.5% amongst those surveyed in 'gay' bars (bars popular with men who have sex with men) compared to less than 5% amongst those surveyed in what were described in the report as 'more mainstream' bars.[8] Surveys carried out in the UK of a self-selected group of 3873 clubbers through the dance magazine *MixMag* between 1999 and 2003 showed lifetime use prevalence rates of GHB varying from 12.8% in 1999 to 17.5% in 2003, and use of GHB in the last month varying from 3.4% in 1999 to 3.1% in 2003.[9,10] These surveys did not include data on use of GBL. The latest *MixMag* survey published in February 2010, which surveyed over 2000 clubbers, also included data on the prevalence of GBL use. The reported lifetime prevalence of use of GHB amongst those surveyed was 15.2% and of GBL was 5.8%; use in the last month was 1.7% for GHB and 1.6% for GBL.[11] It is important to note, when considering the results of surveys of drug use in clubbers and/or those who frequently attend bars, that use of recreational drugs amongst this group is generally higher than that in the population as a whole.[9,10,12]

Some of these user surveys have asked only about use of GHB; others about both GHB and GBL; and some have combined GHB and GBL use. It is therefore difficult to determine the relative use of these two analogues. However, some data from Switzerland, Sweden, and the UK suggests that there has been a switch from using GHB to using GBL that may have been associated with classification of GHB in these countries.[13–15] Furthermore, analysis of liquid samples in nightclub amnesty bins in the UK has confirmed this.[15] There are no data available on the prevalence of use of 1,4-BD; however, Internet drug forums and data from analysis of drug samples from amnesty bins and forensic science services suggests that use and availability of 1,4-BD is limited.[16,17]

Pharmacology of GHB, GBL, and 1,4-BD

GBL and 1,4-BD are both metabolized *in vivo* to GHB. GBL is rapidly metabolized to GHB by calcium-dependent serum lactonases.[18–20] Metabolism of 1,4-BD to GHB occurs in the liver through two-step conversion via hepatic alcohol dehydrogenase to gamma-hydroxybutyraldehyde followed by metabolism onto GHB via hepatic acetaldehyde dehydrogenase.[21,22] Studies in rats have shown that both ethanol and fomepizole competitively block the metabolism of 1,4-BD to GHB.[23–25] Human volunteer studies have shown that there is significant inter-individual variation in the rate of metabolism of 1,4-BD to GHB, possibly related to ADH-IB G143A polymorphism resulting in differences in activity of alcohol dehydrogenase.[26] After administration of 25 mg/kg 1,4-BD to volunteers, the elimination half-life for 1,4-BD was 39.3 $\pm$ 11 min; the time to maximal GHB concentration was 39.4 $\pm$ 11.2 min after 1,4-BD administration.[26]

GHB and its analogues are rapidly absorbed with a time to peak concentration of GHB of 20 to 45 min and of 1,4-BD of 25 min.[26–29] Animal studies have suggested that GBL is more rapidly and completely absorbed, with a higher maximum concentration (Cmax) and shorter time to maximum concentration (Tmax) of GHB after administration of GBL compared to an equimolar dose of GHB.[18,30–32] There are no pharmacokinetic data to be able to determine whether this is also the case in humans, but one study reported more rapid onset of sleep with oral GBL in children than with GHB.[33] GHB is rapidly metabolized via succinic acid semialdehyde to succinic acid with an elimination half-life of 30–50 min.[27–29,34] In addition to conversion of GBL to GHB by enzymatic methods, GBL is hydrolyzed to GHB under basic conditions and therefore changes in pH will result in a change in the GHB-GBL equilibrium *in vivo*.

