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# Gamma hydroxy butyrate abuse and dependency

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## Abstract

The recreational use of gamma hydroxy butyrate (GHB) has gained popularity over the last decade. GHB was initially sold as a safe bodybuilding and fat burning compound. It is now also widely abused by bodybuilders and young ravers. GHB attracts young people due the euphoria that it initially produces, and the claimed increase in sociability and sexual function (it is also known as liquid Ecstasy). Over the last few years, there has been an increase in the number of cases of GHB intoxication, dependence and severe withdrawal, as reported in medical literature. The situation is complicated by the use of GHB analogues, other toxic chemicals that are easily converted into GHB.

GHB has recently been classified as a class 'C' drug in the UK, but no provisions were made in relation to GHB analogues. GHB has been increasingly used in rape cases due to its capacity to produce intoxication and amnesia. The management of patients dependent on GHB is rather complicated due to the high doses of medication that they require to control withdrawal symptoms.

## Keywords

GHB, GHB analogues, physical dependence, ravers

## Introduction

Gamma hydroxyl butyrate (GHB) is an organic compound. It is found in small concentrations in human brains (Bessman and Fishbein, 1963). GHB functions are closely linked to the GABA system, because GHB is a GABA metabolite (Bessman and Fishbein, 1963; Anderson *et al.*, 1977). The main difference between these two compounds is that GABA cannot cross the blood–brain barrier whereas GHB readily crosses biological membranes (Cash, 1994). GHB was discovered in humans at about the same time that it was synthesized by Dr H. Laborit, a French surgeon who was looking for an anaesthetic compound (Laborit, 1964). The discovery of GABA as the main inhibitory brain neurotransmitter was a stimulus to scientists to look for compounds that could interfere or modify GABA activity in the central nervous system (CNS), in the hope of expanding therapeutic options for disorders such as epilepsy, amongst others.

## Clinical use

GHB has been used as an anaesthetic agent in some European countries. However, its use now appears to be in decline. Initially, GHB was believed to be a good anaesthetic agent but, at doses

which it has an anaesthetic effect, it lacks analgesic properties (Miotto *et al.*, 2001). Therefore, high doses are required to induce analgesia when unwanted effects are seen, such as jerking movements and vomiting (Entholzner *et al.*, 1995). These side-effects make the compound rather unpopular. Over the last 20 years, GHB has also been marketed for diverse effects. It has been advertised as anabolic, hypnotic, antidepressant, anxiolytic and as a cholesterol-lowering agent. It is only over the last 10 years that the potential of GHB to produce dependence was recognized.

The most researched use of GHB in medicine is in the field of sleep disorders. GHB has shown to be an effective treatment in cases of narcolepsy associated with cataplexy. GHB consolidates the disturbed sleep architecture seen in this disorder (Broughton and Mamelak, 1979). GHB has also been used in alcohol and opioid detoxification regimes, and also as anti-craving medication following alcohol detoxification (Gallimberti *et al.*, 1989; Gallimberti *et al.*, 1993; Addolorato *et al.*, 1999).

In the early 1990s, GHB became popular with bodybuilders and athletes. GHB was advertised and promoted as a safe, easy to use bodybuilding compound, and an alternative to anabolic androgenic steroids (AASs). GHB was assumed to alter sleep architecture by increasing slow wave sleep at the expense of sleep stages 1 and 2. Thus, GHB is associated with an increase in the production of growth hormone (GH), which is only released during slow wave

sleep (Gallimberti *et al.*, 1989). Together with the belief that GHB would promote fat burning during sleep, this gave GHB great acceptance and popularity. Gonzalez *et al.* (2001) reported the use of GHB in combination with AASs (Gonzalez *et al.*, 2001, 2001).

### GHB misuse (method and route of administration)

GHB is generally found in liquid preparations. It is also available in powder and capsules. GHB is water-soluble, and can be mixed with water or drinks for ingestion and to disguise its salty flavor (Miotto *et al.*, 2001; Degenhardt *et al.*, 2002). GHB analogues such as gamma butyrolactone (GBL), 1,4-butanediol (BD), gamma hydroxyvalerate, gamma valerolactone and sodium oxalate are equally soluble in water (European Monitoring Centre for Drugs and Drug Addiction, 2000; Degenhardt *et al.*, 2003, 2003). GHB could be used in combination with other illicit substances.

In a sample of GHB users, Miotto *et al.* (2001) reported that 40% use GHB to enhance and prolong the 'high' obtained from other drugs. The drugs most frequently used in combination with GHB were Ecstasy (53%), cannabis (50%), cocaine (43%), amphetamines (40%) and alcohol (37%) (Miotto *et al.*, 2001).

