Title: Gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL) and 1,4 butanediol (1,4-BD; BDO): A literature review with a focus on UK fatalities related to non-medical use

Author: John M. Corkery Barbara Loi Hugh Claridge Christine Goodair Ornella Corazza Simon Elliott Fabrizio Schifano

PII: S0149-7634(15)00086-X
DOI: http://dx.doi.org/doi:10.1016/j.neubiorev.2015.03.012
Reference: NBR 2158

To appear in:

Received date: 17-9-2014
Revised date: 8-3-2015
Accepted date: 25-3-2015

Please cite this article as: Corkery, J.M., Loi, B., Claridge, H., Goodair, C., Corazza, O., Elliott, S., Schifano, F.,Gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL) and 1,4 butanediol (1,4-BD; BDO): a literature review with a focus on UK fatalities related to non-medical use, *Neuroscience and Biobehavioral Reviews* (2015), http://dx.doi.org/10.1016/j.neubiorev.2015.03.012

Highlights

- This study constitutes the largest overview of GHB and derivatives' mortality data
- UK GHB/GBL deaths still occur despite the substances being illegal
- This paper demonstrates how GHB/GBL fatalities can be identified with appropriate methods
- Mean post-mortem blood levels are twice as high where GHB/GBL alone or with alcohol is used
- More awareness is needed of potentially fatal outcomes using GHB/GBL

Gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL) and 1,4 butanediol (1,4-BD; BDO): a literature review with a focus on UK fatalities related to non-medical use

John M. Corkery[a b] , Barbara Loi[a b c], Hugh Claridge[a], Christine Goodair[a], Ornella Corazza[b], Simon Elliott[d], & Fabrizio Schifano[a b]

a National Programme on Substance Abuse Deaths, St George's University of London, UK
b Centre for Clinical Practice, Safe Medicines and Drug Misuse Research Department of Pharmacy, University of Hertfordshire, UK
c Neuroscience Institute, National Research Council of Italy, Section of Cagliari, I-09042 Monserrato CA, Italy
d ROAR Forensics, Malvern Hills Science Park, Geraldine Road, Malvern, Worcestershire WR14 3SZ, UK

Running title – UK GHB deaths

Address for correspondence:

John M Corkery, Research Co-ordinator
Department of Pharmacy
University of Hertfordshire
College Lane Campus,
Hatfield, Hertfordshire
AL10 9AB, United Kingdom.
Tel: + 44 (0)1707 281053
Fax: +44 (0)1707 284506
E-mail: j.corkery@herts.ac.uk

Abstract

Misuse of gamma hydroxybutrate (GHB) and gamma butyrolactone (GBL) has increased greatly since the early 1990s, being implicated in a rising number of deaths. This paper reviews knowledge on GHB and derivatives, and explores the largest series of deaths associated with their non-medical use. Descriptive analyses of cases associated with GHB/GBL and 1,4 butanediol (1,4-BD) use extracted from the UK's National Programme on Substance Abuse Deaths database. From 1995 to September 2013, 159 GHB/GBL-associated fatalities were reported. Typical victims: White (92%), young (mean age 32 years); male (82%); with a drug misuse history (70%). Most deaths (79%) were accidental or related to drug use, the remainder (potential) suicides. GHB/GBL alone was implicated in 37%; alcohol 14%; other drugs 28%; other drugs and alcohol 15%. Its endogenous nature and rapid elimination limit toxicological detection. Post-mortem blood levels: mean 482 (range 0 - 6500; S.D. 758) mg/L. Results suggest significant caution is needed when ingesting GHB/GBL, particularly with alcohol, benzodiazepines, opiates, stimulants, and ketamine. More awareness is needed about risks associated with consumption.

Key words = GHB, GBL, Fatalities, Deaths, Toxicity, United Kingdom (UK)

Gamma hydroxybutyrate (GHB), gamma butyrolactone (GBL) and 1,4 butanediol (1,4-BD; BDO): a literature review with a focus on UK fatalities related to non-medical use

Abbreviations

1,4-BD	1,4 butanediol
AM	Ante Mortem
AMCD	Advisory Council on the Misuse of Drugs
BNF	British National Formulary
BZP	Benzylpiperazine
Carboxy-THC	11-nor-9-carboxy-delta-9-THC
CNS	Central Nervous System
CPP	1-(3-Chlorophenyl)piperazine hydrochloride
DEA	Drugs Enforcement Administration
EMCDDA	European Monitoring Centre for Drugs & Drug Addiction
EMEA	European Medicines Agency
GBL	Gamma butyrolactone
GHB	Gammahydroxybutyrate
GHV	Gamma hydroxy valerate
GVC	Gamma-hydroxy valeric acid; 4-methyl-GHB; Gamma-methyl-GHB
GVL	Gamma-valerolactone
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethylamphetamine
MDPV	Methylenedioxypyrovalerone
NMP	N-Methyl-2-pyrrolidone
NPSAD	National Programme on Substance Abuse Deaths
ONDCP	Office of National Drug Control Policy
ONS	Office for National Statistics
PM	Post-mortem
TFMPP	3-Trifluoromethylphenylpiperazine monohydrochloride
THCC	11-nor-delta-9-tetrahydrocannabinol-9-carboxylic acid
TIAFT	The International Association of Forensic Toxicologists

1. Introduction

Gamma hydroxybutyrate, (GHB) is an endogenous chemical found in the human body. The protonated form is gammahydroxybutyric acid, whereas the deprotonated form of the carboxylic acid moiety is gammahydroxybutyrate (EMCDDA, 2002:11). GHB is also known as sodium oxybate, sodium 4-hydroxybutyrate, and 4-Hydroxy-*n*-butyric acid. It can also be easily synthesised from readily obtainable ingredients. GHB's prodrugs gammabutyrolactone (GBL; dihydrofuran-2(3H)-one) and 1,4 butanediol (1,4-BD; BDO) are easily converted into GHB in the body (WHO, 2001).

The misuse of GHB and these prodrugs increased greatly in Western countries from the early 1990s, especially in the club and dance scenes (EMCDDA, 2002; Kelly *et al*., 2006). The period since has been marked by claims that the substances have been implicated in a rising number of deaths in the USA, Western Europe, Australasia, and other developed countries (Caldicott *et al*., 2004; EMCDDA, 2008; Zvosec *et al*., 2011).

The aim of this paper is two-fold: (a) to provide an update on the present state of knowledge of GHB/GBL and (b) to make publicly available detailed particulars of fatalities associated with GHB, GBL and 1,4-BD that have been identified in the United Kingdom (UK). Section 2 gives an overview of the following topics: chemistry and pharmacology; metabolism and pharmacokinetics; medical uses; legal status; addiction potential; non-medical uses; recreational use in the UK; availability; route of administration and usage; effects; hospital presentations; and fatalities. Section 3 looks at UK fatalities in depth, especially: methods and sources of data; detailed analysis of UK data; and a discussion of these data in relation to the wider literature. The latter includes reflections on: socio-demographics; post-mortem toxicology; pre-existing

medical conditions; drug effects and mental health issues; and drug interactions. The paper highlights the risks associated with the consumption of GHB and derivatives, especially with regard to recreational use. It also contributes to the pool of knowledge being built up on these drugs.

2. Overview of the literature on GHB/GBL

2.1 Chemistry and pharmacology

GHB is a natural substance found in the human central nervous system and in other organs such as the liver, kidney, heart, bones as well as brown fat (Nelson *et al*., 1981). The greatest concentration in humans is found in the basal ganglia of the brain, with binding sites in the same location as well as the cortex, hippocampus, mid-brain and substantia nigra (Jones, 2001). Some research suggests that there are alternative sources of GHB, which may play a very significant role in GHB production (Feigenbaum and Howard, 1996; Snead *et al*., 1982), especially in the periphery, since GHB levels there are comparatively high yet peripheral levels of GABA are very low to absent. Its primary endogenous precursor is the neurotransmitter GABA which is converted enzymatically to succinic semialdehyde by mitochondrial GABA transaminase; succinic semialdehyde is then reduced to GHB by cytosolic semialdeyde reductase. It eventually enters the Krebs cycle, the main metabolic pathway in aerobic organisms, (Maitre, 1997). B-oxidation is also a possible elimination route (Keating, 2014; Snead and Gibson, 2005).

Similar to the neurotransmitter gamma-aminobutyric acid (GABA), it possesses distinct excitatory properties (in addition to its sedative and anaesthetic effects) which may be due to its effect on the mesolimbic dopaminergic system (WHO, 2001). Some observations seem to support the hypothesis that GHB is a neurotransmitter with its own receptor system (Absalom *et al*., 2012; Maitre, 1997; Nava *et al.*, 2001). In the brain GHB is synthesised from GABA in cells containing glutamic acid decarboxylase, the marker of GABA-ergic neurons. It is accumulated by the vesicular inhibitory aminoacid transporter (VIAAT) and released by depolarisation via a Ca2+ dependent-mechanism. GHB can be metabolised *in vivo* to gamma-aminobutyric acid (GABA) and trans-4-hydroxycrotonic acid (T-HCA); the first being pharmacologically active at $GABA_B$ receptors (Quang *et al*., 2002a) and the second one binding to the GHB receptor with 4-fold higher affinity than GHB itself (Wellendorph *et al*., 2005). A family of GHB receptors exists in the brain which possesses hyperpolarising properties through Ca2+ and K+ channels. These receptors are thought to regulate GABA-ergic activities via a subtle balance between sensitised/desensitised states. According to Maitre *et al*. (2005), absorption of large amounts of GHB desensitises GHB receptors. This modification, along with direct stimulation of $GABA_B$ receptors by the molecule, creates a disturbance, in several brain areas, of GABA, dopamine and opiate release. They suggest this adaptation phenomenon is probably responsible for the therapeutic and recreational effects of exogenous GHB. The activation of $GABA_A$ and $GABA_B$ receptors induced by GHB's conversion to GABA might be responsible for GHB's anxiolytic and sedative effects (Skala *et al*., 2014). GHB can be converted to GABA at high concentrations, as would be attained during recreational abuse or *in vivo* study of an administered drug (Collier and De Feudis, 1970; Hechler *et al*., 1997; Vayer *et al*., 1985). Experimental data suggest that GHB has alcohol-mimetic effects at low dosages (e.g. 50mg/kg/day) facilitating the suppression of alcohol cravings (Skala *et al*., 2014).

GHB can also be synthesised *in vivo* from its prodrugs or precursors GBL and 1,4-BD, with GHB being the compound exerting the pharmacological effect (Carai *et al*., 2002; Guidotti and Ballotti, 1970; Roth *et al.*, 1966; Poldrugo and Snead, 1984; Quang *et al.*, 2002a, 2002b; Schneidereit *et al.*, 2000; Snead, 1982; Snead *et al.*, 1989;). 1,4 Butanediol, a naturally occurring aliphatic alcohol, has been demonstrated to serve as a source of GHB (Poldrugo and Snead, 1984). GBL, a naturally occurring lactone precursor, is readily and irreversibly metabolised to GHB by peripheral lactonases (Roth and Giarman, 1968).

2.2 Metabolism and pharmacokinetics

Following exogenous (oral) administration, GHB is rapidly absorbed from the gastro-intestinal tract. Single oral doses of 12.5, 25, and 50 mg/kg reached peak plasma concentrations in 25 (range 20-30), 30 (range 20-45), and 45 (range 30-60) min respectively (Palatini *et al*., 1993). This is in line with effects starting 15 min after an oral dose (Galloway *et al*., 1997). The elimination half-life of GHB is 27 min, and proceeds in a dose-dependent saturable manner (Palatini *et al*., 1993). Only 2-5% of GHB is eliminated unchanged in

urine (Hoes *et al*., 1980; Laborit, 1964). The dosage-response curve for GHB is steep. Time to peak concentration of 1,4-BD is 25 min (Thai *et al*., 2007).

The distribution throughout the body is fast and follows a two-compartment model (Brenneisen *et al*., 2004). The apparent distribution volume is reported to be 0.19 to 0.4 L/kg (Baselt, 2008; Borgen *et al*., 2003), and is not significantly affected by gender, food, or liver cirrhosis (Borgen *et al*., 2003; Ferrara *et al*., 1996). The pathway of GHB production after death remains unclear and it has also been suggested that GHB can be a product of post-mortem decomposition (Fieler, Coleman and Baselt, 1998; Sakurada *et al*., 2002).

GBL is metabolised quickly to GHB by peripheral calcium dependent serum lactonases or by nonenzymatic hydrolysis (Arena and Fung, 1980; Roth and Giarman, 1965; Roth *et al*., 1967); the half-life of this conversion being estimated as < 1 min (Roth and Giarman, 1966). Time to peak serum concentration of GBL is 36-57 min, with an elimination half-life of 30-52 min (Meyer *et al*., 2014). Studies of patients suffering from a rare inborn error of metabolism (4-hydroxybutyric aciduria) were found to have very high concentrations of GHB in the urine (typically greater than 200 mg/L), plasma and cerebrospinal fluid (CSF) (Divry *et al.*, 1983; Rahbeeni *et al*., 1994). GBL has greater lipid solubility than GHB, allowing it a more uniform absorption. Its greater lipophilicity may also result in its absorption into a variety of tissues which possibly act as reservoirs lengthening the duration of GBL action (Lettieri and Fung, 1978). It is regarded as more potent than GHB because of its more rapid absorption and greater bioavailability, although its effects are not as long-lasting (Brunt *et al*., 2014).

By contrast, the slower elimination of 1,4-BD, the diol alcohol (dihydroxy) precursor of GHB, suggests its effects last longer than those of GHB (Brunt *et al*., 2014). 1,4-BD undergoes two-stage conversion in the liver *in vivo* via enzymatic biotransformation to gamma-hydroxy butyraldehyde by alcohol dehydrogenase (ADH) and then aldehyde dehydrogenase to GHB (Bessman and Fishbein, 1963; Poldrugo and Snead, 1986; Snead *et al*., 1989; Quang *et al*., 2002a, 2002b; Wang, 2007). There is great inter-individual variation in the speed of metabolism of 1,4-BD to GHB; this may be associated with ADH-IB and G143A polymorphism (Thai *et al*., 2007). The elimination half-life of 1,4-BD is 39 ± 11 min; time to maximal GHB concentration being also 39 ± 11 min (Thai *et al*., 2007). The sedative/hypnotic effect of 1,4-butanediol is mediated by its conversion *in vivo* into GHB which, in turn, binds to $GABA_B$ receptors (Carai *et al*., 2002). The common metabolic pathway of 1,4-BD and ethanol leads to potential interactions between them (Poldrugo and Snead, 1984, 1986). There is a synergistic effect between ethanol and 1,4-BD (McCabe *et al*., 1971; Poldrugo *et al*., 1985), and between ethanol and GHB in respect of synergistic sedative effects (McCabe *et al*., 1971; Van Sassenbroeck *et al*., 2003a).