GHB is an endogenous compound that is present at low concentrations as a metabolite of the neurotransmitter GABA (gamma-aminobutyric acid).[35] Once absorbed, exogenous GHB readily crosses the blood-brain barrier and its behavioural and inhibitory effects relate effects within the central nervous system (CNS). Most of these effects are due to GHB activity at the GABA receptor, in particular the GABA-B receptor.[36] GHB appears to have very limited direct activity at the GABA-A receptor but binds directly to and activates the GABA-B receptor.[36–38] Specific GHB receptors have also been found which are distinct from GABA receptors; however, it is thought that these are less important in producing the behavioural and CNS inhibitory effects of GHB.[39–42] Finally, in addition to activity at GABA-B and GHB receptors, GHB has been shown to produce effects within other neurotransmitter systems, in particular dopamine, serotonin, acetylcholine, and norepinephrine.[43–49] The greatest effects are seen within the dopaminergic system with animal studies showing that GHB results in an initial inhibition of synaptic dopamine release followed by an increase in neuronal dopamine production associated with a dose-dependent, non-functional neuronal dopamine leak.[44–47,49] GHB has also been shown to have neuroendocrine effects including increasing prolactin and growth hormone release.[2] This may be due to the effects of GHB within the hypothalamus, secondary to GHB serotonin/dopamine effects and due to induction of slow-wave and rapid eye movement sleep by GHB all of which increase growth hormone release.[2,50,51]

Analytical Detection

Confirmation of use of GHB and its analogues GBL and 1,4-BD, offers an interesting analytical challenge. As an endogenously

produced compound, the mere presence of GHB in the blood or urine doesn't prove use. A suitable threshold must therefore be established to distinguish exogenous GHB and its analogues from endogenous GHB, with such a value being of sufficient magnitude to provide unequivocal proof of ingestion. Thus a 10 mg/L discriminant limit has generally been accepted in ante-mortem urine where endogenous concentrations are typically around 1 mg/L.[52–58] While urine is often considered the matrix of choice due to an extended detection time in this matrix,[29] blood analysis should not be overlooked. Mean concentrations in blood are generally lower than those found in urine, therefore a lower discriminant limits such as 1 mg/L and 5 mg/L have been suggested.[50,59]

Reported concentrations, however, should not be viewed in isolation, as GHB concentrations in urine and whole blood have been shown to increase with time and temperature during storage.[60,61] This may be of particular concern if there is a substantial delay between specimen collection and analysis. In urine *in vitro* concentrations increases of around 5 mg/L have been reported following storage at room temperature for 244 days. Though significant increased concentrations in urine greater than the 10 mg/L limit have not been reported.[60–62] In vitro production in whole blood is more of a concern, with particularly large increases in samples stored in heparin and sodium citrate.[59,63] For post-mortem samples the problem is even greater with concentrations in excess of 100 mg/L being identified in whole blood in cases not linked to GHB.[64] The mechanisms involved in post-mortem production are not yet widely understood but may involve both bacterial dependent and independent processes.[65]

The retrospective power of the 10 mg/L discriminant limit is reduced by the rapid elimination of GHB meaning that concentrations in the terminal phase of elimination are similar to the upper limit of endogenous concentrations and these are reached extremely quickly following GHB use. Furthermore, GHB is extensively metabolized to carbon dioxide through the Krebs cycle meaning only around 1% of GHB is eliminated in urine.[27,28,66] Therefore though GHB concentrations in non-fatal overdoses have been reported up to 5,581 mg/L in urine and 551 mg/L in plasma,[65,67,68] the rapid elimination and lack of alternative metabolites means typically GHB ingestion can be detected for only around 12 h in urine.[27]

To aid the rapid detection of GHB, both colorimetric and enzyme-based assays have been developed.[69,70] Both assays can be performed in 5 min with LOD of 100 mg/L (colorimetric) and 50 mg/L (enzymatic). The rapid analysis time and reduced need for specialized equipment make these methods attractive for screening purposes; however, both lack true confirmatory power, and could lack sensitivity in retrospective cases where GHB concentrations may have fallen below the LOD of these techniques.

The most popular approach for GHB analysis is gas chromatography (GC) used with either a flame ionization detector (FID) or quadrupole mass spectrometer (MS). As GHB itself displays poor chromatography when analyzed by gas chromatography, GC-FID methods typically involve conversion of GHB to GBL, prior to liquid/liquid extraction (LLE) with a suitable solvent.[54,71,72] LODs of 0.5 mg/L have been reported for this technique which allow determination of both overdose cases and those around the discriminant limits. GC-MS methods though allow both increased sensitivity and discriminative power and are widely covered in the peer reviewed literature. For this approach, GHB is either analyzed following conversion to GBL or following derivatization.[27,54,56,66,72–76] The second method is more common as derivatization typically provides better chromatography than conversion to GBL, and usually involves trimethylsilyl (TMS) derivatization of GHB to form GHB-diTMS. Typically these GC-MS methods have an LOD and limit of quantification (LOQ) in the region of 0.1–5 mg/L depending on the methods employed and amount of sample analyzed. The use of multi-dimensional GC-MS/MS allowed the LOD to be lowered to 0.01 mg/L using only 50 µl of urine, although the presence of interfering peaks resulted in an LOQ of 2.5 mg/L.[77]