Some users dose at regular given intervals, taking the same amount (round-the-clock use). Others take GHB or its analogues when dancing, exercising or before going to sleep (Galloway *et al.*, 1997; Gonzalez *et al.*, 2001). The recreational dose of GHB is believed to be approximately 20–30 mg/kg (Table 1) (Li *et al.*, 1998; Craig *et al.*, 2000; European Monitoring Centre for Drugs and Drug Addiction, 2000; Nicholson and Balster, 2001). However, the concentration that users take is quite difficult to determine because there is no means of control over the purity of the products that they use. This is especially difficult for those users that prepare GHB at home, or for users of GHB analogues. The symptoms observed after GHB administration depend on the

**Table 1** Clinical effects associated with gamma hydroxyl butyrate

Dose (mg/kg)	Effect
10	Anxiolytic effect
20–30	Euphoria, drowsiness, somnolence, and dizziness
30–40	Abrupt onset of sleep, enuresis, hallucinations, myoclonic jerks
40–50	Induces anaesthesia
> 60	Coma

**Table 2** Symptoms associated with the recreational use of gamma hydroxyl butyrate

Euphoria	Increased libido
Somnolence	Confusion
Ataxia	Headaches
Vomiting	Nausea
Aggression	Incontinence

doses administered. Table 2 shows the symptoms associated with increasing doses of GHB.

Home production of GHB is not difficult, nor does it require an advanced knowledge of chemistry. A GHB precursor is mixed with sodium hydroxide or potassium hydroxide, with heating for approximately 45–60 min, followed by filtering and cooling down. The final mixture is then stored in empty water bottles and kept in the fridge.

GHB was classified as a class 'C' drug from 1 July 2003 in the UK. This means that it is illegal to produce and distribute GHB (Home Office, 2003). GHB is controlled under the misuse of drug legislation in Belgium, France, Ireland, Italy and Sweden. The situation is different in Austria, Germany, Finland and the Netherlands, where GHB is controlled by the Medicines Act. (European Monitoring Centre for Drugs and Drug Addiction, 2000). GHB is under strict control in the USA since 2000, when it was classified as a schedule I substance. This change in legislation has had a positive effect because it appears to have been accompanied by a decrease in the number of cases seen at Accident and Emergency Department (A&E) departments in recent years (Miotto *et al.*, 2001, 2001).

GHB-containing pharmaceutical preparations are available in four European countries. It has been licensed in Austria and Italy to control alcohol craving. In France and Germany, it is still employed as an anaesthetic (European Monitoring Centre for Drugs and Drug Addiction, 2000).

The European Monitoring Centre for Drugs and Drug Addiction reported that GHB was associated with 11 deaths in the European Union (EU) between September 1995 and January 2000. UK and Sweden reported four deaths each. In the same period, Finland reported two deaths, and Denmark reported one (European Monitoring Centre for Drugs and Drug Addiction, 2000).

The situation is further complicated by the use of GHB analogues. These are compounds that can be converted into GHB via a simple chemical reaction (e.g. they can be metabolized to GHB by plasma enzymes after being ingested). Control of these products is more challenging. GHB analogues are industrial solvents that are relatively easy to obtain because they are used for the production of polyurethane, pesticides and elastic fibres, among others (European Monitoring Centre for Drugs and Drug Addiction, 2000; US Department of Justice, 2002). In the UK, GBL is easily found in nail polisher removal products.

### Biochemistry

Succinic semialdehyde dehydrogenase (SSADH) deficiency, also known as 4-hydroxybutyrate aciduria, is a genetic condition associated with a deficiency of the enzyme SSADH (Onkenhout *et al.*, 1989, 1989; Pearl *et al.*, 2003). In this condition, there is a mutation in the SSADH gene (Rating *et al.*, 1984; Rahbeeni *et al.*, 1994) on chromosome 6p22 (Pearl *et al.*, 2003) and the condition is inherited as an autosomal recessive (Rahbeeni *et al.*, 1994; Pearl *et al.*, 2003). The mutation of the SSADH gene reduces mitochondrial SSADH activity, thus stopping Krebs cycle, and there is an increase in succinic semialdehyde (SSA) that is then converted to

GHB, resulting in high concentrations of GHB and SSA in the brain (Onkenhout *et al.*, 1989, 1989; Pearl *et al.*, 2003, 2003). This condition tends to follow a chronic course, characterized by learning difficulties, psychomotor retardation, delayed speech, hypotonia, behavioural difficulties, seizures and electroencephalogram abnormalities (Rating *et al.*, 1984; Pearl *et al.*, 2003, 2003). These symptoms resemble some of the symptoms observed in cases of chronic GHB consumption.