The pharmacokinetics of GBL and 1,4-BD, including their initial distribution and rate of conversion to GHB, may influence their pharmacological actions. Hence, GBL and 1,4-BD may not display actions identical to GHB nor to each other. Early studies of these agents support non-identical time courses of action, suggestive of differences in their pharmacokinetics seen in mice; however, stimulatory effects are more pronounced for 1,4-BD than for GBL (Fiebre *et al*., 2004). The hypothermia produced by GBL is more pronounced than that produced by 1,4-BD (Fiebre *et al.*, 2004). These data, conducted with a limited number of non-equivalent doses of these drugs, suggest that GBL and 1,4-BD may have differential effects. These different effects, whether pharmacodynamic or pharmacokinetic, may contribute to the abuse potential and/or pharmacological or toxicological actions of each agent (de Fiebre *et al*., 2004), as well as different overdose risks (Brunt *et al*., 2014).

2.3 Medical uses of GHB

GHB decreases the oxygenation needs of tissues and protects cells during states of hypoxia. For these reasons it has been suggested to have some potential for use in emergency treatment, especially for haemorrhagic and septic shock (Jones, 2001). When exogenously administered, GHB is rapidly absorbed. It crosses the blood–brain barrier with relative ease, penetrates into the brain, and exerts a number of psychopharmacological effects. Acute effects include euphoria, ataxia, confusion, hallucinations, anxiolysis, amnesia, sedation/hypnosis, loss of consciousness, and anaesthesia (Laborit, 1964; Maitre, 1997; Shannon and Quang, 2000; Snead and Gibson, 2005; Teter and Guthrie, 2001). In animals, this drug causes alterations in locomotor activity (Cook *et al*., 2002; Davies, 1978), loss of the righting

response (Dudek and Fanelli, 1980), seizures (Snead, 1990) and hyper/hypothermia (Kaufman *et al*., 1990).

In 1960 Dr Henri Laborit synthesised GHB while trying to produce a GABA analogue or precursor capable of easily crossing the blood-brain barrier (Laborit *et al*., 1960a, 1960b). GHB was initially used as an anaesthetic (Vickers, 1969). However, it remained undeveloped for this use because of the high incidence of adverse effects, especially vomiting and seizures, during early clinical trials (Wood *et al*., 2011). In the mid-1990s GHB's role underwent re-evaluation in the emergency and critical care fields, especially long-term sedation, due to its rapid metabolism and reliable induction of sedation/anaesthetic without depression of cardio-circulatory or respiratory measures, kidney and other functions (EMCDDA, 2002).

GHB is a medicinal product by definition of Article 1 of EC Directive 2001/83/EC5 and in the UK is controlled by the Medicines Act 1968 and associated regulations. In the UK, it is an unlicensed medicinal product and can only be sold or supplied to the public by a doctor or dispensed by a pharmacist in response to a prescription written by a doctor. GHB is not manufactured legally in the UK. The British National Formulary (BNF) lists Xyrem® as a hypnotic for use in treating narcolepsy with cataplexy (under specialist supervision). It is supplied as an oral solution of 500mg/mL (BNF, 2014).

In only five EU Member States is GHB a licensed medicine for human use; it is not authorised for veterinary use. GHB is used in France and Germany (Andresen *et al*., 2010) as a surgical anaesthetic (Gamma OH™ and Somsanit™ respectively), and in Austria and Italy (Alcover®) to treat alcohol withdrawal symptoms (Gallimberti *et al.,* 1989). In Italy it has been tested to treat opiate addiction as well (Gallimberti *et al.,* 1993; Maremmani and Pacini, 2007). GHB was licensed in Europe in 2005 (EMEA, 2007) for use in the treatment of narcolepsy (a rare sleep disorder characterised by excessive daytime sleepiness and presence of irresistible daily attacks of refreshing sleep) and cataplexy in narcoleptic patients (Gallimberti *et al.*, 1994; Mamelak *et al.*, 1986). It is also approved for treating narcolepsy in Canada, Switzerland and the USA (Skala *et al*., 2014). In 2002, the US FDA gave approval for Xyrem® (with GHB as an active ingredient) to be used in the treatment of cataplexy attacks in patients with narcolepsy (ONDCP, 2002). It is available in the Netherlands for this purpose (van Amsterdam *et al*., 2012). It has been suggested for the treatment of fibromyalgia (Maitre *et al*., 2005).

2.4 Legal status of GHB, GBL and 1,4-BD

In the USA GHB was classified as a DEA-listed Schedule 1 drug on 18 February 2000, and thus is not licensed for use in medical treatment. On the advice of the World Health Organisation, the United Nations Commission on Narcotic Drugs added GHB to Schedule IV of the 1971 UN Convention on Psychotropic Substances on 29 March 2001. The EU agreed in the same month that individual Member States should closely monitor GHB and also decided that the UN decision should be implemented by incorporation into domestic legislation as Member States saw fit (EMCDDA, 2001). GHB is now controlled in at least 22 Member States and Norway, as well as Chile. GHB is regulated in Hong Kong as a prescription medicine. GBL and 1,4-BD are controlled in Bulgaria, Italy, Latvia, Norway and Sweden under identical or similar legislation to that relating to GHB (Andresen *et al*., 2010). GBL is controlled in Austria, Canada, Israel, Romania, Russia and the USA. GHB, GBL and 1,4-BD are controlled in Australia and New Zealand as Class B drugs, i.e. having a 'high' risk of harm. Action was also taken against GHB in Switzerland in 2001. GBL is controlled as a precursor in Turkey, and 1,4-BD similarly in Canada.

On 1 July 2003 GHB became controlled in the UK under the Misuse of Drugs Act 1971 as a Class C drug. This means that anyone possessing the drug can face two years in prison, while suppliers can expect a jail term of up to five years. GHB also became a substance listed under Schedule 4 Part I of the Misuse of Drugs Regulations 2001. The legislation makes it an offence to manufacture, supply, import, export and possess GHB without lawful authority. GBL and 1,4-BD became Class C drugs under Schedule 2 from 23 December 2009 where they are intended for human consumption.

2.5 Addiction potential

Tolerance develops to GHB/precursor effects in rodents (Colombo *et al*., 1995a; Gianutsos and Moore, 1978; Itzhak and Ali, 2002). Abanades *et al*. (2007) suggest that GHB is both physically and

psychologically addictive, and has a high abuse potential, appearing to cause physical dependence (EMCDDA, 2002; Galloway *et al.*, 1997). Data from a study of primates indicate that chronic 1,4-BD administration produces physical dependence (Goodwin *et al*., 2013). Cross-tolerance may exist between GHB and alcohol in humans (EMCDDA, 2008), as it does in animal models (Colombo *et al*., 1995b; Fadda *et al*., 1983).

Those developing dependency are likely to have been using these substances for several months, several times a day (McDonough *et al*., 2004; Wojtowicz *et al*., 2008). However, there is little evidence of abuse amongst those patients using GHB for narcolepsy (Brunt *et al*., 2014), when taken at the recommended dosage. A study of 26,000 narcolepsy patients treated with sodium oxybate found that adverse effects included: abuse (0.0390%); dependence (0.0016%); withdrawal symptoms (0.0310%); overdose with suicidal intent (0.0031%); and death (0.0800%) (Wang *et al*., 2009). Between 2.6% and 10.1% of patients with alcohol dependence treated with sodium oxybate developed craving for the drug and increased their dose to 6-7 times the recommended one (Beghè and Carpanini, 2000). The likelihood of craving is highly elevated for such patients who also have a psychiatric condition (Caputo *et al*., 2011). Those with a previous history of opioid or cocaine dependence are also at such risk (Caputo *et al*., 2009).

In rare cases, withdrawal symptoms might be observed following withdrawal from sodium oxybate (EMEA, 2007, 2014). Withdrawal syndrome (characterised by insomnia, muscular cramping, tremors and anxiety) has been reported in some patients following cessation of long-term administration of high doses of GHB (Galloway *et al*, 1994; LeTourneau *et al*., 2008), GBL/GHB (Durgahee *et al*., 2014), and GBL and 1,4-BD (Catalano *et al*., 2001; Dyer *et al*., 2001; Evans and Sayal, 2012; Zvosec *et al*., 2011), similar to those seen in respect of withdrawal from alcohol and benzodiazepines (Le Tourneau *et al.*, 2008). The symptoms appear within a few fours of the last dose taken, becoming severe by 24 h (Wood *et al*., 2011). There is a risk of delirium, hallucinations and/or acute psychosis if left untreated (Skala *et al*., 2014). Cases of GBL withdrawal have been successfully treated through the use of clonazepam/lorazepam in conjunction with haloperidol (Meyer *et al*., 2014a, 2014b; Sewell *et al*., 2015).

2.6 Non-medical uses of GHB and its precursors

GHB was first sold as a dietary supplement, and by the late 1980s was marketed in the US as a steroid replacement for body-builders and weight lifters. It has been shown to stimulate the release of human growth hormone, which could increase muscular mass (Sivilotti *et al.*, 2001; Takahara *et al.*, 1977). Growth hormone release from the anterior pituitary occurs during slow wave sleep which is increased by GHB (Bluet-Pajot *et al*., 1978; Gerra *et al.*, 1994; Mamelak, 1997; Takahara *et al*., 1977;). However, there is no clear evidence that the short-term elevations in growth hormone produced by GHB result in any increase in muscle mass (Vayer *et al*., 1987). Despite this, GHB has been widely used among the body-building community and is believed by some to have been the primary focus of GHB misuse in the mid-1990s in the USA (Friedman *et al.*, 1996) and Sweden (EMCDDA, 2002). GHB's ability to decrease body fat makes its use attractive as a means of weight loss (Chin *et al*., 1992; Friedman *et al*., 1996; Luby *et al*., 1992; Vayer *et al*., 1987). GHB has also been used as an appetite suppressant (EMCDDA, 2002).

GHB has been promoted as an aphrodisiac in both heterosexual and homosexual markets (Romanelli *et al*., 2003). It is used particularly in the latter population because of its energy boost and increase in libido (Palamar and Halkitis, 2006), as well as to relax (muscles) and give more confidence (Bourne *et al*., 2014), as well as to facilitate sex-work and 'chem-sex' (Durgahee *et al*., 2014). GHB, GBL and similar substances have also been linked to cases of so-called 'date-rape' reported by the media, both in the USA, Europe (Andresen *et al*., 2010; Németh *et al*., 2010) and the UK, including a recent case where GHB/GBL was administered with the Novel Psychoactive Substance DOC (2,5-Dimethoxy-4-chloroamphetamine) (Bennett, 2014); inaccurately in some instances (EMCDDA, 2008; Hagemann *et al*., 2013; Sturman, 2000). More recently, the industrial solvent NMP (N-Methyl-2-pyrrolidone) or more accurately its metabolites have been identified in cases of sexual assault in Europe (DPA, 2013). NMP is sometimes used as a substitute for GBL (Reisch, 2008), and has been found in some GHB solutions (DEA, 2004). Also of interest is that a related substance GVL (gamma-valerolactone) is being used recreationally in Europe; it has similar effects to GHB and its pro-drugs, and is metabolised by a lactonase to GVC (gamma-hydroxy valeric acid, 4-methyl-GHB, gamma-methyl-GHB) (Carter *et al*., 2005). It is a legal substance but has a two-fold lower affinity for the GHB receptor (Andresen-Streichert *et al.*, 2013). Higher doses of GHV (Gamma hydroxy valerate) are needed to achieve similar results to GHB, thereby

increasing the risk of poisoning and death. It is used recreationally in a similar way to GHB, e.g. by mixing with water or alcohol (Erowid, 2004).

The more recent primary mode of GHB abuse worldwide has been for its subjective (empathogenic), hypnotic, euphoric, disinhibitive and potentially hallucinogenic effects (ReDNet, 2012). Illicit GHB/GBL users describe their subjective effects as comparable to alcohol (Colombo *et al*., 1995a), MDMA/ 'ecstasy' (Galloway *et al*., 2000), and flunitrazepam (Abanades *et al*., 2007). Drug workers and some user fora comments suggest that GHB may be used as a substitute for alcohol or other drugs to get intoxicated so as to avoid detection by testing in situations such as treatment compliance, driving and the workplace (EMCDDA, 2002). It does not react with the reagents in the commonly used field test-kits. At the same time it provides a cheap alternative to such substances (EMCDDA, 2002).

GHB and its prodrugs are often used recreationally with other substances (Erowid, 2013b, 2013c), including alcohol, cannabis, and stimulants (ecstasy, cocaine, amphetamines) (Durgahee *et al*., 2014; Korf *et al*., 2002; Miotto *et al*., 2001; Sumnall *et al*., 2008). Many GHB users employ MDMA to extend its effects (Kim *et al*., 2007; Korf *et al*., 2002). It causes the extracellular concentrations of key neurotransmitters to increase, e.g. 5HT is a principal element providing ecstasy's sought-for effects, but dopamine and noradrenaline have stimulant effects. GHB is taken to moderate the latter's effects, especially the almost re-experiencing of MDMA hit and delaying the come-down (Uys and Niesink, 2005). GHB and its derivatives are more likely to be used in private settings rather than in public night life settings (67% vs. 26% respectively; Sumnall *et al*., 2008). A similar pattern is noted in Australia (Sindicich and Burns, 2013). A shift in GHB use from dance venues and events to private homes and parties was noted in Australia between 2001 and 2007 (Dunn *et al*., 2009). Settings for use appear to influence adverse effects, being more negative in club rather than domestic settings (Sumnall *et al*., 2008).