Liquid chromatographic (LC) methods for GHB detection are less prevalent but allow simultaneous detection of GHB, GBL, and 1,4-BD with rapid sample analysis. An LC-MS/MS method was shown to have an LOD for all analytes of 1 mg/L following a simple 'dilute and shoot' method and a total analysis time of just 12 min.[78] A similar approach has been developed for capillary electrophoresis, although a slightly higher LOD of 5 mg/L for the three analytes was reported.[79,80] The limited sample preparation and short analysis time of these approaches combined with the sensitivity and discriminatory power of mass spectrometry may offer a solution for both screening and confirmatory purposes if the appropriate equipment is available.

Another less conventional approach for detecting GHB ingestion is gas chromatography isotope ratio mass spectrometry (GC-C-IRMS). In brief, the technique accurately determines the ratio of two isotopes of an element (in this case C12 and C13) which can vary depending on the source materials and processes used in the compounds production. This facilitates the discrimination of endogenous and exogenously produced GHB. The first paper to use this approach analyzed GHB following TMS derivatization, which adds six additional carbons to the molecule originating from the derivatizing agent, and thereby considerably alters the isotope ratio of the analyte.[81] The authors reported that the delta value for 4 GHB standards and 5 GHB seizure samples ranged from −38.2‰ to −50.2‰ (following correction for the influence of TMS), which are outside the range considered to be endogenous (−18 to −24‰). These authors then determined the delta value of GHB in urine samples collected post-mortem, concerning cases not linked to GHB administration. The delta values reported ranged from −20.6‰ to −24.7‰ and are thus consistent with endogenous production. But as the reported GHB concentrations in these samples (13.8 mg/L to 86.3 mg/L) was much greater than endogenous ante-mortem samples, a cautious interpretation of their findings is merited. Rather than these values being representative of endogenous production, it is possible they have been influenced by GHB produced post-mortem. In the second paper by same author, GHB is analyzed following conversion to GBL thus avoiding any additional carbons.[81] Here the values reported for GHB standards and seizure samples (n = 10) ranged from −34.5‰ to −45.8‰. Individuals known to be exposed to GHB with concentrations well in excess of 10 mg/L showed delta values of −32‰ to −42.1‰. As expected, this contrasted greatly with the delta value determined in endogenous GHB from ante-mortem and post-mortem urine where values ranged from −23.5‰ to −27.0‰, although as before these samples had concentrations well above those generally considered endogenous. Work has since demonstrated that this technique may also offer the capacity to trace GBL samples from distinct sources based on their carbon isotope ratio.[83]

Acute Toxicity

There have been reports of acute toxicity associated with the use of GHB, GBL, and 1,4-BD.[14,15,84,85] As noted in the prevalence of use

section, GHB is the most commonly used of these compounds and in keeping with this most of the literature on toxicity associated with these compounds concerns GHB toxicity.[15] We will therefore focus this section on acute GHB toxicity.

The overall frequency of acute unwanted effects related to the use of GHB and its analogues is not known. In one study from Australia of 76 GHB users, 53% reported that they had suffered at least one GHB overdose related to its use (an overdose in this study was defined as 'having lost consciousness, and unable to be woken up').[86] There are a number of reasons why the true frequency of acute harm related to the use of GHB and its analogues is not known. First, we do not have a true background rate of GHB and analogue use to compare the reported rates of acute toxicity to. Secondly, not all patients who develop acute, unwanted effects related to the use of GHB and its analogues will present to healthcare facilities for assistance. Some individuals who become drowsy will be looked after by 'friends' until they get better. Finally, the recording of acute GHB or analogue toxicity by healthcare professionals may not always occur; for example, if there is no history of use or the healthcare practitioner is not aware of the clinical toxidrome associated with toxicity from GHB or its analogues, then the presentation may be attributed to ethanol or another depressant drug. Routine toxicological screening is not undertaken in the majority of emergency departments, as the results are often not available in a time frame to alter the individual patient's management. Therefore the diagnosis of acute GHB or analogue toxicity is based upon the recognition of the clinical toxidrome associated with the overdose of GHB or its analogues. A previous study in patients with significant neurological depression has demonstrated that GHB concentration at the time of presentation to the hospital did not correlate well with either the degree of neurological compromise or the time to recovery.[87]