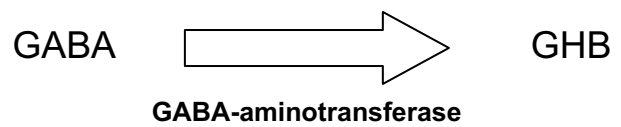
## Physiology

GABA is the precursor of GHB in human brains (Anderson *et al.*, 1977, 1977; Docherty *et al.*, 1978) with the substitution of a hydroxy group for the GABA amino group resulting in GHB (Cash, 1994). The enzyme responsible for this reaction is GABA aminotransferase (Onkenhout *et al.*, 1989, 1989) (Fig. 1).

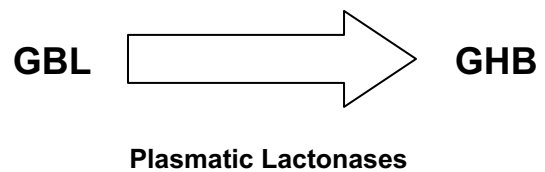
GHB is released from the pre-synaptic neurones in a process dependent on  $\text{Ca}^{2+}$  (Li *et al.*, 1998). GHB binds in a reversible manner to specific GHB receptors (Snead and Liu, 1984; Tunnicliff, 1997) that are widely distributed in the human brain. The highest receptor density is found in the pons and hippocampus, followed by the caudate nucleus and cortex (Docherty *et al.*, 1978; Hechler *et al.*, 1987; Tunnicliff, 1997). The GHB receptor is a G-protein linked receptor (Snead, 2000). GHB receptors are found exclusively in the CNS. No GHB receptors are found outside CNS despite GHB being found in high concentrations in peripheral tissues. GHB has weak agonist properties at  $\text{GABA}_B$  receptors in the brain, but it does not interact with the  $\text{GABA}_B$  receptors in the spinal cord (Hechler *et al.*, 1987; Mathivet *et al.*, 1997; Carrai *et al.*, 2001). GHB has no affinity for  $\text{GABA}_A$  receptors (Mathivet *et al.*, 1997). GABA lacks affinity for the GHB receptor (Bernasconi *et al.*, 1992). A specific GHB antagonist known as NCS-382 has been isolated. It can displace GHB binding and, in a dose-dependent fashion, it is capable of reversing the effects associated with GHB administration such as catalepsy, sedation and an increase in dopamine synthesis (Hechler *et al.*, 1993; Maitre, 1997).

GBL, BD and other GHB analogues are converted into GHB as soon as they are absorbed; in this respect, they should be considered as pro-drugs (Roth and Giarman, 1966, 1966; Roth and Giarman, 1968). BD appears to be able to interact with GABA receptors, but the available data are not conclusive (Roth and Giarman, 1968) (Fig. 2).

The GHB-specific mechanism of action in human brains is poorly understood. It is still open to debate whether GHB is a neurotransmitter or a neuromodulator (Maitre, 1997). Currently, the consensus appears to be that endogenous GHB is an inhibitory neuromodulator (Bernasconi *et al.*, 1999). Its action is associated with diverse brain functions such as the control of glucose metabolism, oxygen consumption and temperature regulation (Mamelak, 1989; Li *et al.*, 1998). The exact mechanism of action in the brain and peripheral tissues remains unknown. GHB interacts with diverse neurotransmitter systems. However, the actions of GHB in the brain are believed to be secondary to its effects on the dopamine system (Hechler *et al.*, 1993; Fiegenbaum and Howard, 1996).



**Figure 1** GABA is metabolized into gamma hydroxyl butyrate (GHB) by the enzyme GABA-aminotransferase



**Figure 2** Gamma butyrolactone (GBL) is metabolized into gamma hydroxyl butyrate (GHB) by plasmatic lactonases. These enzymes break the lactone ring

GHB receptors are found on dopamine containing neurones, which are more abundant towards the synapses (Mathivet *et al.*, 1997; Tunnicliff, 1997). GHB is found to produce an increase dopamine activity. This effect is mediated by an enzymatic induction of tyrosine hydroxylase activity and therefore an increase of dopamine synthesis (Fiegenbaum and Howard, 1996). GHB also produces an increase in dopamine release (Mamelak, 1989; Fiegenbaum and Howard, 1996).

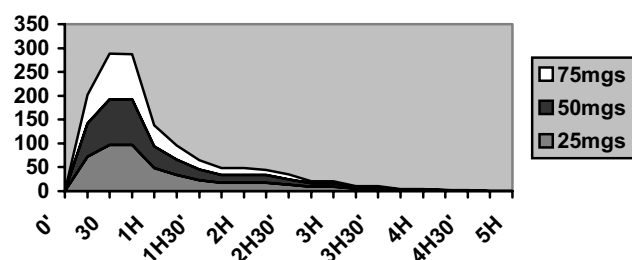
High GHB doses are thought to produce an increase of dopamine function, whereas low doses tend to downregulate the dopamine system (Spano *et al.*, 1971; Cheramy *et al.*, 1977). The effects of GHB in central serotonin are not fully understood but GHB appears to increase the turnover of serotonin in the CNS (Miguel *et al.*, 1988; Gobaille *et al.*, 2002). Gobaille *et al.* (2002) postulated that the increase of serotonin turnover may be due to an increase in tryptophan transport to the brain and its subsequent uptake by serotonergic cells (Gobaille *et al.*, 2002).