2.7 Recreational use in the UK

For much of the period up to the end of 1990s, there is little, if any, reliable information on the recreational use of GHB in the UK. However, there are some sources that can throw some light on the topic, especially those that cover specific drug user subcultures.

The intoxicating and euphoric effects of GHB were discovered by recreational users and first appeared on the UK dance and club scenes during the spring of 1994, initially in 'gay' circles before spreading to other populations. Combined results from Independent Drug Monitoring Unit (IDMU) surveys conducted between 1999 and 2002 of GHB/GBL users found that very few respondents had used those substances before 1994 and even fewer prior to 1990 (Atha and Davis, 2003). GHB became increasingly popular in dance and club circles during the 2000s, as well as GBL and 1,4-BD several years later.

Self-selecting respondents to the UK Mixmag magazine's survey (initially postal and more recently online) of individuals predominantly in their early twenties found that lifetime use of GHB was 12.8% in 1999, 15.9% in 2000, 14.1% in 2001, 12.8% in 2002, and 17.5% in 2003. Mean age at first use during this period varied between 21.4 and 24.5 years. Current i.e. last month use was 3.4% in 1999, 4.0% in 2000, 2.7% in 2001, 3.9% in 2002 and 3.1% in 2003 (McCambridge *et al*., 2007; Mixmag 2002, Winstock, 2001).

A decade later, the online 2009 Mixmag survey and subsequent Global Drug Survey showed that 15.2% had ever tried GHB compared to 5.8% for GBL. Last month use levels were similar (1.7% and 1.6% respectively; Dick and Torrance, 2010). Lifetime use of GHB and GBL in 2010 was 11.8% and 5.8%, with last year (i.e. 12 months prior to the survey) use rates at 2.5% and 2.4% (Mixmag, 2011). The 2011/12 survey (n = 7,700) revealed that 7.7% of UK respondents had ever tried GBL compared to 3.8% for GHB; the proportions for last year use were 1.6% and 1.5% respectively, and for regular clubbers 2.5% and 2.0% (Mixmag, 2012; Winstock, 2012). The 2012/13 survey reported that respondents scored GHB 6.8 out of 10 for "value for money" (Winstock, 2013); this rating fell to 6.4 for GHB/GBL in 2014 (Winstock, 2014).

Surveys in 1999 and 2000 by IDMU also revealed that less than 3% of those interviewed at pop festivals and similar large events had ever used GHB (Atha and Davis, 2001). Both the IDMU and Mixmag surveys report that most users had tried many other drugs before experimenting with GHB. The peak age of initiation in the IDMU surveys was 17 or 18 years, with another peak at around 25 years (Atha and Davis,

2001). These findings are not inconsistent with the Mixmag results as the latter captures a different, typically older, age group. IDMU suggest that the relatively widespread of initiation ages is in line with the fairly recent arrival of recreational GHB usage (at the time of the surveys), and that those taking the drugs are not naïve users (Atha and Davis, 2003; Sumnall *et al*., 2008; Wood *et al*., 2009).

A survey (n = 308) by Measham *et al*. (2011) conducted in "gay friendly" dance clubs in south London in July 2010 found that GHB and GBL were used relatively more often than in other types of venue. Lifetime use of these substances was 34% and 27%, with last year use being 22% and 24% respectively. This, perhaps, indicates a move towards GBL from GHB. This was underlined by a higher proportion having used or planning to use it at the time of interview. These patterns are echoed in a survey of attendees at genito-urinary clinics in July-September 2011 conducted in London which found higher rates of lifetime and last month use of both GHB and GBL by gay men than in heterosexual males. Lifetime use of GHB and GBL amongst gay men was 22.7% and 16.1% respectively; last month rates were 2.4% and 3.1% (Hunter *et al*., 2014). Lifetime use of GHB/GBL amongst gay males in the south London boroughs of Lambeth, Southwark and Lewisham between August 2013 and March 2014 was 30.6%, with 20.1% using in the previous year and 10.5% in the previous 4 weeks (Bourne *et al*., 2014). The latter rate of 10.5% for previous month use contrasts with 5.5% (Odds Ratio (OR) 2.00, 1.58-2.53) elsewhere in London and 1.6% elsewhere in England (OR 6.94, 5.38-8.97; Bourne *et al*., 2014). The highest level of previous month use was amongst 30-39 year olds. A survey of Lancashire nightclubs (n = 343) in spring 2012 found that lifetime use of GHB/GBL was 4% with last year use at 1%; lifetime use had been 6% in autumn 2010 (Measham *et al*., 2012).

The 2011 sweep of the ESPAD survey (European School Survey Project on Alcohol and Other Drugs) of students aged 15-16 years found that 1% of boys and girls in the UK had ever used GHB; the same as the wider survey average. By comparison, the 2003 and 2007 sweeps found that the rate in 2003 was given as 0% and 1% in 2007 (Hibell *et al*., 2004, 2009, 2012).

The Crime Survey for England and Wales (formerly the British Crime Survey), which monitors drug use in a general household survey of adults aged 16-59 years, only asked about GHB use in 2010/11 and 2011/12 (Home Office, 2012). Last year use amongst this age-group was 0.0% in 2010/11 and 0.1% in 2011/12. These low rates illustrate the difficulties that such surveys have in capturing drug use amongst difficult to access groups. Unfortunately, no other information is presented for GHB.

Analyses of liquid samples in UK nightclub 'amnesty' bins appears to confirm a move from GHB to GBL in the years following the former's control (Wood *et al*., 2008). A similar trend was reported in France in respect of 1,4-BD (EMCDDA, 2002).

Limited data are available on the extent of GHB/GBL dependence in the UK. However, unpublished information from the National Drug Treatment Monitoring System (NDTMS) for England during the period 2005/6 to 2013/4 indicates that for those under 18 years of age presenting for treatment with a primary dependence on GHB the number has not exceeded more than about 5 cases per year. However, the number of adults presenting rose from 10 in 2005/6 to 50 in 2007/8 to 2008/9, and then to 100 in 2010/1 and 150 in 2011/2, but falling back to 130 in 2013/4 (personal communications to lead author from NDTMS, 16 January and 25 February 2015).

2.8 Availability

GHB usually exists as either the free acid or as the sodium base (sodium oxybate). It is soluble in water and methanol. It is usually sold as a clear, odourless, salty-tasting liquid but can be found in powder or tablet form, and occasionally as a bright blue liquid ('blue nitro'). The diversion of prescribed sodium oxybate appears to be very low; 0.00009% in the period 2002-8 in 15 countries worldwide (Wang *et al*., 2009). GHB is usually obtained from friends and known dealers (Brunt *et al*., 2014; Sindicich and Burns, 2013). Sharing GHB/GBL between not only friends and partners but also relative strangers in some settings (parties, clubs and saunas) is common in the male gay community (Bourne *et al*., 2014). Retailers are easy to find on the Internet, together with recipes for making it (EMCDDA, 2002, 2008; Sanguineti *et al*., 1997). Individuals also manufacture GHB themselves being able to easily obtain precursors (Brunt *et al*., 2014).

UK authorities took a range of actions to reduce supply and demand of GHB following increasing concern about its abuse and adverse effects. The Medicines Control Agency (MCA) undertook proactive enforcement activities in 1999-2000 involving retail premises in the Soho area of London. The Committee of Advertising Practice, together with the MCA, released an advertising alert to its members reminding the media that it is illegal to advertise GHB. The MCA set up a special unit to tackle internet advertising and supply and importation. Between 1995 and 2000 there were 23 charges brought under the Medicines Act 1968, 10 of which were successful (Hansard, 2000).

The disruption of overt supply in retail outlets, including sex-shops, and catalogue sales led to patterns of distribution similar to those of illicit drugs (EMCDDA, 2002). The availability and use of 1,4-BD appears limited (ACMD, 2008). Although the apparent availability in terms of internet retailers has diminished, at the time of writing (February 2015) sites are offering 500ml of GBL cleaner for as low as €55 (Polish site: www.gbl.com), or up to 50L for US$1475 (Chinese site: www.yunxiangchem.com). 1,4-BD is on offer; 100ml is US$50 with 16L available for US$1428 (an apparent US site: www.rightpricechemicals.com).

The IDMU 2002 survey suggested a bottle of GHB (typically containing 62.5ml) then cost £19.50 (€27) (Atha and Davis, 2003). £15 will purchase 30ml, while 1L of 'GBL cleaner' retails at about £80 (ReDNet, 2012). In early 2006, 2ml of GBL was retailing in Austrian clubs for €10. In Finland, 50 ml of GHB costs €5-6 (Boyd et al., 2012). In the USA a 'swig' or capful retails in bars and at 'raves' for US$5-25 (DEA, 2012). The price per ml in Australia in 2012 ranged from Australian $ 3 to 9 (Sindicich and Burns, 2013).

There have been very few convictions or cautions in England and Wales for production, possession with intent to supply, or supplying GHB. However, the number of offenders dealt with in this way rose from zero in 2002 to 20 in 2011 but fell to 6 in 2013 (personal communication from the Ministry of Justice to JC, 10 August 2014, 582-14 FOI 92136 Reply). The increased use of GHB/GBL amongst the male gay community in south London, and more generally, has been attributed by Bourne *et al*. (2014) to "the rising cost, poor quality and reduced availability of ecstasy and cocaine".

Before control in 2003, GHB itself was available for purchase from premises in the Soho district of London and in many clubs and pubs. In dance settings at the beginning of the century GHB was often sold in 3ml plastic bottles, containing about 3g, being offered for social use for relaxation, mild euphoria or post-party for sleep. Many illicit forms of GHB are available under a range of names, including: sodium oxybate, sodium 4-hydroxybutyrate, Grievous Bodily Harm (GBH), Liquid Ecstasy, "Georgia Home Boy", "Juice", "Liquid Ecstasy", "Mils", "G", "Liquid X", and "Liquid G", as well as "Fantasy". The precursors gammabutyrolactone - GBL - (also known as by such names as Renewtrient and Blue Nitro), and 1,4-butanediol (BDO) (also known as Serenity, Enliven, Somato Pro), are used in the chemical industry, and in some cleaning and cosmetic products. In excess of 200,000 tons of GBL is produced globally each year, principally in China, Germany, India and the USA (Pazos *et al*., 2013). It is rarely controlled under national legislation as it is a commonly used industrial solvent. Internet sites offering supply and distribution of GBL are mainly (60%) based in the Netherlands, but also Poland and the UK. Pazos *et al*. (2013) identified 39 sites selling GBL in 2010/1. Some nail varnish remover pads and solutions contain GBL, and have become a source for recreational use (EMCDDA, 2002). The Internet provides easy access to instructions on how to synthesise GBL and 1,4-BD as well as the materials to do so. These pro-drugs are mainly seized in liquid form (EMCDDA, 2002). It is also worth noting that Xyrem® is also available without prescription from sites posing as legitimate online pharmacies. For example, one site (drugstrading.biz), apparently based in Pakistan (based on the telephone number for queries), offers 500mg/ml vials for US$4 for a minimum order of 20 vials.

Information on seizures of GHB and its prodrugs are not given in the statistics published by the Scottish and Northern Ireland authorities. However, the most recent Home Office figures show that the number of GHB seizures by police forces in England and Wales and the UK Border Agency (formerly Customs) rose from 29 in 2003 (when it became controlled) to 66 in 2010/11 before falling to 45 in 2011/12 but increasing to 61 in 2012/3, but falling back to 41 in 2013/4 (Dhani, 2014). The quantity seized has not exceeded 10kg in any year apart from 2003 (40kg), varying from year to year (Coleman, 2013; Dhani, 2014).

2.9 Route of administration and usage

Although GHB is available as a salt or powder form, Wood *et al*. reported in 2011 that there had been no reports up till then of nasal insufflation. However, there are occasional reports of such use (Barker *et al*., 2007). Typically, it and its analogues are used orally, although there are occasional reports of intravenous (IV) use (EMCDDA, 2002), of "shelving" (insertion into the vagina), and of "shafting" (insertion into the rectum) (Sindicich and Burns, 2013). Powder is usually dissolved in water or other drinks prior to use (EMCDDA, 2002). Occasionally, capsules containing GHB's salt (sodium oxybate) are used (Andresen *et al*., 2010).

The median quantity of GHB used was 3ml in a typical session and 4ml in a heavy session in a study by Sindicich and Burns (2013). Issues can also arise because of inter-person variability in effects (Kam and Yoong, 1998), the selection of the correct dosage or taking doses too close together (EMCDDA, 2002). Depending upon tolerance levels, recreational doses range from 1-5g daily, 15-70mg/kg for a 70kg adult (Friedman *et al.*, 1996; Hodges and Everett, 1998). Durgahee *et al*. (2014) report mean daily usage of 53ml (median 40, range 5-200) in a group (n = 27) of patients presenting to drug services in Brighton & Hove (UK) with primary GHB/GBL dependence during 2008-13, with 'top ups' at 1 hr (41%) or 2 hr (44%) intervals. Suggested dosages are: 0.5g for relaxation and disinhibition, 1g for euphoric effects, and 2-3g for deep sleep (Erowid, 2013a; Lycaeum, 1998; Ward *et al*., 1998). Typical recreational doses are reported to be 2.5g (EMCDDA, 2008). Variation in the GHB concentrations in such solutions, as well as pre-prepared ones, can give rise to some of the dangers associated with illicit use (Hodges and Everett, 1998; van Rij *et al*., 2004; Williams, 1998). GHB 40ml (3 - 9 doses) could hold a dose of as little as 3g or a potentially toxic one of 20g (Thomas *et al*., 1997). Such variations in concentration mean an increased risk because of GHB's narrow therapeutic window and steep dose-response association (van Amsterdam *et al*, 2012). The GBL dose range is typically 1-3ml, with user fora suggesting taking initial doses of 1.5-2ml with a follow-up dose of 1ml 30 to 60 mins later (drugs-forum, 2014). Suggested dosages are: "a good relaxing/mood enhancing" 0.5-1ml; "f**k you up" 1.5-2ml; and "knock you out" 3ml, based on a conversion rate of pure GBL 1ml = GHB 1.65g (drugs-forum 2014; bluelight, 2014; mindandmuscle, 2014).