The clinical features of acute GHB and analogue toxicity have been well described in large case series from London, UK; Zurich, Switzerland; San Francisco, USA, and Barcelona, Spain.[14,15,88,89] Overall, the most common clinical feature seen in all of these case series was neurological depression; other commonly seen clinical features included bradycardia, hypotension and mild hypothermia. The concurrent use of ethanol and/or other recreational drugs was commonly reported with only 34.6% reporting lone GHB/GBL use in one large series of acute GHB/GBL toxicity.[15] Therefore some of the clinical features classically associated with acute toxicity related to GHB and its analogues may be 'masked'. For example, an individual who has used both GHB and cocaine may not have hypotension or bradycardia due to the opposing 'adverse effects' of these drugs.[15] Additionally, the concurrently used ethanol and/or other recreational drugs may contribute to some of the other clinical features seen in patients presenting with GHB and/or GHB analogue toxicity. This is particularly important for ethanol; a number of authors have suggested that GHB users who co-ingest ethanol are more likely to develop severe complications related to GHB use.[14,90,91] This has been confirmed by a double-blind, placebo-controlled, cross-over volunteer study that investigated the potential for toxicity associated with GHB alone compared to GHB and ethanol co-ingestion.[92] This showed that GHB plus ethanol was associated with more adverse effects in particular hypotension and hypoxia; this was not explained by a pharmacokinetic interaction as there was no difference in ethanol or GHB concentrations between the groups.

The overall frequency of vomiting in these series, is reported as 23% (range 17–31%).[14,15,88,89] Vomiting in individuals with a reduced level of consciousness, especially those with a Glasgow coma scale (GCS) of less than 8/15, is thought to increase the risk of aspiration due to the lack of protective airway reflexes in an individual with neurological depression. The rate of aspiration and aspiration pneumonia was not reported in all of the case series. However, in the US series, although the majority of vomiting (88%) occurred in those with a GCS score of $\leq$8, there were no recorded episodes of pulmonary aspiration.[89] The overall rate of 'non-responsive coma', typically defined as a GCS of 3/15, from these case series was 22% (range 16–34%).[14,15,88,89] Despite this proportion of individuals with a 'non-responsive coma', overall only 7% (range 3–17%) required endotracheal intubation for management of their airway. The frequency of seizures reported in these case series was 6% overall (range 2–10%).[14,15,88,89] It is difficult to determine if this is the true frequency of 'seizures', as GHB and its analogues are known to cause myoclonic jerks. The majority of seizures reported in these case series are likely to have occurred in the pre-hospital environment, where the myoclonic jerking may have been misinterpreted as a seizure.

There have been deaths related to acute toxicity from GHB and its analogues.[15,75,84,85,93,94] It is not possible to determine the true risk of death related to acute GHB or analogue toxicity. The detection and interpretation of GHB or its analogues in biological fluids post mortem is difficult, as discussed above. Additionally, the majority of fatalities will have involved the co-use of one or more other substances, and therefore it is not always easy to determine what significance the detection of GHB or its analogue has to the actual cause of death. However, despite these caveats, there are deaths that are directly attributable to the use of GHB or its analogues. The predominant reason for death in these cases is respiratory depression and aspiration or respiratory arrest as a consequence of GHB- or analogue-induced neurological depression and coma.