GHB also interacts with the opioid system, probably by interfering with the production of prodynorphin and proenkephalin because GHB itself lacks affinity for mu, kappa or delta receptors (Fiegenbaum and Simantov, 1996; Schmidt-Mutter *et al.*, 1999). Finally, GHB is also associated with an increase of acetylcholine release in the brain (Giarman and Schmidt, 1963; Li *et al.*, 1998).

## Clinical pharmacology

The structure of GHB [ $(\text{C}_4\text{H}_8\text{O}_3)$   $\text{OH}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OOH}$ ] is quite similar to that of GABA [ $\text{N}_2\text{H}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{OOH}$ ]. GHB is a four-carbon fatty acid with a molecular weight of 104.11 (Scharf *et al.*, 1998). It is a small lipophilic molecule that easily crosses the blood-brain barrier and the placenta (Palatini *et al.*, 1993; Scharf *et al.*, 1998). GHB is rapidly absorbed 15–30 min after oral administration (Palatini *et al.*, 1993). Its absorption is saturable, meaning that it is dose-dependent (Lettieri and Fung, 1976; Palatini *et al.*, 1993). GHB serum peaks levels are delayed

### GHB KINETICS AT DIFFERENT DOSES



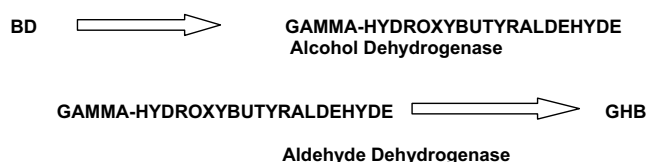
**Figure 3** Gamma hydroxyl butyrate (GHB) kinetics at different doses. There is a shift towards the right after increased doses of GHB. A similar effect is seen after repeated doses of GHB

depending on the dose (Lettieri and Fung, 1976; Palatini *et al.*, 1993) (Fig. 3).

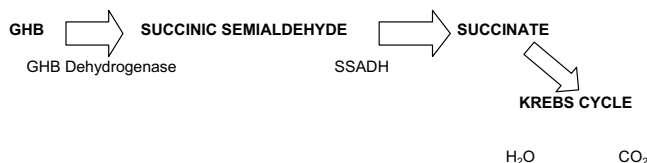
GHB serum levels peak 35–45 min after oral ingestion (Palatini *et al.*, 1993; Galloway *et al.*, 1997), or later after the ingestion of food because this delays absorption (Lettieri and Fung, 1976). GHB circulates freely because it does not bind to proteins (Palatini *et al.*, 1993; Scharf *et al.*, 1998). GHB distribution follows a two-compartment model (Roth and Giarman, 1966). It has been postulated that rectal administration increases its bioavailability, by avoiding first pass metabolism in the liver (Graig *et al.*, 2000). GHB clinical effects last approximately 3–4 h (Galloway *et al.*, 1997; Miotto *et al.*, 2001; Degenhardt *et al.*, 2003). GHB can be detected in urine samples up to 8–10 h after ingestion, and in blood samples up to 4–5 h after being ingested (Ferrara *et al.*, 1992).

### GHB and GHB analogue metabolism

GBL is converted into GHB by peripheral lactonase (Fig. 4) (Roth *et al.*, 1966). The half-life of GBL is approximately 1 min (Roth *et al.*, 1966; Lettieri and Fung, 1978). BD is metabolized into GHB by action of the same enzymes that are responsible for alcohol metabolism (Tabakoff and Von Watburg, 1975; Cash *et al.*, 1979). BD is oxidized by alcohol dehydrogenase to gamma hydroxybutyraldehyde, which is converted to GHB, by the enzyme aldehyde dehydrogenase (Tabakoff and Von Watburg, 1975; Cash *et al.*, 1979).



**Figure 4** Butanediol (BD) is metabolized to gamma hydroxybutyraldehyde (GHB) by the enzyme alcohol dehydrogenase. Gamma hydroxybutyraldehyde is further metabolized into gamma hydroxyl butyrate by aldehyde dehydrogenase



**Figure 5** Gamma hydroxyl butyrate (GHB) metabolism. GHB is metabolized into succinic semialdehyde by the enzyme GHB dehydrogenase. This intermediate compound is further metabolized into succinate by the enzyme succinic semialdehyde dehydrogenase (SSADH). Succinate then enters the Krebs cycle, producing water and carbon dioxide

GHB metabolism is saturable and can follow three metabolic routes. The main route involves the conversion of GHB into SSA by the enzyme GHB dehydrogenase (Kaufman and Nelson, 1991; Craig *et al.*, 2000). This intermediate compound is then metabolized to succinate by the enzyme SSADH (Cash *et al.*, 1979; Kaufman and Nelson, 1991). Succinate enters the Krebs cycle to produce  $\text{CO}_2$  and  $\text{H}_2\text{O}$ , which are eliminated by the lungs (Fig. 5) (Roth *et al.*, 1966). Alternatively, it can be transformed to succinate via  $\beta$ -oxidation in the liver. The urine eliminates a small proportion of GHB, ranging from 2–5% (Dyer, 1991).