2.10 Effects

Early work on GHB as an anaesthetic demonstrated altered levels of consciousness associated with the following serum concentrations: (a) greater than 260 mg/L, patients were unresponsive to painful stimuli (comatose); (b) 156-260 mg/L, patients were asleep but responsive; (c) 52-156 mg/L, patients exhibited spontaneous movement with occasional eye opening; and (d) less than 52 mg/L, patients awoke (Helrich *et al*., 1964).

Clinical effects become evident about 5-20 minutes after ingestion (peaking after 30-60 mins (Mason and Kerns, 2002), and can last for up to 7 hours, depending on the dose. The duration of the effects is also influenced by combination with other substances ingested/taken at the same time (EMCDDA, 2002:13). Initial feelings after ingestion are euphoria and calmness, and then intoxication. A low to moderate oral dose of 10mg/kg (0.75g) can produce short-term amnesia and hypotonia, inhibitions are lowered and libido increased. A high dose of 20-30 mg/kg (1.5-2.5g) leads to drowsiness and sleep, and can cause nausea, vomiting, muscle stiffness, dizziness and confusion. Very high doses of 50-70 mg/kg (4-5g) lead to convulsions (Cagnin *et al*., 2011), amnesia, hypotonia, and coma; it may also cause bradycardia and cardiopulmonary depression is enhanced. Doses in excess of 70mg/kg (5g) can cause cardio-respiratory collapse (van Amsterdam *et al*., 2012; van Rij *et al*., 2004). A case of sodium oxybate-induced central sleep apnoea has been reported in a patient treated for narcolepsy and cataplexy with no previous history of apnoea (Frase *et al*., 2013).

However, it should be noted that these ranges are far from being absolutes. The same dose can have very varied effects on different individuals. The same individual may react differently to oral ingestion of GHB on various occasions (Teter and Guthrie, 2001). Variability in the effects of GHB and related substances also arises from the way in which their manufacture can cause differences in purity levels. Furthermore, the effects of GHB are exacerbated by use with alcohol and other drugs, especially benzodiazepines, opiates, etc. (EMCDDA, 2002). Combining a normal dose with alcohol can cause unrouseable sleep. Lamb *et al*. (2003) suggest that alcohol and GHB may not have a synergistic effect, but their combined effect is "less than additive". Loss of consciousness for short periods during sex with GHB/GBL appears to be common and is considered "relatively normal" by males in the South London gay community (Bourne *et al*., 2014:59).

Additional symptoms such as aggression, hypothermia and tonic-clonic convulsions do not have a clear dose relationship (van Amsterdam *et al*., 2012). Galloway *et al*. (2000) suggest that a potentially lethal dose of GHB ranges from 15-50g (250-750mg/kg).

2.11 Hospital presentations

The true extent of acute undesired effects of GHB and its analogues is not known, especially since routine toxicological screening is not undertaken in most Emergency Departments (EDs) (EMCDDA, 2002). This is because the results are not available in an adequately timely fashion to inform treatment options (Wood *et al*., 2011). Furthermore, there appear to be many unconfirmed anecdotal instances of intoxications (Erowid, 2013a).

The growing recreational use of GHB during the 1990s led to increased numbers of admissions to European EDs (up to 200 by 2000, chiefly in Sweden, the UK, the Netherlands, Denmark, Belgium, Finland, Spain and Norway) and calls to poisons centres in the EU (EMCDDA, 2002; Galicia *et al*., 2011), and to ED admissions in the USA (ONDCP, 2002) and Australia (Dietze *et al*., 2008; EMCDDA, 2002). Between 2006 and 2010, the number of ED visits recorded by the US NEW DAWN monitoring system increased by 65% from 1084 to 1787 (DEA, 2012). Oslo saw an increase in the number of admissions due to GHB from 68 in 2003 to 96 in 2008; these accounted for 7% and 9% respectively of all admissions in those years (Rønning, 2013). Helsinki experienced a more than doubling in such incidents in 2006-7 (Boyd *et al*., 2012). These patterns reflect the dangers inherent in its misuse.

An analysis of ambulance attendances involving GHB in Melbourne, Australia found there were 618 incidents in a 46 month period between March 2001 and October 2005, of which 362 involved the drug on its own (Dietze *et al*., 2008). Such attendances increased by an average of about 4% per month. Most patients were <25 years, females ranged from 35-40%, were attended in public places (78-85%), and had Glasgow Coma Scores <10. About 90% were taken to hospital.

One central London ED recorded 158 GHB/GBL presentations in 2006; there were no cases of 1,4-BD (Wood *et al*., 2008). Most presentations involved males aged 20-34, but it should be noted that this ED's catchment area includes a "substantial" 'gay' club scene (Hunter *et al*., 2014). Only 34% reported having used GHB/GBL alone; other combinations included alcohol (34%), MDMA (32%), ketamine (22%), cocaine (14%), amphetamine (14%). One Edinburgh hospital reported an increase in admissions from 3 in 2000 to 39 in 2006 (EMCDDA, 2008).

The UK National Poisons Information Service (NPIS) records telephone inquiries and TOXBASE sessions concerning GHB and GBL; TOXBASE is the primary NPIS clinical toxicology database. These data are not a direct measure of the frequency of toxicity or hospital admissions, but do provide an indirect measure, and also reflect what patients think they have used (NPIS, 2013). Figures from the agency indicate that the proportion of telephone inquiries involving GHB fell from 0.046% in 2007/8 to 0.028% in 2012/3, whereas for GBL the fall was from 0.017% to 0.012%. The proportion of TOXBASE sessions during the same period for GHB fell from 0.195% to 0.171%, but that for GBL rose from 0.028% to 0.086%.

Patients typically present to EDs in a varying range of conditions, from initial confusion, dizziness or euphoria, to collapse and vomiting, through to loss of consciousness or coma (EMCDDA, 2002). Presentations are often related to altered conscious state (89%), psychological concerns or nausea/vomiting (Horyniak *et al*., 2014), as well as generally 'feeling unwell' and having low body temperature (Krul *et al*., 2011). The typical characteristics reported in a study of 505 admissions to a Spanish ED for GHB intoxication was young (mean age 24.7 years), male (68%), at weekends (89%), early morning (75%), by ambulance (98%), Glasgow Coma Score <12 (72%), with co-consumption of alcohol (64%) and use of other illicit drugs (76%): amphetamines and derivatives (30%), cocaine (28%), ketamine (11%), cannabis (9%), others (5%) (Galicia *et al*., 2011). Symptoms were more severe for those who had taken GHB with other substances. These characteristics are very similar to those found by Lietchi *et al*. (2006) in a study of 65 GHB/GBL ED admissions: male 63%; median age 24 (range 16-41) years; co-intoxicants of alcohol or illicit drugs (mainly cocaine and MDMA) 65%; presenting with coma

83%. Bradycardia was observed in 38% of cases, hypotension 9%, hypothermia 48%, agitation 17%; vomiting 31%.

The most common clinical features of GHB toxicity are: neurological depression, bradycardia, hypotension and mild hypothermia. The concurrent use of other substances, including alcohol may contribute to other clinical symptoms such as vomiting and non-responsive coma (Wood *et al*., 2011). This is of particular importance in respect of alcohol (Barker *et al*., 2007; Kim *et al*., 2007; Liechti *et al*., 2006).

Cases of toxicity involving GBL and 1,4-BD are similar to GHB presentations, and are consistent with *in vivo* conversion of these substances to GHB (EMCDDA, 2002). An intoxication from GBL was reported by an ED concerning a 36-year-old woman who was hospitalised due to her comatose state and loss of adverse effects reflexes (Lenz *et al*., 2008). A UK case involved a 44 year-old male who suffered coma and life-threatening respiratory depression after an accidental overdose of GBL contained in a "health drink" (Dupont and Thornton, 2001). Two cases were recently reported from the Netherlands involving males aged 25 and 45 years, who both lost consciousness but recovered 16 h and 12 h later (van Vugt and Hofhuizen, 2012). Roberts *et al*. (2011) report that a patient who ingested a 'massive' dose of GBL with suicidal intent suffered severe metabolic acidosis and an asystolic cardiac arrest, but survived following treatment. In a similar case involving GBL ingestion the metabolic acidosis was accompanied by a highly increased anion- and osmolal gap; a GHB plasma level of 4398mg/L was recorded. Treatment including haemodialysis led to a full recovery (Heytens *et al*., 2014; Neels *et al*., 2014). It is hypothesised that the simultaneous intake together large quantities of alcohol (blood alcohol level of 279mg/dL) disturbed the metabolism of GHB with a consequent long-lasting acidosis and coma (Heytens *et al*., 2014).

2.12 Fatalities

One measure of the risks inherent in the misuse of GHB and its prodrugs GBL and 1,4-BD is deaths associated with their use. GHB-related fatalities have been reported primarily from Western countries, such as the USA, Canada, Australasia, and Europe (Caldicott *et al*., 2004; EMCDDA, 2008; Simonsen *et al*., 2015; Zvosec *et al*., 2011). This measure is often used as part of a range of indicators/parameters in national and international risk assessments of substances of concern (EMCDDA, 1999; Nutt *et al.*, 2007; van Amsterdam *et al*., 2012) and provides "signals of emerging harms" (EMCDDA, 2014:8). It is difficult to undertake epidemiological comparisons between and within countries for several reasons, including (EMCDDA, 1998): lack of systematic data on the topic; absence of routine hospital and forensic testing for GHB and its prodrugs; little standardisation in the identification, investigation, recording and certification of drug-related fatalities at local, national and international levels; lack of ICD coding for GHB and analogues as a cause of death (Zvosec et al., 2011); and no consensus on the post-mortem blood and urine concentrations to be used to distinguish between endogenous and exogenous origins/sources of GHB.

Several reports and papers have now been published documenting significant numbers of deaths associated with recreational GHB use (e.g. Caldicott *et al*., 2004; Knudsen *et al*., 2010; Kugelberg *et al.*, 2010; Zvosec *et al*., 2011), as opposed to single case and small case series a decade ago (Davis, 1999; DEA, 2002; Karch *et al.*, 2001; Morbidity and Mortality Weekly Report, 1997; Zvosec *et al*., 2011). Many other fatalities allegedly involving/attributed to GHB have been reported in both the printed media and on the Internet (e.g. Erowid, 2013a) but these do not necessarily translate into actual officially-confirmed deaths. The key features emerging from these case-series are briefly described here. However, there is considerable overlap between Zvosec *et al*.'s overview (2011) and other sources.

The main demographics of decedents are: mostly male (range 69-91%); average age 25-28 (range 15-53) years, males tending to be older than females by about 5 years (Caldicott *et al.*, 2004; Kugelberg *et al*., 2010); and mostly White (94%; Zvosec *et al*., 2011). Deaths have been ascribed to accidental overdoses, suicide, and drug-impaired driving. However, in certain cases there was a suggestion of alleged surreptitious administration of GHB via a "spiked drink" (Elliott, 2003). There is at least one death associated with complications arising from GHB withdrawal (Dyer *et al*., 2001). In the majority of reported cases attributed to GHB, the mechanism of death has been attributed to respiratory depression. For example, cardio-respiratory arrest accounted for 213/226 (94.2%) of the deaths between 1995 and 2005 reviewed by Zvosec *et al*. (2011).

Zvosec *et al*. (2011) classified deaths using a combination of GHB concentrations above their cut-off level, death investigations, and cause of death rationales to derive the following categories: “drug-caused” – direct and toxic effects of GHB caused/contributed to death; “drug-related” – GHB intoxication associated accidents that directly caused death (e.g. drowning, road traffic accidents); and “indeterminate” – GHB detected above cut-off (50mg/L in blood (bl), 20mg/L in urine (ur)) but its role in the cause of death was unclear. The proportions occurring in each category were: “drug-caused” 91.6%, “drug-related” 5.8%, and “indeterminate” 2.6% respectively. Knudsen *et al.* (2010), using a cut-off of 30mg/L blood, employed the following categories: GHB poisoning without influence of any other drugs and no other substances detected; GHB poisoning with minor influence of other drugs on GHB as well as other drugs but other drugs presented concentrations within therapeutic ranges and were less than 5; and GHB poisoning with a major influence of other drugs were positive for GHB as well as other drugs. All opiates were included. All cases that presented with more than 5 different substances even if concentrations were low because interactions with a negative influence on outcome could not be excluded. The proportions occurring in each category were: 8.7%, 39.1% and 52.2% respectively.

The mode of misuse of GHB frequently involves the use of other substances. The presence of alcohol has been noted to range from 20-37% of fatal cases; cocaine 8-26%; codeine 18-22%; morphine 16-26%; amphetamines 10-35%; diazepam 22-26%; and MDMA 2-20%. Zvosec *et al*. (2011) report that 28% of cases involved GHB on its own, GHB + one or more CNS depressant 27%, GHB + 1 or more stimulants 9%, GHB + 1 or more CNS depressant and stimulants 13%. The presence of alcohol and other depressant or psychoactive substances is widely believed to exacerbate the toxic effects of GHB ingestion, e.g. causing respiratory depression (Louagie *et al*., 1997; Zvosec *et al*., 2011), or even aspiration and asphyxiation. Therefore, the presence of such substances in deaths involving GHB should be taken into consideration when assessing fatalities attributed to GHB intoxication (Kugelberg *et al*., 2010; Snead and Gibson, 2005). Ferrara *et al*. (1995) reported a death involving GHB and heroin (diacetylmorphine), a high concentration of morphine was detected in the blood (770 mg/L). In five other reported GHB deaths, ethanol has also been involved at significant concentrations (Davis, 1999; Elliott, 2000, 2001). In these cases, the mechanism of death was recorded as respiratory depression. More recently a death involving GHB and mephedrone was noted in Italy (Aromatario *et al*., 2012).

Due to the previous anaesthetic therapeutic use of GHB, data relating to plasma concentrations and effects were largely based on IV administration rather than oral administration (the primary route of abused GHB). Such IV studies had indicated that plasma concentrations exceeding 260 mg/L could result in deep sleep (Helrich *et al.*, 1964). In cases of non-fatal GHB intoxication resulting in various degrees of sedation, plasma and urine concentrations are typically greater than 100 mg/L and 1000 mg/L respectively (Couper and Logan, 2000; Elliott, 2004b). In fatalities, post-mortem blood and urine concentrations have been reported to be between 27 - 1400 mg/L and up to 6000 mg/L respectively (Baselt, 2008; Duer *et al.*, 2001; Karch *et al.*, 2001; Mozayani *et al*., 1998). Sporer *et al*. (2003) report a median blood level of 180mg/L (range 45-295). Kugelberg *et al*. (2010) report a blood level of 2220mg/L.