In 2008, there were reports of a number of young children presenting to Emergency Departments in the UK, Australia, and North America with significantly reduced levels of consciousness and, in some instances, non-responsive coma, with rapid recovery and no long-term neurological sequelae.[95,96] The clinical picture of these children was in keeping with acute GHB or analogue toxicity; subsequent toxicological screening detected the presence of GHB. On further questioning of the children, parents, and/or siblings, it was noted that the common feature was that the child had been playing with a toy bead product, marketed as Aqua Dots in North America and as Bindeez Beads in Europe and Australia. There was no mention on the product labelling that the beads contained GHB or its analogues; however, it stated that it contained 1,5 pentanediol (1,5-PD). Toxicological analysis of the beads (both Aqua Dots and Bindeez Beads) showed that 1,5-PD was not detected, but 1,4-BD was present instead.[95–97] It is likely that during the manufacture in China, the wrong solvent was used. Following the discovery of the GHB analogue, there was an international recall of this product to prevent further cases of accidental 1,4-BD toxicity.

Management of Acute Toxicity

The management of acute toxicity from GHB or its analogues is largely supportive. The duration of the reduced level of consciousness, particularly the non-responsive coma is generally short-lived. On average, the majority of patients have recovered fully within 2–3 h of the onset of the coma. Therefore there is debate as to whether patients with 'non-responsive coma' should be intubated for airway protection. As noted, GHB and its analogues are associated with vomiting which, in the presence of a reduced level

of consciousness and therefore loss of protective airway reflexes, can be associated with aspiration. In non-intubated patients with acute toxicity with GHB and its analogues, vomiting in those with the greatest degree of neurological compromise was not associated with aspiration, suggesting that 'prophylactic' intubation in the case of vomiting is not indicated.[89] From the evidence from our own clinical practice and that reported in the other large case series, it would seem that routine intubation of patients with acute GHB or analogue toxicity is not recommended unless they exhibit vomiting, seizures, or another clinical indication for intubation.

There is no specific antidote to reverse the acute effects of GHB or its analogues. Previously it has been suggested that naloxone may be beneficial in the management of patients with acute GHB or analogue toxicity. We feel that the only role for naloxone in the management of these cases is where diagnosis of GHB or analogue toxicity is not apparent to exclude opioid toxicity as a cause for the clinical features. However, in patients where acute GHB or analogue toxicity is clinically the most likely diagnosis, there is no pathophysiological or pharmacological basis for the routine use of naloxone, as the mechanisms of action of GHB and its analogues are different to those of opioids.

Chronic Dependency and Withdrawal

The first case of GHB-related dependency was reported in the medical literature in 1994 and was of a female patient using 25g of GHB per day in five divided doses over a period of two years.[98] Since then, there have been numerous published case reports and small case series of dependency developing in individuals following chronic use of GHB and its analogues.[99–113] The reported cases have been reviewed in several, large semi-systematic reviews, the latest of which was published in 2008.[102] This included 36 GHB cases, 18 GBL cases, and 3 1,4-BD cases. The lower reported frequency of dependency and withdrawal related to 1,4BD are likely to reflect the lower use rates of this analogue, rather than an association with a lower risk of dependency and/or withdrawal.

The proportion of individuals who use GHB and its analogues and increase their use to a level where they are at risk of developing dependency is not known. The European Monitoring Centre for Drugs and Drug Addiction noted in a recent report on GHB that there is no pan-European system for reporting or collating data on the frequency of GHB/GBL dependency.[17] There are some data available where GHB has been used in the management of ethanol withdrawal, reporting the risk of individuals misusing GHB that they had been prescribed and/or developing dependency symptoms. In clinical trials using GHB for the management of ethanol withdrawal, up to 15% of individuals either increased their dose of GHB above that recommended in their treatment or developed a craving for it.[114–116] In addition, it was thought that around 5% of individuals could be considered dependent on GHB.[114,116] However, this population may not be reflective of the population as a whole as they already have a tendency to be dependent.

Typically, individuals who develop dependency to GHB and/or its analogues have been using for several months and on multiple occasions throughout the day.[102,112] It is estimated that the minimum duration of use is 2–3 months, using more than 3–4 times per day on a regular basis. The majority of users are using considerably more frequently and/or in larger volumes by the time they present to healthcare professionals either in withdrawal or requesting help for their dependency. In addition, a proportion of users may have tried self-treatment with benzodiazepines, ethanol and/or baclofen prior to presentation to healthcare professionals. Although, as noted, dependency typically develops after prolonged regular use, there has been one reported case of a female who used '3 ounces' of GHB every 2–3 hours for 7 days and then developed withdrawal symptoms when she stopped.[117]