### Clinical features of misuse

There are certain individuals who are believed to be at increased risk of abusing GHB. Athletes, body builders, gymnasium members, models, disk jockeys, ravers, frequent travellers across different time zones, and employees who are subject to regular drug testing, among others. Airline pilots and airplane technicians could represent high-risk groups because they are tested regularly for drugs of abuse. GHB is not tested during routine drug screens and its short half-life reduces the duration of detectability. A survey on the effect of GHB conducted among 42 GHB users in Los Angeles found that 76.2% were male, mean ( $\pm$  SD) age  $26.3 \pm 9.8$  years; 73.8% were Caucasians, 70.7% were heterosexuals and 39% were in employment (Miotto *et al.*, 2001). This is quite similar to the figures obtained from an Australian sample, where 79% were males, aged  $27 \pm 6.7$  years, 50% were self-identified as homosexuals and 11% as bisexuals, and 89% were in full time employment or attending university, (Degenhardt *et al.*, 2002).

The symptoms associated with recreational GHB use are mainly its effects on the CNS. Euphoria appears to be a common effect, as well as somnolence and confusion (Table 2). GHB is also associated with nystagmus, aggression, ataxia, increased libido, more sociability, enhancement of tactile sensations, and urinary incontinence (Galloway *et al.*, 1997; Miotto *et al.*, 2001; Degenhardt *et al.*, 2003). GHB increases the gag reflex, and nausea and vomiting are commonly observed after GHB administration (Galloway *et al.*, 1997; Miotto *et al.*, 2001; Degenhardt *et al.*, 2003). In a sample of 76 Australian GHB users, Degenhardt *et al.* (2002) that 99% reported at least one side-effect. The mean ( $\pm$  SD) number of side-effects reported was  $6.5 \pm 3.0$ . Their results are quite alarming because 39% reported previous episodes of accidental overdose,

**Table 3** Clinical manifestations of gamma hydroxyl butyrate (GHB) intoxication

Somnolence	Coma
Agitation	Seizures
Vertical nistagmus	Myoclonic jerks
Respiratory arrest	Bradycardia
Vomiting	Mild hypothermia
Amnesia	Non-specific electroencephalogram changes

The most common symptoms associated with GHB intoxication are shown. Neuropsychiatric symptoms, cardiovascular and respiratory depression are also commonly seen.

53% reported vomiting after using GHB and 8% had experienced a seizure (Degenhardt *et al.*, 2002).

Three main syndromes appear to emerge as a consequence of GHB misuse. They are secondary to CNS depression in cases of overdose, followed by CNS hyperactivity in cases of withdrawal. Degenhardt *et al.* (2003) found that overdoses were common among a sample of new GHB users, with 53% having experienced a GHB overdose (Degenhardt *et al.*, 2003). In those who had used GHB more than 15 times, 75% had overdosed at least once. A staggering 33% of those who had overdosed had done so more than three times, and 63% had seen another person overdose after using GHB (Degenhardt *et al.*, 2003). A GHB overdose can comprise an acute life-threatening event in some cases (Thomas *et al.*, 1997; Chin *et al.*, 1998; Craig *et al.*, 2000; Timby *et al.*, 2000). It typically occurs as a consequence of ingesting large concentrations of GHB over a short period of time, or when using GHB in combination with other CNS depressant drugs such as alcohol or benzodiazepines (Craig *et al.*, 2000; Miotto *et al.*, 2001; Degenhardt *et al.*, 2002). Alcohol administration produces a release of endogenous GHB (Poldrugo *et al.*, 1984), and it can also inhibit or compete with the liver enzymes responsible for GHB metabolism (McCabe *et al.*, 1971; Poldrugo *et al.*, 1984). GHB and alcohol simultaneously produce CNS and respiratory depression (Table 3).