Reports of GBL-related fatality have been infrequent: two in Germany (Lenz *et al*., 2008), one in the USA (Duer *et al*., 2001), and one in the UK (Dargan *et al*., 2009; included in the present sample). The German fatalities involved males aged 38: the first had GHB equivalent concentrations of cardiac bl 1089mg/L, femoral bl 957mg/L, urine 1019mg/L, gastric 14,464 mg/L, bl ethanol 67mg/dL, amphetamine bl 207.4mg/L, MDMA 5.8mg/L; the second case had a GHB blood concentration of 165mg/L and urine level of 916mg/L. The cause of death in each case was attributed to GHB intoxication; the manner of death was suicide in the first case and accidental in the second one. A non-fatal intoxication of a female aged 36 had a GHB serum level of 161mg/L and urine level of 2594 mg/L. The US case involved a 38 year-old male whose death was attributed to chronic drug abuse from the combined effects of the drugs detected. Post-mortem toxicology was positive for multiple drugs including GHB, GBL, MDMA, morphine, codeine, and 6-MAM. The concentrations of drugs detected in the urine were: GHB 320 mg/L, GBL 66 mg/L, 6-MAM 1.12 mg/L, codeine 0.11 mg/L, and morphine 3.10 mg/L. MDMA was detected in the urine. Only morphine was detected in the post-mortem heart blood at a concentration of 0.07 mg/L. The contents of the bottle recovered had a determined concentration of 19,000 mg/L GBL. GHB testing in the ocular fluid and brain detected levels of 37 mg/L and 44 mg/kg, respectively. The depressant action of GHB, GBL, and heroin may have caused the decedent to become unconscious for a period of time prior to death allowing him to metabolise the majority of the drugs from the blood. The manner of death was accidental (Duer *et al*., 2001).

Deaths involving 1,4-BD are also rare. One death in New Zealand has been linked to the use of 1,4-BD. It involved a 22 year old male who had consumed 15 ml of 1,4-BD. He had a seizure but was found not breathing 3 hours later. The blood level of GHB on admission to hospital was 220 mg/L. A chest X-ray indicated aspiration pneumonia. Brain death was confirmed the next day. There was no evidence for the use of any other drugs. It was concluded from the post-mortem examination that death resulted from complications due to a 1,4-BD overdose. Vomitus was inhaled resulting in pneumonia, shock, cardiac/respiratory arrest and brain damage (Theron *et al*., 2003). A case in the USA involved a 21 year-old male who died of accidental intoxication of 1,4-BD. The peripheral blood concentration was 70mg/L and 78mg/L for cardiac blood, the urine level was 870mg/L. The weighted mean for the GHB concentration was 303 mg/L in the heart; 1513 mg/L in the urine, and 260 mg/kg in the brain (Duer *et al*., 2001). Kugelberg *et al*. (2010) found 1,4-BD in the post-mortem toxicology of 4 deaths attributed to GHB intoxication (2 intentional, 1 accidental, 1 undetermined intent). No other substances were found. Concentrations were: ur 3400; bl 42, ur 1200; bl 25; bl 25 mg/L. The highest levels were in the intentional cases.

A number of deaths have been associated with the use of Xyrem® (sodium oxybate), a pharmaceutical preparation of GHB initially approved for treatment of narcolepsy with cataplexy. One death appears associated with Xyrem® abuse, with extremely high post-mortem blood GHB levels documented (bl 3500mg/L, vitreous 1800mg/L) together with drugs, including amphetamines. Although post-mortem blood GHB levels in two other deaths are consistent with therapeutic levels (110 and 141mg/L), cause and effect cannot be established although other drugs were again present, including CNS depressants. It is likely that Xyrem® contributed to the deaths in this way (Zvosec *et al*., 2009). Another case involved a 53-year-old woman undergoing treatment with Xyrem® for narcolepsy; the decedent was also prescribed tramadol, gabapentin, cetirizine, modafinil, and carisoprodol. Toxicological analysis of the blood revealed GHB 165.6 mg/L, and 90.7 mg/L in the urine. Blood GHB concentrations in the range 156-260 mg/L have been reported to induce moderately sound sleep. The combined use of prescribed CNS depressant drugs, together with her problematic sleep apnoea, and snoring (both contraindications for GHB use) were determined to have caused this subject's death. The manner of death was determined to be accidental (Akins *et al*., 2009). One death has been associated with the use of Alcover®. This case also involved moderate blood levels of morphine (bl 0.77, vitreous 0.3mg/L) together with GHB levels in blood 11.5, vitreous 84.3 and urine 258.3 mg/L (Ferrara *et al*., 1995).

Kilgore and Petullo (2010) note that an Agency Xyrem® Post-marketing Review between 17 July 2002 and 27 July 2010 recorded 91 reports of death, of which 21 were determined unlikely related to Xyrem®, 63 were indeterminate causality due to insufficient data, and 7 cases in which a contribution by Xyrem® could not be excluded. In general, at the time of death, the patients received recommended Xyrem® doses, and were using concomitant CNS depressants such as alcohol and sedative hypnotics. The causes of the 7 deaths were: unknown (5) drowning (1), and completed suicide (1). Wang *et al*. (2011) reported that worldwide there had been a total of 227 deaths in sodium oxybate patients between 2002 and May 2011. Cause of death was documented in only 88 (39%) of the cases, some of the major causes being: overdose (19 cases); cardiac events (17); malignancy (15); suicide (8); accidental death (7); cerebrovascular accident (5); and respiratory events (5).

Whilst the most comprehensive review of case series of GHB-associated deaths is that of Zvosec *et al*. (2011), it mainly focused on toxicity and trauma based on data obtained from a convenience sample of medical examiners/coroners in the USA, UK and Canada and from media reports. It provides a useful summary of basic demographics, ethnicity and manner of death. It provides a synthesis of blood GHB levels, details of dosages and clinical effects where available.

There have been several previous reports on UK GHB/GBL fatalities, including single case studies such as Elliott (2000) and Jones (2001). Details of GHB concentration, co-intoxicants and cause of death in 47 cases occurring between 1993 and 2005, identified by the National Programme on Substance Abuse Deaths (NPSAD), where GHB/GBL was found at post-mortem and/or implicated in death were included as an appendix in the ACMD risk assessment of GBL and 1,4-BD (ACMD, 2008:34-44; EMCDDA, 2008:21). One death involving GBL has been reported by Dargan *et al*. (2009). Here we give details of the largest number of fatalities associated with GHB and its pro-drugs to be documented so far in the UK. Not only are a range of key demographic features described but also circumstances of death, causes of death,

detailed toxicological levels for blood and urine, drug combinations, etc. for these cases. The existing literature on dosages and GHB/GBL levels in human tissues is presented for a range of scenarios.

3. UK GHB/GBL-related fatalities

3.1 Methods and source(s) of UK data

3.1.1 National Programme on Substance Abuse Deaths (NPSAD)

NPSAD regularly receives information from coroners on a voluntary basis on deaths related to drugs in both addicts and non-addicts in England and Wales, Northern Ireland, the Channel Islands and the Isle of Man. Since 2004, information has also been received from the Scottish Crime and Drug Enforcement Agency and the General Register Office for Northern Ireland. Since 1997 details of about 30,000 deaths have been received. The annual response rate from coroners in England and Wales to NPSAD has been consistently over 75%. To be recorded in the NPSAD database as a drug-related death, at least one of the following criteria must be met: (a) presence of one or more psychoactive substances directly implicated in death; (b) history of dependence or abuse of drugs; and (c) presence of controlled drugs at post-mortem. Ethical approval is not required in the UK for studies whose subjects are deceased, and solely involves retrospective reviews of death records.

3.1.2 Case identification

A range of documents are contained in coronial inquest files, although the variety differs from case to case. Typically, the coroner has access to: statements from witnesses, family and friends; General Practitioner records (if the deceased is registered with one); reports from ambulance, police or other emergency services; hospital EDs and clinical ward reports; psychiatric and substance abuse team reports; as well as post-mortem and toxicology reports.

In 2007 anonymised information was exchanged between the first and sixth authors in order to identify further cases (N = 2) and toxicological data. In 2009, enquiries were also made of the General Register Offices for England and Wales (through the Office for National Statistics - ONS), Scotland; and Northern Ireland to ascertain if there were any further cases known to them. Searches were made of the cause of death and toxicology text fields (where appropriate) of their electronic databases using the names for GHB, GBL and 1,4-BD. As a result of these initiatives, three further cases were identified in England that had not been reported to NPSAD. Contact was then made with the relevant coroners and details of these previously unknown cases were obtained and are included in the results presented here. Information provided from the drug-related deaths database maintained by the General Register Office for Scotland (GROS) indicated that there had been two additional cases in that country (in February 1999 and November 2001). Both involved White males, aged 30 and 32 respectively. One case involved other drugs, and one GHB alone (personal communication to first author from Graham Jackson, 12 March 2002). There have been none involving GBL or 1,4-BD (personal communication to first author from Frank Dixon, 15 July 2014). All cases registered by GROS up to the end of 2013 are included in this dataset. There have been no known deaths involving GHB or its derivatives in Northern Ireland (personal communication to first author from Northern Ireland Statistics and Research Agency, 18 July 2014).

Internet searches of toxicological as well as media websites revealed information on further cases and assisted in identifying potential new cases (about 10%). When the full text of the newspaper reports were not available on-line, it was necessary to view the original paper versions of the articles were retrieved. Media reports available for some cases were used to supplement the information provided on the NPSAD data collection form, especially where access to the full coronial files was not possible. Members of the London Toxicology Group (LTG) were also canvassed to see if they were aware of any cases; no further cases were reported. In all but two cases, full details of named individuals were known and thus prevented double-counting of cases. In the remaining two cases (from GROS – see previous paragraph), although anonymised, sufficient detail was provided to enable the exclusion of cases already known.
A retrospective study design was employed to identify relevant cases associated with the use of GHB, GBL and 1,4-BD by searching the NPSAD database with the following terms - 'GHB', 'GBH', ‘GBL’, ‘1,4-BD’, ‘BDO’, 'gamma hydroxybutyrate', ‘gamma butyrolactone’ and 'sodium oxybate', and any variants in

spelling. The fields searched on the database were those holding data on - drugs present at post-mortem, cause(s) of death, verdict, accident details, and 'other relevant information'.

3.1.3 Interpretation of toxicological levels

There has been a lengthy debate about what should be the appropriate minimum levels for GHB and its analogues in human ante- and post-mortem samples for its presence to be deemed non-endogenous in origin (Andresen *et al*., 2010). This is an important consideration as GHB is produced in the body after death (Moriya and Hashimoto, 2004; Sakurada *et al*., 2002), levels can vary according to the site from where the sample was taken (Mazarr-Proo and Kerrigan, 2005), and because of post-mortem blood redistribution (Pounder and Jones, 1990). Other factors to be taken into account when interpreting GHB concentrations include: longer storage time leads to higher sample concentrations; preservatives and additives may have an effect; storage temperatures; drugs such as valproate, phenobarbital, barbital and chlorpromazine may cause interactions with metabolic pathways (Andresen *et al*., 2010; Andresen-Streichert *et al*., 2015; Busardò *et al*., 2014). Only about 5% of GHB is eliminated in urine as it is metabolised extremely quickly to carbon dioxide through the Krebs cycle (Brenneisen *et al*., 2004; Ferrara *et al*., 1992). Typically GHB ingestion can only be detected for about 12 h in urine (Brenneisen *et al*., 2004), and 5-8 h in blood (LeBeau *et al*., 1999). However, a recent study of healthy volunteers administered doses of 2.1g (equivalent to a therapeutic dose for the treatment of narcolepsy) found that after 4-5 h the GHB concentrations in serum and blood fell below the analytical level of 1ug/ml and in urine after 10 h (Shröck *et al*., 2014).

For ante-mortem urine samples Mari *et al*. (2009) suggest a level of 3-10mg/L as indicating the possibility of exogenous GHB; whereas McCusker *et al*. (1999) and Crookes *et al*. (2004) suggest 5mg/L and Andresen *et al*. (2010) 6mg/L. Others have proposed a 10mg/L limit for discrimination to identify exogenous GHB (Bosman and Lusthof, 2003; Brailsford *et al*., 2010; Elian, 2002; Elliott, 2003; Wood *et al*., 2011; Yeatman and Reid, 2003; Zvosec *et al*., 2011); however, the possibility of false negatives exists when using this cut-off level (Andresen *et al*., 2010). Levels of 1mg/L and 5mg/L have been suggested for blood (Chin *et al*., 1992; Shima *et al*., 2005; Shröck *et al*., 2014; Zvosec *et al*., 2011;). Elliott's (2003) suggestion of 4mg/L for ante-mortem blood is endorsed by Andresen *et al*. (2010). These suggested cut-offs are not to be seen as rigid requirements, but as aids to interpretation.

There is now a general consensus that post-mortem blood concentrations of >50mg/L and urine concentrations >10mg/L are indicative of GHB (and analogue) consumption (Bosman and Lusthof, 2003). Moriya and Hashimoto (2005) proposed 10 mg/L for urine and 30 mg/L for blood in decedents showing little or no putrefaction (post-mortem interval <48 h). This cut-off was supported for femoral vein blood samples by two recently published retrospective studies from Sweden (Knudsen *et al*., 2010; Kugelberg *et al*., 2010). However, Kintz *et al*. (2004) argue that detection of GHB in urine is not necessarily indicative of use, and that levels in blood above 50mg/L alone are insufficient to prove an exogenous source; triangulation is essential. Kugelberg *et al*. (2010) and others (Elliott 2004a; Moriya and Hashimoto, 2005) have used a cut-off concentration of 30mg/L in femoral blood. Zvosec *et al*. (2011) suggest cut-offs of 50/20/7 mg/L for blood/urine/vitreous respectively for GHB, ≥ 1 mg/L for 1,4-BD blood levels. Andresen-Streichert *et al*. (2015) suggest a cut-off of 30mg/L for venous blood, urine and cerebrospinal fluid. Some authors recommend analysis of urine in addition to blood samples because of typically (but not generally) lower GHB concentrations due to less post-mortem generation. Other authors suggest vitreous humour as the specimen of choice, in addition to femoral vein blood but the comparative data for this fluid are limited.