The clinical features of GHB and its analogue withdrawal are similar to those seen with ethanol and/or benzodiazepine withdrawal; often it is not possible to differentiate them clinically without a history of dependent GHB or analogue use. The most commonly seen features of withdrawal include tremor, tachycardia, anxiety and agitation, hallucinations (predominantly auditory and visual), delirium, diaphoresis (sweating), hypertension, and confusion. Seizures appear to be less common than with ethanol withdrawal, and have been reported in less than 10% of cases. Delirium, agitation, and other neuropsychiatric features appear to be more common and more marked in patients with withdrawal from GHB and its analogues than those with ethanol withdrawal. From the published cases, and our own clinical experience, the onset of symptoms of withdrawal in those with a dependency on GHB and its analogues tend to occur sooner after the last used dose compared to the onset in those with a dependency on ethanol or benzodiazepines. Typically, symptoms tend to occur within a 'few hours' of the last dose and can be 'very severe' within 24 h.[102] It should be noted that withdrawal may actually occur in patients presenting with acute overdose or another medical problem if they remain in hospital for too long.[118] One individual is reported as having developed Wernicke-Korsakoff syndrome following GHB abuse; however this individual had an underlying ethanol dependency and also was noted to have very poor food intake when using GHB.[119] Therefore we feel that it is likely that this was not directly related to the GHB dependency, as seen with ethanol dependency, but rather a consequence of both the underlying ethanol dependency and the poor nutritional intake. There has been only one death reported during treatment for GHB dependency.[103] This individual was treated for 12 days with benzodiazepines for GHB withdrawal and during this time they developed pneumonia; on day 13 of treatment, the patient developed 'spontaneous generalised spastic muscular contraction' with an 'upward gaze', which was shortly followed by a cardiac arrest and death. The cause of death was determined as 'complication of GHB withdrawal resulting from chronic substance abuse'; however, we feel that it is likely that other medical complications played a significant role given the fact that the patient deteriorated so late in the course of treatment.

There is no agreed management strategy for patients presenting with acute withdrawal related to dependence on GHB and its analogues, and there is no pharmacological reason as to why the management should differ between the different analogues. A suggested management algorhythm for determining whether patients with GHB/GBL dependency need treatment as an inpatient or an outpatient has been previously published.[112] This distinction is largely based on the frequency and amount of GHB/GBL used per day. For those with infrequent use (<3 times per day) or small volume use (<30 g GHB or <15 g GBL), it is suggested that management with diazepam is appropriate. It is likely that, similar to ethanol withdrawal, there is little difference between benzodiazepine classes and that other benzodiazepines such as lorazepam or chlordiazepoxide could be used. Admission and treatment as an inpatient is recommended for those with more frequent use and/or higher volume use. In this group, the management strategy is differentiated based on whether there is delirium present; where it is absent, diazepam is recommended over a 0–7 day period. In those with delirium present at the time

of presentation, high-dose diazepam, up to 200 mg in the first 24 h, is the initially recommended management, with barbiturates for resistant cases. There is no recommendation on ongoing management after the first 24 h. In our experience, almost 50% of those patients presenting to secondary care facilities (hospitals) with acute withdrawal will end up requiring barbiturates and admission to an Intensive Care Unit, typically as those presenting to hospital already have delirium at the time of presentation.[113] In the management of ethanol withdrawal, the CIWA-AR (Clinical Institute Withdrawal Assessment-Alcohol Revised) scale is used to objectively determine when benzodiazepines should be administered. Currently, there is no similar scoring system for the objective management of withdrawal from GHB and its analogues. We would, however, advocate the use of a subjective assessment system, where individuals are administered benzodiazepines in the first 24 h on the basis of withdrawal symptoms, particularly neuropsychiatric features; this treatment approach, initially based on symptoms rather than a scoring system, has also been suggested by others.[113,120] After the initial period of assessment, we would then recommend the use of a reducing regimen based on the requirements in the first 24 h; this may need an extended tapering course, since the withdrawal from GHB and its analogues tends to be more prolonged compared to ethanol.[102] Despite the previously reported case of Wernicke Korsakoff Syndrome related to GHB dependency,[119] we would not routinely recommend the use of vitamin B treatment as we feel that it is likely that the patient's condition in this case report was related to other factors rather than purely to the GHB dependency. It should, however, be considered in patients with a history of ethanol excess and/or malnutrition.