### GHB intoxication

Manifestations are characterized by cardiac, respiratory and CNS depression. Several neuropsychiatry manifestations are seen in this group, and somnolence that progresses to coma is quite frequent (Galloway *et al.*, 1997; Thomas *et al.*, 1997; Chin *et al.*, 1998; Craig *et al.*, 2000; Miotto *et al.*, 2001; Nicholson *et al.*, 2001). Seizures are also seen in more severe cases. Vomiting and ataxia are also observed quite frequently in this group. Dystonic and jerking movements are quite severe and common (Li *et al.*, 1998; Miotto *et al.*, 2001; Degenhardt *et al.*, 2002) and can be so severe that patients may be injured as a consequence of sudden loss of muscular tone. Vertical nystagmus, bradycardia, hypotension and mild hypothermia are also common (Table 4). There is an abrupt resolution of the symptoms after 2–3 h (Thomas *et al.*, 1997; Chin *et al.*, 1998; Craig *et al.*, 2000; Mason and Kerns, 2001). Reports of patients waking up in a state of extreme agitation have also been described (Li *et al.*, 1998; Chin *et al.*, 1998; Miotto *et al.*, 2001).

**Table 4** Gamma hydroxyl butyrate (GHB) and alcohol intoxication

	GHB intoxication	Alcohol intoxication
	Rapid onset	Progressive onset
Unconsciousness	√√√	√
Gag reflex	√√	√
Slurred speech	√√	√
Lack of coordination	√√	√
Vertical nystagmus	√√	∅
Attention impairment	√√√	√
Coma	√√	∅ <sup>a</sup>
Vomiting	√√	√
Jerking movements	√√	∅

<sup>a</sup>Not commonly seen in alcohol intoxication. GHB and Alcohol intoxication both share similar symptoms. The differential diagnoses are particularly difficult because GHB is quite often ingested in combination with alcohol. A rapid progression of unconsciousness in a young man should alert clinicians to GHB involvement.

GHB has been used in cases of drug-facilitated sexual assault, mainly due to its amnesic properties, and also because GHB apparently disinhibits sexual urges. It has been used alone or in combination with other compounds such as alcohol, flunitrazepam and ketamine. Unfortunately, GHB is not tested routinely in drug screening, and the sample would need to be refrigerated. Blood samples for GHB must be preserved with NaF because citrate will give false raised GHB levels (LeBau *et al.*, 1999). GHB is detected by mass spectrometry and gas chromatography (Ferrara *et al.*, 1993).

### GHB withdrawal

The symptoms typically start a few hours after the last GHB ingestion. This short latency is an important characteristic because it helps to differentiate GHB withdrawal from alcohol withdrawal. These symptoms are consistent with an abrupt onset of nausea, vomiting, anxiety, sweating, craving for more GHB and insomnia (Li *et al.*, 1998; Craig *et al.*, 2000; McDaniel *et al.*, 2001). These symptoms could be self-limited in some patients. However, many patients present a more severe withdrawal that progresses to delirium (Li *et al.*, 1998; McDaniel *et al.*, 2001; Nicholson and Balster, 2001). GHB users that consume the drug at regular intervals during the day and night (1–3 h during the day) appear to be particularly at risk of becoming dependent. (Li *et al.*, 1998; McDaniel *et al.*, 2001; Degenhardt *et al.*, 2002). The symptoms are quite similar to those seen during withdrawal from other CNS depressant drugs such as benzodiazepines, alcohol or barbiturates (Table 5). In their sample, Miotto *et al.* (2001) reported that 21% were physically dependent on GHB. By contrast, Degenhardt *et al.* (2002) reported 4% dependence on GHB among a sample of recreational GHB users. Recently, an animal model of severe  $\gamma$ -hydroxybutyric acid withdrawal was induced in rats by the administration of intraperitoneal GBL, every 3 h, for 6 days (Bania *et al.*, 2003). This animal model should contribute to a better understanding of the mechanism associated with GHB withdrawal

**Table 5** Clinical manifestation of gamma hydroxyl butyrate (GHB) withdrawal

Tremor	Agitation
Sweating	Insomnia
Tachycardia	Hypertension
Delirium	Paranoid ideation
Wernicke-Korsakoff	Auditory and visual hallucinations

GHB withdrawal is dramatic in many cases. The symptoms can manifest after 90 min from the last dose. Cardiovascular instability and neuropsychiatric manifestation are quite common. Wernicke-Korsakoff syndrome has been reported as a rare late onset complication of GHB use.

and the evaluation of therapeutic options in the treatment of GHB dependence (Table 5).

### Chronic GHB use

This is comprised of those patients who are taking GHB regularly. A common presentation is the combination of mild to moderate psychiatric symptoms such as insomnia, hallucinations, anxiety, irritability, mood swings, aggression and behavioural disturbances (Miotto *et al.*, 2001; Nicholson *et al.*, 2001). These symptoms are similar to those observed in cases of 4-hydroxybutyric aciduria (Onkenhout *et al.*, 1989; Pearl *et al.*, 2003). Miotto *et al.* (2001) found that 21.4% of their sample were using GHB on a daily basis (Miotto *et al.*, 2001). There is also a report in the literature of Wernicke-Korsakoff encephalopathy secondary to chronic GHB use (Friedman *et al.*, 1996).