As with other psychoactive substances, the levels of GHB found in fatalities overlap with levels found in drivers under the influence of the substance (Bosman and Lusthof, 2003; Pan *et al*., 2001) and therapeutic levels (Moriya and Hashimoto, 2004). In post-mortem peripheral blood samples, depending on the methodology used, high concentrations of GHB from zero to 197 mg/L could be measured, even in cases without GHB ingestion. These levels overlap with the range of reported fatal GHB intoxications with concentrations of 27 to 2937 mg/L and could possibly lead to misinterpretation as intoxication (Andresen *et al*., 2011). Concentrations in non-fatal intoxications as high as 551 mg/L have been reported (Couper and Marinetti, 2002; Elliott, 2004b; Van Sassenbroeck *et al*., 2007), whilst fatalities with concentrations of 303 mg/L have been recorded (Duer *et al*., 2001; Marinetti *et al*., 2005).

3.1.4 Toxicological screening

Historically, analysis for the presence of GHB was not performed routinely in clinical or post-mortem investigations in the UK or other countries (Caldicott *et al*., 2004; Jones *et al*., 2007). The drug and its prodrugs have been typically looked for only after a direct approach from the medico-legal investigators, often if anecdotal or circumstantial evidence points to its use (EMCDDA, 2002). If screening for other drugs proves negative, but signs and symptoms of drug influence have been noted, a search for GHB may be made. However, over the past decade the provision of this service has improved; it is not at all uncommon for GHB and its derivatives to be tested for in the UK (Korb and Cooper, 2014), USA, Sweden and certain centres in Australia. Since GHB is metabolised relatively quickly in the body, it may not be present in toxicology screens, even if they are made. Thus, the number of identified cases reported historically is likely to be an underestimation.

All cases reported here have either confirmatory evidence of GHB, GBL, etc. ingestion and/or the tissue levels are consistent with exogenous intake/misuse (as outlined in Section 3.1.3).

3.1.5 Data analysis

Data entry and analysis were performed using IBM ® SPSS™ Statistics for Windows version 19 employing descriptive statistics. Data on blood, urine (and vitreous) GHB concentrations are presented as mean, median and range. Statistics for each test are based on all cases with valid data for the variables used in that test. A two-tailed p-value of ≤0.05 was considered to indicate statistical significance.

3.2 UK Results

3.2.1 Number of cases

A total of 159 fatalities that met the above inclusion criteria were identified on the NPSAD database as having been reported by September 2013. The first known death in the UK related to GHB consumption occurred in 1995. Of these 159 cases, the role of GHB was uncertain in one case. At least 55 (34.6%) are considered to have involved the use of GBL; there were none attributed to the taking of 1,4-BD. Although the number of deaths was low (mean 1.5 p.a.) during the second half of the 1990s, there was a notable increase in 2001 and 2002 (7 and 6 cases respectively), followed by a rapid fall to just one case in 2003 (Figure 1). The period from 2004 to 2009 witnessed a rapid and progressive rise to 25 deaths, this peak being maintained in 2010 at 21. However, this was followed by a steep decline in 2011 (to 10), followed by a doubling to 20 in 2012.

< insert Figure 1 about here >

3.2.2 Socio-demographics

The mean age of decedents was 32.1 (range 18.9 - 60.1) years, males being 2.7 years older than females on average (Table1). About 91% were aged less than 45 years. Most were male (81.9%). Where known, the ethnicity of most (91.9%) of the deceased was described as 'White'. Where place of birth was given, 77.0% were born in the UK, 10.7% in another European country, and 8.2% elsewhere. Where known, 70.7% were in employment, 17.9% were unemployed. Half (51.6%) were living with someone else and 27.0% lived alone. Information on prescribed psychoactive medications was available for 90 cases (Table 2). In 29 (32.2%) medications were prescribed; most were antidepressants, antipsychotics or benzodiazepines. Where information was available on past drug use, 69.8% were known to have previously used drugs or to have been dependent on them. Ten out of 56 individuals (17.9%) were known to have been injectors at some time.

< insert Table 1 about here >

< insert Table 2 about here >

3.2.3 Circumstances of death

All of the deaths reported thus far have occurred in Great Britain: England 123, Scotland 27 and Wales 9 (Table 3). Where known, the majority of cases died at home or in another private residence (friend's or relative's home) (77.1%), and 14.6% in hospital (Table 4). From the few details available, it seems that in many instances there was an assumption that the deceased would 'sleep it off'. The manner of death in most cases was accidental (79.2%), with 6.9% being regarded as suicidal and undetermined in 13.2% of cases. This closely reflects the verdicts of coroners or other formal determinations, where accidental/misadventure verdicts were given in 60% of cases; along with drug-related conclusions being recorded for a total of 35 cases (22%), non-dependent abuse of drugs (14%), abuse of drugs (5%) and drug dependence (3%); and (possible) suicides for the remaining 29 cases (18%). Deaths were proportionately (36%) more likely to occur at weekends (between Saturday and Sunday) than on a week-day ($\chi^2 = 4.463$, df = 1, p = 0.0346).

< insert Table 3 about here >

< insert Table 4 about here >

3.2.4 Events leading to death

In at least six cases GHB was sourced from the Internet as well as four cases of GBL (including one decedent who ran a site selling the substance). Another was a dealer in GBL and one made his own GBL.

In line with half of the deaths occurring at home, half of the events leading to such events also occurred at home or that of another person. In many instances, such deaths followed recreational use of GHB in these settings. A range of other locations witnessed GHB consumption including pubs/clubs, music festivals, motor vehicles, and open spaces (Table 4).

GHB/GBL consumption was not always for recreational purposes, for example: body-building/fitness; to aid sleep; to prevent alcohol craving; and to enhance sexual experiences. Whilst there were at least 7 suicides and 2 cases of probable suicide where GHB/GBL was deliberately consumed so as to apparently cause death, a number of deaths (n = 7) were 'accidental' in the widest sense of the term – being mistaken for water, or in drinks not intended for the deceased.

3.2.5 Cause of death

When considering the underlying cause of death (Table 5), the majority of deaths were attributed to accidental poisoning (76.7%), with intentional self-poisoning (6.3%) and poisoning of undetermined intent (12.6%). In terms of the proximal (immediate) cause of death, the proportions for these categories fall to 59.7%, 5.7% and 8.8% respectively. There were more deaths where natural causes played a role as a consequence of taking GHB/GBL and/or other substances. The principal causes in this category can be grouped as follows: respiratory (6.9%); cardiac (2.5%); cardio-respiratory (2.5%); aspiration of gastric contents (3.8%); asphyxia/anoxia/hypoxia (3.1%).

< insert Table 5 about here >

3.2.6 Post-mortem toxicology

Blood concentrations of GHB > 0mg/L were available in 118 (73.8%) of the 159 cases; of these 13 (11.1%) were ≤30mg/L and 3 (2.6%) were >30mg/L but ≤40mg/L; 5 (4.3%) were >40mg/L but ≤50mg/L; and 96 (82.1%) were >50mg/L. The mean blood level was 481 (range 0 – 6500; S.D. 758.26) mg/L (Table 6). Urine levels were available for 36 cases (22.6%); 5 (13.9%) of these were ≤10mg/L and 31 (86.1%) were >10mg/L. The mean urine level for cases was 1444.17 (range (0 – 7600; S.D. 1632.42) mg/L.

< insert Table 6 about here >

The commonest groups of substances found, apart from GHB/GBL, were: alcohol; stimulants (cocaine, amphetamine/methylamphetamine, MDMA/MDA, mephedrone); benzodiazepines (principally diazepam); opiates/opioids; ketamine; and cannabinoids (Table 7). There was a mean of 3.47 post-mortem

substances, reflecting polysubstance use. The range of substance types listed above were also evident in the most common combinations reported (Table 7). The most prominent were: GHB/GBL and alcohol (13.8%); GHB/GBL alone (12.6%); and GHB/GBL and stimulants and alcohol (11.9%).

< insert Table 7 about here >

3.2.7 Drugs implicated

GHB /GBL was implicated on its own in more than one-third (36.5%) of cases (see first 4 rows of Table 6); GHB/GBL and alcohol alone were implicated in 13.8% of cases; GHB/GBL and other drugs in 28.3%; and GHB/GBL with other drugs and alcohol in 14.5%.

The typical profile of cases where GHB/GBL was the sole substance implicated in death (n = 59) is: male (88%); mean age 32 years. Where known, victims were of White ethnicity (89%); and with a history of drug use/dependency (67%). Most deaths (72%) occurred at the home of the deceased or a friend/relative, usually following consumption in such locations (Table 8).

< insert Table 8 about here >

3.3 Discussion

3.3.1 Number of cases

Since the first known death in the UK associated with the ingestion of GHB and its prodrugs in 1995, there have been a minimum of 159 cases in which these substances were implicated. Of these, at least 55 (34.6%) involved GBL, increasing between 2006 and 2010 and then declining. The increase in NPSAD GHB/GBL deaths occurring in 2012 is echoed by an increase in the number of deaths involving these substances registered during 2013 in England and Wales (ONS, 2014). The patterns shown in Figure 1 reflect, to a certain extent, the effects of control of GHB in 2003 and GBL in 2009 in terms of a displacement from controlled to illegal forms of the substance(s) and then a fall, as was seen with GHB and GBL in Switzerland (Liechti *et al*., 2006), GHB in Sweden (Mikelsson, 2005) and the Netherlands (Van Amsterdam *et al*., 2014), and mephedrone in the UK (Corkery *et al*., 2012).

The overall proportion of all deaths notified to NPSAD for the period 2000-12 accounted for by GHB/GBL was 0.58% (range 0.06 – 1.24). The total number of cases reported here is likely to be an under-estimate due to: (a) incomplete geographical coverage by the Programme; (b) unidentified cases due to a lack of historic systematic screening for GHB and its prodrugs in post-mortem toxicology of suspected drug-related fatalities; (c) further cases awaiting the conclusion of formal investigations; (d) the voluntary nature of the NPSAD reporting system; etc. For example, media reports suggest 4 further GBL deaths have had inquests completed on them by the end of July 2014. Of these, one occurred in 2011, two in 2012 and one in 2013. Two additional GHB deaths have been reported for 2012 and one for 2013. These additional data were not included in this study.

Presently, analysis for the presence of GHB is not usually performed routinely in clinical or post-mortem investigations in the UK, although it is not all uncommon in the USA and certain centres in Australia. Hence the number of identified cases reported here is likely to be an underestimation. Since GHB is metabolised relatively quickly in the body, it may not be present in toxicology screens, even if they are made.

3.3.2 Socio-demographics

About 82% of victims were male. This proportion is only slightly higher than that seen in 'typical' NPSAD cases (about 75%). A probably elevated contribution to this male proportion (about 11%) was made to this sample by males known to be homosexual; with two further deaths recently reported for 2012 that occurred in the same venue (a sauna catering for a gay clientele) as a case included here (Cheston, 2014). (Information on sexual orientation was found in coroners' records, e.g. known to have a male partner, engaged in homosexual activities around time of death, etc.) The proportion of homosexual men in the general population of the UK is about 1.5% (ONS, 2013). However, in some areas, such as Brighton

& Hove, the Lesbian Gay Transsexual and Bisexual (LGTB) community may account for as much as 15% of the local population; Durgahee *et al*. (2014) report that 4/5 of their GHB/GBL dependence sample in the area identified themselves as being from the LGTB community. NPSAD has been notified of 4 GHB/GBL deaths in this area (Table 3). The finding of the present study in respect of the gender split (percentage male) lies between those of Caldicott *et al*. (2004) of 80% and Kugelberg *et al*. (2010) at 86%; Zvosec *et al*. (2011) report a rate of 69% and Knudsen *et al*. (2010) one of 91%.

The mean age at death in this study was 32.1 (range 18.9 – 60.1) years compared to 38.5 (range 0.0 - 99.0) years in typical NPSAD cases during the same period, probably reflecting the different nature of the two samples - recreational versus mostly problematic users. The median age of those dying in 2012 with a known history of drug use was 38 years (Corkery *et al*., 2014a); for all other deaths it was 40 years. The average age is higher than for GHB fatalities in the USA; here 40% of deaths were amongst those aged 15-24 and a further 27% aged 25-29 (DEA, 2002). The large age range reported here is consistent with the IDMU survey results (Atha and Davis, 2001, 2002).

As with most reported GHB-related deaths (in the US and elsewhere), the cases detailed here mostly involved Caucasian individuals (92% where known). Where known, most victims (94/122; 77.0%) were born in the UK, but there were also a number of individuals born elsewhere in Europe (13; 10.7%) or on other continents (10; 8.2%).

Where known, the majority (87/123; 70.7%) of cases were in employment and more than half (82/127; 64.6%) were living with others. This is in distinct contrast to typical drug-related deaths (366/1154, 31.7%; and 521/1170, 44.5% respectively) (Corkery *et al.*, 2014a). This, no doubt, reflects the lower mean age of the GHB/GBL cohort.

A past history of drug use was known for 106 cases; of these 74 (70%) had such a history. About 18% of the decedents were known to be injectors; this is lower than the 41/90 (46%) of ED cases reported by Boyd *et al*. (2012). Where the circumstances were known, the majority (82/115; 71%) of deaths followed recreational use, often by individuals with a history of substance use. Several (n = 6) cases involved the use of GHB/GBL directly in connection with sexual activities. Where information was available, a small number of individuals used of GHB to aid sleep (n = 4) or to assist in body-building (n = 4), whilst two others were known to use gyms regularly.

The temporal pattern of most GHB/GBL deaths occurring in the UK on Saturday or Sunday (36%, compared to an expected proportion of 28.6%) probably reflects higher consumption rates on Friday to Sunday. These findings echo ED admissions in other studies (Boyd *et al*., 2012; Liechti *et al*., 2006; Miró *et al*., 2002; Munir *et al*., 2008).