In our experience, the limitation of outpatient detoxification from GHB/GBL dependency is largely due to the lack of appropriate facilities in the community with the necessary experience in managing this group of patients. Currently in the UK we are aware of a number of small services being developed in areas where there is high use of GHB and its analogues, and where there is likely to potentially be a large number of individuals with dependency. Typically these services have been targeted towards the gay community, since, as previously noted, these men have the highest frequency of use of GHB and its analogues. There is the potential that there is greater need for these services than is currently anticipated. Further expansion of these treatment services needs to be targeted to areas of greatest need, with appropriate ongoing psychological support to try and reduce relapse and reuse of GHB and its analogues.

The majority of treatment regimens recommend/describe the use of benzodiazepines in the management of acute GHB/GBL withdrawal.[102,112,113] However, in a number of these reports, a proportion of individuals fail to respond to high-dose benzodiazepines. This may, in part, be due to the fact that benzodiazepines, similar to some barbiturates, are indirect GABA-A agonists; however, as summarized earlier, GHB and its analogues act primarily at the GABA-B receptor.

Baclofen is a GABA-B receptor agonist. In animal models, chronic administration of GHB has been shown to induce cross-tolerance to baclofen.[42,121] There has been one case report of the use of baclofen in a patient with acute GHB-related withdrawal (agitation, tremor, and seizures), who was failing to respond to increasing doses of benzodiazepines as her GHB dose was reduced.[122] With the addition of baclofen to her treatment regimen, there was an improvement in her symptoms and the GHB could be weaned entirely. However, it should be noted that whereas in the majority of cases managed with high-dose, short-term benzodiazepine withdrawal, this patient continued to use regular baclofen at 10 weeks. It would appear that the baclofen, as would be expected from its similar mechanism of action but with a longer half-life, had simply substituted for the GHB rather than acting as a withdrawal agent.

Pentobarbital, unlike other the majority of other barbiturates, is able to directly open GABA-A and voltage-gated chloride channels.[123] Therefore, there is the potential that pentobarbital may be more beneficial in patients with severe withdrawal than benzodiazepines. There has been a case series of four individuals with severe GBL withdrawal, where pentobarbital was used in their management.[124] Two patients received pentobarbital after treatment failure with 6 h of high-dose Lorazepam; it significantly improved their clinical condition. The other two patients received pentobarbital at the onset of treatment, with clinical improvement; subsequent weaning of the pentobarbital resulted in a recurrence of the withdrawal symptoms. All four patients were managed without the need for intubation and mechanical ventilation; additionally all remained GBL-abstinent at follow-up (minimum follow-up was four months).

The optimal management regimen for acute GHB, GBL, and 1,4-BD withdrawal still needs to be determined. Based on the evidence described here, we would recommend at this time that patients are initially managed with benzodiazepines. Ideally, these should commence prior to the development of withdrawal symptoms, and in particular delirium, to reduce the total dose required and the duration of treatment. In resistant cases, the use of baclofen and/or other agents such as barbiturates should be considered as second-line management options.

Summary

GHB and its analogues GBL and 1,4-BD are used as recreational drugs; there are limited data available on the epidemiology of their use, but it appears that they are most commonly used in the gay community and by clubbers. GBL and 1,4-BD are metabolized to GHB *in vivo* and GHB causes its effects largely through activity at the GABA-B receptor; but it also has effects at GHB receptors and on dopamine and other neurotransmitters, including serotonin and norepinephrine. The pattern of acute toxicity seen with GHB and its analogues has been well described in large published series from around the world. CNS depression predominates, but other features, such as vomiting and seizures, can occur. The coma seen with GHB toxicity is usually short-lived and most patients, even those with profound coma, can be managed without the need for intubation. Recently, there has been increasing evidence of dependence associated with regular use of GHB and/or its analogues. This can be associated with significant physical withdrawal symptoms with prominent neuropsychiatric features requiring inpatient management. This is best treated with high-dose benzodiazepines titrated to neuropsychiatric features, although barbiturates, or potentially baclofen, may be required in those who are resistant to benzodiazepine therapy.

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