## Case reports

### Case 1

The patient was a 28-year-old farmer. He was an insulin-dependent diabetic. He started to use GHB as a safe alternative to AASs, and rapidly became dependent in GHB. He has been using GHB for the last 5 years in a round-the-clock fashion. He takes a jug full of GHB every 3 h and even wakes up at night to take GHB. He tried to stop GHB without help but became tormented by auditory and visual hallucinations, together with paranoid persecutory ideas.

### Case 2

The patient was a 30-year-old painter and decorator. He had a long history of anger difficulties, and low self-esteem. He was bullied at school for many years. He has always been concerned about his weight and shape. He started to use GHB in combination with AASs as a less expensive alternative to GH. His mood and anger become difficult to control when on GHB and he has been quite violent towards his wife, to the extent that she is now living in a women refuge. He has accidentally overdosed on many occasions. He has been able to stop GHB with help from his GP, who prescribed a low dose of benzodiazepines.

### Case 3

The patient was a 24-year-old mechanic, who uses AASs for bodybuilding proposes. He has used GHB quite regularly over the weekends for the last 3 years. His reasons for use are an increased libido and enhanced sexual performance. He claims that he only uses it when going to a party or as a part of the dance scene. He said that he could stop using at any time without major complications.

### Case 4

The patient was a 27-year-old student nurse. He has tried GHB on a few occasions, but he dislikes its effects. However, he uses AASs for bodybuilding.

### Case 5

The patient was a 42-year-old music teacher. He has used GHB round the clock over the last 4 years. He had been involved in approximately 20-road traffic accidents. He describes an episode of sudden lost of consciousness when driving. He presented for psychiatric help after spending 8 months in a Canadian prison following a rage incident when on board a commercial aircraft across the Atlantic.

## Management

The management of GHB overdoses or withdrawal should be dependent on the individual clinical presentation. In cases of GHB overdose, a full medical history, including current drug use, is paramount in all patients for whom GHB use is suspected, followed by a thorough physical and mental state examination. Alcohol is commonly used in combination with GHB or GHB analogues. An unusual degree of stupor, or a clinical presentation suspicious of alcohol intoxication that is unusually dramatic or out of proportion, should alert the personnel at the A&E about possible GHB use or likely contribute to the clinical picture. This assessment would generally take place at the A&E Department where the ambulance services or a relative has taken the patient. It has been reported that 84% of GHB-related admissions to A&E departments comprise young Caucasian males, who attend between 00.00 h to 06.00 h (Li *et al.*, 1998).

GHB intoxication tends to resolve spontaneously after a few hours, and the majority of patients are well enough to be discharged home a few hours after their admission to the department, unless a complication occurs (Garrison and Mueller, 1998; Li *et al.*, 1998; Mahon *et al.*, 1999). The evidence appears to indicate that the management of GHB intoxication should be restricted to cardiovascular and respiratory support. The use of naloxone and phisostigmine, or neostigmine, to revert coma associated with GHB overdose is not supported by current evidence-based practice. Indeed, the available evidence suggests that using these two compounds might be associated with more serious side-effects

such as cardiac dysrhythmias and seizures. Despite GHB overdose presentation being quite dramatic, due to the severity of the symptoms, and particularly the profound level of depressed consciousness, the majority of the cases tend to resolve spontaneously over the next 3–4 h after admission to the A&E Department. Recovery is characterized by a sudden regain of consciousness accompanied by intense psychomotor agitation.

GHB detoxification deserves particular attention for psychiatrists and mental health workers. Although GHB intoxication appears to be rather self-limited, progressing without serious complication in the majority of cases, GHB detoxification can be quite challenging. Cardiovascular and respiratory support is mandatory during the initial stages of treatment, as well as the control of aggression and psychotic symptoms. Benzodiazepines and barbiturates appear to be the drugs of choice when treating GHB withdrawal symptoms, and are sometimes required at high doses. The psychiatric team should work closely with the medical team, A&E and intensive care unit (ICU). The ICU should be notified in advance of any potential need for admission in cases of severe dependency. The most severe cases of severe GHB dependency may require the patient to be transferred to the ICU because of the need for mechanical ventilation in some cases, due to the high amount of sedative medication used to control the symptoms. The use of benzodiazepines in these groups of patients should be carefully monitored by medical or nursing staff. Unfortunately, no withdrawal rating scales specific for GHB withdrawal are available to date. It would appear reasonable to use an alcohol or benzodiazepine withdrawal scale before medication is given. Physiological-based withdrawal scales can also be used, such as the CIWA-Ar. It is mandatory to gain a baseline assessment of the effective required dose of benzodiazepine to be used for suppressing withdrawal symptoms. The total dose of benzodiazepine used to bring the withdrawal symptoms under control during the first 24 h is then prescribed daily for the next 7 days. After the second week, daily doses of benzodiazepine should be reduced. Antipsychotic medication should be used only in those cases presenting with psychotic manifestations or violent behaviour. Haloperidol has been used in low doses with a good response (Craig *et al.*, 2000; McDaniel *et al.*, 2000). Patients who take large GHB doses at short intervals (e.g. every 2 or 3 h) have the highest risk of being refractory to treatment when withdrawing from GHB (Craig *et al.*, 2000; Miotto *et al.*, 2001; Degenhardt *et al.*, 2002). The most extreme cases may require the use of an intravenous anaesthetic. Propofol has been reported to be successful in bringing in difficult cases under control, especially those that are unresponsive to high doses of benzodiazepines or barbiturates (Dyer *et al.*, 2000). Serious and sometime life-threatening GHB withdrawal symptoms can arise even after the first 2 weeks of detoxification. It is therefore mandatory to treat GHB-dependent patients as inpatients.