All parts of the UK, except Northern Ireland, have experienced GHB/GBL deaths. None had been reported so far from the Islands by the end of September 2013. Many cases appear to have occurred in Metropolitan areas. Of note is the fact that 17 cases (12% of the overall total and 48% of the total for Greater London) occurred in just one coroner's area (Inner South London). Many of these cases involved homosexual males who had frequented well-known gay clubs in the Vauxhall area. A number of deaths in 2005 and 2006 connected with these clubs led to materials being prepared to give advice on safer use of GHB/GBL (Daily Mail, 2006; FIRE, 2006). Clubs started issuing warnings that they had a 'zero tolerance' approach to the possession and use of drugs including GHB and its derivatives. For example, FIRE, a well-known gay venue, provided information to clubbers on the adverse effects of GHB and GBL (http://www.harderfaster.net/text/news/11814). It also had fully qualified paramedics on duty whilst the club was open to the public, with a close working partnership with the London Ambulance Service. However, these dangers still persist (Hopkins, 2012) and there is so much concern that community leaders in the area arranged an open discussion with guest panellists in May 2013 (Zapata, 2013).

3.3.3 Post-mortem toxicology and other findings

There remains some uncertainty about what constitutes a fatal level of GHB/GBL. See Table 9 for a summary of findings from previous studies. Detailed information for the cases reported here is available in Table 10. Suggested estimates of GHB blood levels sufficient to cause death include those given by TIAFT (www.TIAFT.org) - 280 mg/L, and Kugelberg *et al*. (2010) – 300mg/L. Knudsen *et al*. (2010) argue

that because of the wide range of factors influencing outcomes after a severe overdose e.g. anatomical, physiological, pharmacological, etc., a level of toxicity can only serve as a guide for when severe toxicity should be suspected/investigated. Galloway *et al*. (2000) suggest that a potential lethal dose may be between 15 and 50g (250-750mg/kg) for a 70 kg person. Knudsen *et al*. (2010) found that although blood concentrations of GHB were higher with alcohol than without (320 vs. 235mg/L) these findings were not statistically significant. The median concentration in urine was twice as high in cases negative for alcohol, but not statistically significant. A lower GHB urinary value may suggest higher toxicity with alcohol consumption since less GHB has been excreted into urine before death, thereby reflecting a slower metabolism and earlier death (Knudsen *et al*., 2010).

Post-mortem blood concentrations found in this study range from 8 to 2794 mg/L for polysubstance deaths and from 159 to 6500 mg/L for cases involving GHB (or its derivatives) on its own (Table 6). These results are in line with previous findings for GHB-associated fatalities, medical examiner cases, and cases with known GHB uptake (Table 9). However, some post-mortem levels reported here are in excess of previous reports. It is important to note that 82% of cases had GHB levels > 50mg/L where blood levels were reported, indicating exogenous intake. The remaining cases (with lower levels) had evidential proof for exogenous intake.

GHB/GBL alone was identified at post-mortem on 58 occasions (36.5% of the present sample). ONS figures for death registrations in England and Wales during the period 1993-2013 show that overall the proportion of GHB/GBL cases involved the drug without other drugs was 54.7%, and with alcohol 36.7% (ONS, 2014). The findings in the present study confirm the results of other studies (e.g. Caldicott *et al*., 2004) that GHB (and GBL) can prove fatal on its/their own. The majority of cases involved the ingestion of at least two other substances, typically combinations of any of the following: alcohol; stimulants; diazepam; opioids; and ketamine. Co-ingestion with other sedatives such as alcohol or ketamine increases the likelihood of intoxication (Brunt *et al*., 2014). Polydrug intoxication is likely to be a significant factor in the cases presented here, in line with Kugelberg *et al*. (2010). There was considerable variability in the range of GHB/GBL levels at post-mortem. In many instances the effects on respiratory depression of GHB/GBL were enhanced by the presence of alcohol (46%) and other CNS depressants such as benzodiazepines, antipsychotics, and opiates/opioids. Both alcohol and GHB are metabolised by alcohol dehydrogenase and potentiate the effects of each other (Galloway *et al*., 2000; Smith *et al*., 2002; Vree *et al*., 1975). Recent animal studies have concluded that alcohol potentiates the sedative and respiratory depressant effects, especially the tidal volume, of GHB, thereby increasing the risk of death (Morse and Morris, 2013). The findings of the present study for humans echo those of Adinoff *et al*. (1988), Altose and Hudgel (1986), Mason and Kerns (2002), and Zvosec *et al*. (2011).

High doses of GHB can cause cardio-pulmonary depression (McDowell, 2000). These effects are made worse by being consumed with other substances. In the present study GHB was used with alcohol in 14% of cases; with other drugs in 28%; and with other drugs and alcohol in 15%. As Table 5 demonstrates in respect of proximal cause of death, the consumption of GHB/GBL alone or with other CNS depressants led to cardiac, respiratory and cardio-respiratory failure, the reduction of oxygen to the brain (asphyxia, anoxia, hypoxia), and physical obstruction of the airways due to aspiration of gastric contents. Together these cases account for about one-fifth (19%) of cases. If fuller information was recorded in the medical certificate of death in respect of the actual mechanism(s) of death, this proportion is likely to be much higher since one would expect more deaths involving these mechanisms. Vomiting is often seen in GHB intoxications (Mason and Kerns, 2002), especially with alcohol ingestion (Liechti and Kupferschmidt, 2004), and can lead to asphyxiation.

3.3.4 Pre-existing medical conditions

Pre-existing medical conditions (see next paragraph) may have contributed to death or been exacerbated by the use of GHB/GBL in some cases. Respiratory diseases/conditions, such as those reducing the lungs' ability to supply oxygen to the cardio- and cerebral-vascular systems, will be compromised by the use of the drug(s), especially with co-administration of other CNS-depressants. In the present study only one case had a known history of respiratory problems (emphysema) which was considered to have contributed to or caused death.

Bradycardia has long been recognised as a complication in the therapeutic use of GHB and also in those using it recreationally (Mason and Kerns, 2002). There have been some cases of GHB causing other cardiac problems, typically arrhythmias; where it has it often has been co-ingested with traditional stimulants such as cocaine (Mason and Kerns, 2002), or more recently with mephedrone (Aromatorio *et al*., 2012). In two cases there was a known history of heart disease (coronary artery atheroma were severe stenosis; coronary atherosclerosis and hypertensive heart disease) and in a third instance the post-mortem found an enlarged heart consistent with dilated cardiomyopathy leading to pulmonary embolism. Cardiac problems caused/exacerbated by stimulant use were noted in three cases and caused solely by GHB in another case. These problems led to cardiac failure in three instances and to ischaemic heart disease and severe coronary atheroma in a fourth case. Only two of those on prescribed medication were known to have used stimulants on a regular basis compared to 16 of the remaining cases. The latter were more likely to have a history of using non GHB/GBL drugs than those on medication (29 vs. 4). Tricyclic antidepressants can cause sodium channel blocking leading to cardiac complications such as ventricular tachycardia and torsades de pointes arrhythmia (Gheshlaghi *et al*., 2012). Co-ingestion of tricyclic antidepressants may be a risk factor for GHB/GBL usage, especially when taken together with stimulants. In the case of decedents prescribed psychoactive medications, one prescribed dothiepin had ingested cocaine and piperazines, and another prescribed amitriptyline had used mephedrone. Neither of these or any other cases appear to have experienced such a complication.

3.3.5 Drug effects and mental health issues

In the 1960s GHB showed promising effects on agitation and depression, acting as an anxiolytic and an antidepressant. However, with the growing use of benzodiazepines and tricyclic antidepressants, GHB was forgotten about in this context. However, in recent years it has started to be reconsidered as an anti-depressant and/or in the treatment of depressive disorders (Bosch *et al*., 2012; Snead and Gibson, 2005). Bosch *et al*. 2012 suggest that GABAergic mechanisms with secondary effects on serotonin, norepinephrine and dopamine systems may contribute to the antidepressant qualities of GHB. However, there may be an additive effect between sodium oxybate and antidepressants, with increased likelihood of adverse incidents with tricyclic antidepressants (Gerot Lannach, 2011).

Where known, one-third (32%) of the decedents in this sample were prescribed psychoactive medications, mostly antidepressants, antipsychotics or hypnotics/sedatives, often in combination (Table 2). This appears to be a higher proportion than in the general population. A survey conducted in June 2011 suggests that 13% of adult females and 10% of adult males in the UK were currently taking antidepressants (Our insight, 2011). This is echoed in Scotland where 15% of the population have taken such drugs (Herbert, 2014), and 9% reported by Blanchflower and Oswald (2011). Overall, one percent of UK patients in primary care received an antipsychotic between 1995 and 2011 (Marston *et al*., 2014). In the latest General Household Survey, in 2007, asking about prescription medications, 0.5% reported using tranquillisers in the previous year (ONS, 2009). Thus is similar to the level of 0.5% last year use of illegal tranquillisers reported by households on England and Wales in 2013/14 (Home Office, 2014).

This observation of prescribed medications points to these individuals having pre-existing psychiatric disorders. In fact, an examination of the 29 cases supports this. Depression is mentioned in six cases, suicidal ideation/suicide attempts in four cases, misuse of drugs or dependence in five cases, alcoholism in two cases, bipolar disorder in two cases, psychosis in one case, and paranoia in one case. Fourteen (48.3%) of these 29 cases had one or more of these conditions. In the remaining 130 cases depression was only mentioned six times, psychosis twice, paranoia once, and anxiety with depression once. Previous suicide attempts had been made by four of those prescribed medication compared to only three of the remaining 130 decedents.

Overall, 69.0% of those on medication had at least one prescribed medication found in the post-mortem toxicology, but only 34.5% of the medications were implicated in death. When the number of prescribed drugs is considered, these proportions fall to 44.3% and 21.3% respectively. The highest proportions were found amongst those prescribed opioids, benzodiazepines (diazepam), non-benzodiazepine hypnotics and antipsychotics. The combination of such prescribed medications along with GHB/GBL use underlines the dangers of potential drug interactions. These findings for those on medications echo the literature described earlier in respect of sodium oxybate patients in terms of substance abuse, dependence, withdrawal symptoms, and overdose with suicidal intent (Wang *et al*., 2009).

Case studies indicate that sodium oxybate on its own has led to depression and anxiety with suicidal ideation (Ortega-Albás *et al*., 2010), psychosis (visual hallucinations, paranoid delusions, derealisation, hyper-religiosity, and anxiety; Langford and Gross, 2011) and traumatic suicide attempts (Chien *et al*., 2013). In conjunction with modafinil this may lead to depression, derealisation, and suicidal ideation (Rossetti *et al.*, 2010). These clinical symptoms appear to resolve with reduced dosages and re-titration or total withdrawal of sodium oxybate. Although the pathogenic mechanism in such cases is unknown, Rossetti *et al.* (2010) suggest it may be due to the substance acting on $GABA_B$ receptors. Depression was reported by patients receiving sodium oxybate (U.S. Xyrem® Multicenter Study Group, 2003), and anxiety by patients receiving both sodium oxybate and modafinil (Black and Houghton, 2006).

There are issues around withdrawal of GHB (Langford and Gross, 2011; McDaniel and Miotto, 2001; van Noorden *et al.*, 2014), both from clinical doses as well as recreational doses. Severe cases of withdrawal can feature extreme agitation, delirium and rhabdomyolysis and should be regarded as medical emergencies (van Noorden *et al*., 2014). Case studies of GHB withdrawal show similar symptoms to the effects of high doses of sodium oxybate: agitation, anxiety, delirium with disorientation, auditory/visual hallucinations, fluctuations in/disturbance of consciousness. Paranoid delusions; hypertension, tachycardia and seizures can also occur (van Noorden *et al*., 2014). Return to GHB or GBL use may occur soon after treatment of withdrawal as patients seek to overcome their cravings not only for GHB/GBL but also for alcohol, opioids (including heroin/morphine) and cocaine (Bosch *et al*., 2012), etc. through self-medication or by increasing dosages of sodium oxybate above the recommended dosages (Beghè and Carpanini, 2000).

3.3.6 Drug interactions

There are several known interactions between GHB and other drug(s), e.g. drug-drug interactions. Antiretrovirals such as ritonavir and saquinavir inhibit the cytochrome p450 system, which may decrease first-pass hepatic metabolism of GHB, leading to the potentiation of its effects, i.e. slow down its elimination and allow levels to build up (Mason and Kerns, 2002). This complication could be important to communicate to those in the gay community receiving antiretrovirals who may wish to use GHB or its derivatives. GHB has a potentially important synergistic interaction with PCP and ketamine, as they act as NMDA receptor antagonists (Sevak *et al*., 2004). Possible interactions may occur between sodium oxybate and drugs that induce or inhibit the GHB dehydrogenase enzyme; these could include antiepileptics such as sodium valproate, phenytoin and ethosuximide (Gerot Lannach, 2007). Whereas Navarro *et al*. (1998) suggested a synergistic interaction between GHB and the neuroleptic haloperidol, Sevak *et al*. (2004) did not. SSRIs, such as the antidepressants citalopram and fluoxetine were here prescribed to a number of decedents; however the literature does not suggest any SSRI/GHB interactions. Many of those prescribed psychiatric medications in the sample described above (Section 3.3.5) were prescribed medications (Table 2) with possible interactions with GHB/sodium oxybate.

The Patient Information Leaflet for Xyrem® states the medication is contraindicated for “patients being treated with opioids or barbiturates” (EMEA, 2014). It also advises that patients be warned about the use of alcohol in conjunction with sodium oxybate, and to avoid concomitant use of benzodiazepines because of the CNS-depressant effects. The general advice is not to use it in combination with sedative hypnotics, other CNS depressants or antiepileptics; or by those suffering from epilepsy or epileptiform seizures. Use of sodium oxybate is also contraindicated for those with previous or current addiction to opioids and other CNS depressants, those with a previous cocaine addiction (Caputo *et al*., 2009), or those with mental health issues/disorders (Gerot Lannach Pharma, 2007; Laboratorio Farmaceutico C.T.Srl., 2007; Murali and Kotagal, 2006). The UK cases examined here included individuals contraindicated for such combinations. This highlights the need for such interactions to be brought to the attention not only of patients treated with sodium oxybate but also to recreational users of GHB and its derivatives.