The general management should also include adequate maintenance of fluid and electrolyte balance during detoxification to prevent more serious complications such as hyperthermia and rhabdomyolysis. The actions of GHB on the central dopamine system possess at least a theoretical risk for the development of neuroleptic malignant syndrome.

The medical team should discuss the treatment options available with the patient before admission for detoxification. Discharge back to the community, with the intention of completing treatment at home, must be avoided for GHB-dependent individuals who have taken benzodiazepines for more than 72 h because it can be extremely dangerous. After repeat doses, the half-life increases for benzodiazepine, and particularly diazepam and its active metabolites. One reason for requesting discharge home with medication could be due to the intense cravings for GHB, probably occurring in cases that have been under medicated. If these patients are allowed to go home, there is a high risk of them taking GHB again. The use of GHB and benzodiazepines in high doses can be life-threatening, leading to respiratory depression and coma. A short-acting benzodiazepine, such as lorazepam, may be a better option in such cases.

An alternative method for controlling GHB withdrawal symptoms involves the use of sodium oxybate (Xyrem®), a GHB salt, as a substitute for GHB during inpatient detoxification regimes instead of using a benzodiazepine or barbiturate regimen. Following their admission into hospital, patients should be assessed every 4–6 h over the next 48 h to determine the total amount of GHB necessary to control their withdrawal symptoms. At the end of the initial 48 h, the mean of the total GHB doses used is prescribed, and progressive reduction is then tailored to fit individual patient requirements. The principle is similar to that used for other drugs, such as heroin, alcohol or benzodiazepines. Although sodium oxybate is not available in the UK at present, it will be soon.

## Discussion

GHB is gaining great popularity in UK and its use is spreading among the young. Over the next few months or years, clinicians will certainly see more cases associated with the use of GHB. Unfortunately, current knowledge is provided by a few surveys conducted in the USA and Australia. The prevalence, characteristics and patterns of use in the UK remain largely unknown. The trend for increased GHB use will be reflected by an increased number of GHB users attending mental health centres or general practice.

Miotto *et al.* (2001) and Degenhardt *et al.* (2002) both described a high number of GHB users in full time employment or attending higher education, with little or absent social decline as typically observed in cases of other addictions, such as for opiates. This may be a reflection of the relatively short time of progression for exposure to the drug.

The use of GHB appears to be more prevalent in large cities such as London and Manchester. Anecdotal information indicates the existence of a chain of gymnasiums that have taken strict control on the use of GHB in their establishments. In many cases, the ambulance service has been required to assist gymnasium members who have collapsed after taking GHB.

The control of the production and trafficking of GHB and its analogues is difficult to enforce. Despite being classified as a class 'C' drug from 1 July 2003 by the Home Office, there are no legal

restrictions in place for GHB analogues in the UK. GBL is currently on the voluntary monitoring list of the Drug Precursors Committee of the European Commission. However, 1,4-butanediol has not been included in the list.

The cases presented here illustrate the most common presentation observed in our clinical practice, and indicate some of the most common complications seen in this group. Although comprising a small group of patients, the cases deserve particular attention because of the variability of manifestations associated with GHB use.

The use of GHB poses significant danger not only to individuals, but also to the community. The use of GHB is associated with abrupt onset sleep, which in turn could be extremely serious if an individual is driving or operating heavy machinery. Clinicians should advise their patients to contact the Driver Vehicle Licensing Agency (DVLA) and notify them regarding their current drug use. If they do not receive written notification from the DVLA after a reasonable period of time (i.e. when a report would normally be requested), then it would be the clinician's duty to contact the DVLA.

Current knowledge about the short- and long-term effects of GHB remains largely unknown. 4-GHB-aciduria is a clinical model that will help us gain a better understanding of chronic exposure to high concentrations of GHB.

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