Self-medication by GHB/GBL has not only been reported to treat depression but also for sleep disorders, bodybuilding, and alcohol-related disorders (Mason and Kerns, 2002), and in this study to aid relaxation. This study reinforces the contribution this phenomenon makes to GHB/GBL related overdoses and fatalities.

The role of alcohol in potentiating the depressive effects of GHB/GBL has been widely documented (Adinoff *et al*., 1988; Altose and Hudgel, 1986; Mason and Kerns, 2002; Zvosec *et al*., 2011). The dangers of mixing GHB/GBL with alcohol and/or other CNS-depressant substances need to be better described in prevention campaigns. Recreational users need to be reminded of the dangers of this substance, especially when taken in combination with other substances, including stimulants. The dangers of using GHB, on its own and in combination with other substances, have become more widely recognised and disseminated in the last decade (e.g. ACMD, Mixmag magazine, initiatives in Vauxhall clubs, etc.). These activities, together with the classification of GHB as a Class C drug in 2003 and subsequently its prodrugs in 2009 may have contributed to the fall in use recorded by the Mixmag Survey over the past decade, and the decline in recent years to the number of TOXBASE sessions and telephone inquiries received by the NPIS (2013). However, the number of deaths rose again in 2012. The potential dangers of GHB/GBL consumption need to be brought to the attention of would-be users.

3.3.7 Limitations

A number of further limitations have to be borne in mind when interpreting these findings. The submission of data is done on a voluntary basis. Thus, as explained above (Section 3.1.1), coverage by NPSAD of coroners' jurisdictions is not complete but has remained at a consistently high level over the past decade or more. To counter this limitation, other sources of information are used, including newspaper articles, as well as historic checks with all of the General Register Offices in the UK. Since those who die from GHB use appear to differ in a number of ways from 'typical' victims of drug-related deaths, it is possible that Investigators may have missed other cases. These factors may mean that the cases reported here are a skewed sample and an underestimate of actual deaths during this period. However, they are probably representative of UK fatalities involving GHB and its derivatives.

We believe that we have minimised the risk of false-positives by either including cases above our cut-off levels and/or where there was clear evidence of exogenous sources. However, false-negatives may have been excluded due to adherence to high cut-off levels. There are problems in trying to assess the exact risk of death due to toxicity from GHB and its analogues: the inclusion of only cases where exogenous GHB is implicated, e.g. based on interpretation of post-mortem blood and urine concentrations; and polysubstance use as well as evidential data overcome this issue. However, as this study clearly demonstrates, it is possible to attribute deaths directly to consumption of these substances. Their use still continues.

4 Conclusions

This is the most comprehensive and detailed report of UK fatalities associated with non medical use of GHB and its derivatives produced to date. Evidence emerging from the NPSAD and other UK databases shows that such deaths are continuing despite legal controls on their possession and trade. Many GHB deaths involve alcohol and other CNS depressants. These themes are consistent with cases reported in other countries, chiefly the US, Australasia, and Europe, where GHB has been used in similar ways. However, this study indicates that many cases involve the co-ingestion of stimulants and ketamine.

The misuse of GABA-analogues such as baclofen, gabapentin and pregabalin is also a related concern in Europe and the UK (Schifano *et al*., 2015; Kapil *et al*., 2013). There is some evidence of all three being misused in the UK (Kapil *et al*., 2015). Three of the present sample reported on were prescribed gabapentin (Table 2). The combination of a therapeutic level of baclofen and GHB can lead to coma, bradypnoea and hypotonia. The overlapping neurobiological pathway can enhance the agonist role of GHB (Kamal *et al*., 2015).

NMP (Reisch, 2008), and similar molecules, including GHV (Brunt *et al*., 2013; Carter *et al*., 2005), phenibut (O'Connell *et al*., 2014; Samokhvalov *et al*., 2013; Schmitt *et al*., 2013) and baclofen (Franchitto *et al*., 2014; Gahr *et al*., 2014; Weißhaar *et al*., 2012) are now starting to emerge as substitutes for GHB/GBL. Some internet sites that formerly offered GHB and GBL for sale to assist sleep, as an aid in bodybuilding, for energy boosts, as an antidepressant, etc. have discontinued these lines. Instead they offer (August 2014) "Ghb Furanone Alternatives" such as "U4EA X", "Legato", Renew G", "Liquid Relaxation", "Gabatrol-90" (www.ghb-furanone.com; www.eurolab-replenish.com). The GHB analogue

GHV (gamma-hydroxyvaleric acid) may also be seen as an alternative molecule to take, being advertised as a dietary supplement (Penberthy *et al*., 2010).

Although these 'legal alternatives' come with detailed warnings about careful use and lists of ingredients, it seems sensible to advise potential consumers of the inherent risks in taking such substances. Medical practitioners and other health professionals need to be aware of the likelihood of coming across patients consuming GHB and related substances (typically in combination with CNS depressant substances and/or stimulants), and of their severe and often unpredictable effects, including their addiction potential and withdrawal issues.

Conflicts of interest

No conflicts of interest are declared here that may have influenced the interpretation of present data. Please note the following: F.S. is a full member of the UK Advisory Council on the Misuse of Drugs (ACMD); F.S. and J.C. are members of the ACMD's NPS Committee; S.E. is a member of DrugScience (formerly the Independent Scientific Committee on Drugs - ISCD). The views expressed here reflect only the authors' views and not necessarily those of the Home Office, the ACMD, or DrugScience.

Acknowledgements

The authors wish to thank coroners in England & Wales, Northern Ireland, and the Islands; procurators fiscal in Scotland; and the Scottish Crime & Drug Enforcement Agency for their assistance in providing data to the National Programme on Substance Abuse Deaths (NPSAD). In turn, we are grateful to the NPSAD Programme, St. George's University of London as owners of the data, for allowing data to be used for this publication. We are grateful to the European Monitoring Centre on Drugs and Drug Addiction (EMCDDA), Medicines and Healthcare products Regulatory Agency (MHRA) and the Communities and Law Enforcement Section of the Home Office Drugs Unit for advice on the legal status of GHB, GBL and 1,4-BD. We acknowledge the kind assistance of staff (past and present) at the Office for National Statistics, the General Register Office for Northern Ireland and the Northern Ireland Statistics and Research Agency, and the General Register Office for Scotland (now part of the National Records of Scotland) in helping to identify cases. Finally, the reviewers of this paper are thanked for their helpful suggestions for improvements to this paper.

Declaration

This work has not been previously published and has not been submitted for publication elsewhere. Some of the summary findings have been presented in the form of an oral presentation at the 3rd International Conference on Novel Psychoactive Substances, Rome, 15-16 May 2014 and abstract thereof (Corkery *et al.*, 2014b). Publication is approved by all authors and the responsible authorities where the research was undertaken. If accepted, the paper will not be published elsewhere in the same form, in English or in any other language, without the written consent of the copyright holder.

Funding

Data used in this paper were collected during routine NPSAD surveillance activities. Financial support was provided during 2004-10 by the Department of Health (England) and 2010-11 by the National Treatment Agency (for England). These agencies had no involvement in preparation of the article, study design, collection, analysis and interpretation of data, writing of the article, or the decision to submit for publication.

Ethical approval

The Central Office for Research Ethics Committees (COREC), National Patient Safety Agency confirmed in writing (February 2006) that the NPSAD Programme does not require NHS REC review as the subjects of the research are deceased.

Contributors

Data collection was undertaken by NPSAD team members. John Corkery conceived the paper, undertook case identification, data preparation and analysis, and led on writing. Barbara Loi assisted in data preparation and data analysis. Hugh Claridge and Christine Goodair assisted in case identification, data collection and analysis. Simon Elliott supervised/undertook and interpreted the toxicological analysis for many of the cases notified to NPSAD and included in this study, and advised on interpretation of toxicological results. Ornella Corazza provided information on epidemiological data from online websites and on market availability. Fabrizio Schifano contributed information on pharmacology and market availability. All authors contributed to the writing of the paper. Christine Goodair also assisted in checking of references.

References

Abanades, S., Farré, M., Barral, D., Torrens, M., Closas, N., Langohr, K., Pastor, A., de la Torre, R., 2007. Relative abuse liability of gamma-hydroxybutyric acid, flunitrazepam, and ethanol in club drug users. *J. Clin. Psychopharmacol*. 27(6):625-638. PubMed PMID: 18004131.

Abanades, S., Farré, M., Segura, M., Pichini, S., Barral, D., Pacifici, R., Pellegrini, M., Fonseca, F., Langohr, K., De La Torre, R., 2006. Gamma-hydroxybutyrate (GHB) in humans: pharmacodynamics and pharmacokinetics. *Ann. N. Y. Acad. Sci*. 1074, 559-576. PubMed PMID: 17105953.

Absalom, N., Eghorn, L.F., Villumsen, I.S., Karim, N., Bay, T., Olsen, J.V., Knudsen, G.M., Bräuner-Osborne, H., Frølund, B., Clausen, R.P., Chebib, M., Wellendorph, P., 2012. α4βδ GABA(A) receptors are high-affinity targets for γ-hydroxybutyric acid (GHB). *Proc. Natl. Acad. Sc.i U. S. A*. 109(33):13404-13409. doi: 10.1073/pnas.1204376109. PubMed PMID: 22753476; PubMed Central PMCID: PMC3421209.

ACMD., 2008. *GBL & 1,4-BD: assessment of risk to the individual and communities in the UK*. Advisory Council on the Misuse of Drugs.Home Office, London. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119047/report-on-gbl1.pdf Accessed 7 September 2014.

Adinoff, B., Bone, G.H., Linnoila, M., 1988. Acute ethanol poisoning and the ethanol withdrawal syndrome. *Med. Toxicol. Adverse Drug Exp*. 3(3):172-196.
PubMed PMID: 3041244.

Akins, B.E., Miranda, E., Lacy, J.M., Logan, B.K., 2009. A multi-drug intoxication fatality involving Xyrem (GHB). *J. Forensic Sci*. 54(2):495-496. doi: 10.1111/j.1556-4029.2008.00965.x. PubMed PMID: 19187456.

Al-Samarrie, M.S., Karinen, R., Mørland, J., Opdal, M.S., 2010. Blood GHB concentrations and results of medical examinations in 25 car drivers in Norway. *Eur. J. Clin. Pharmacol*. 66(10):987-998.

Altose, M.D., Hudgel, D.W., 1986. The pharmacology of respiratory depressants and stimulants. *Clin. Chest Med*. 7(3):481-494. PubMed PMID: 2876801.

Andresen, H., Aydin, B.E., Mueller, A., Iwersen-Bergmann, S., 2011. An overview of gamma-hydroxybutyric acid: pharmacodynamics, pharmacokinetics, toxic effects, addiction, analytical methods, and interpretation of results. *Drug Test. Anal*. 3(9):560-568. doi: 10.1002/dta.254. PubMed PMID: 21381220.

Andresen, H., Sprys, N., Schmoldt, A., Mueller, A., Iwersen-Bergmann, S., 2010. Gamma-hydroxybutyrate in urine and serum: additional data supporting current cut-off recommendations. *Forensic Sci. Int*. 200(1-3):93-99.

Andresen-Streichert, H., Jensen, P., Kietzerow, J., Schrot, M., Wilke, N., Vettorazzi, E., Mueller, A., Iwersen-Bergmann, S., 2015. Endogenous gamma-hydroxybutyric acid (GHB) concentrations in post-mortem specimens and further recommendation for interpretative cut-offs. *Int. J. Legal Med.* 129, 57-68. doi: 10.1007/s00414-014-1051-8. PubMed PMID: 25084768.

Andresen-Streichert, H., Jungen, H., Gehl, A., Müller, A., Iwersen-Bergmann, S., 2013. Uptake of gamma-valerolactone--detection of gamma-hydroxyvaleric acid in human urine samples. *J. Anal. Toxicol*. 37(4):250-4. doi: 10.1093/jat/bkt013. PubMed PMID: 23486087.

Arena, C., Fung, H.L., 1980. Absorption of sodium gamma-hydroxybutyrate and its prodrug gamma-butyrolactone: relationship between in vitro transport and in vivo absorption. *J. Pharm. Sci.* 69(3):356-358. PubMed PMID: 7381722.

Aromatario, M., Bottoni, E., Santoni, M., Ciallella, C., 2012. New "lethal highs": a case of a deadly cocktail of GHB and Mephedrone. *Forensic Sci. Int*. 223(1-3):e38-41. doi: 10.1016/j.forsciint.2012.09.014.

Atha, M., Davis, S., 2001. Gamma Hydroxy Butyrate Usage, Effects and UK prices. online. Independent Drug Monitoring Unit, Wigan, UK. Available at: http://www.idmu.co.uk/ghb.htm
Accessed 7 September 2014.

Atha, M., Davis, S., 2003. Results from 1999-2002 IDMU Surveys – update. online. Independent Drug Monitoring Unit, Wigan, UK. Available at: http://www.idmu.co.uk/ghb2003.htm
Accessed 7 September 2014.

Barker, J.C., Harris, S.L., Dyer, J.E., 2007. Experiences of gamma hydroxybutyrate (GHB) ingestion: a focus group study. *J. Psychoactive Drugs.* 39(2):115-129. PubMed PMID: 17703706; PubMed Central PMCID: PMC2257870.

Baselt, R.C., 2008. GHB, in *Disposition of Toxic Drugs and Chemicals in Man*, 8th ed. Biomedical Publications: Foster City, CA. pp. 680–684. ISBN 978-0-9626523-7-0

Beghè, F., Carpanini, M.T., 2000. Safety and tolerability of gamma-hydroxybutyric acid in the treatment of alcohol-dependent patients. *Alcohol.* 20(3):223-225. PubMed PMID: 10869863.

Bennett, G., 2014. Bristol man, 47, found dead with two hard-boiled eggs in his rectum. *The Bristol Post*. 23 September. Available at: http://www.bristolpost.co.uk/Victim-degrading-acts-died-drugs-overdose-court/story-22965155-detail/story.html
Accessed 15 Februay 2015.

Bessman, S.P., Fishbein, W.N., 1963. Gamma-hydroxybutyrate, a normal brain metabolite. *Nature*. 200, 1207-8. PubMed PMID: 14089913.

Black, J., Houghton, W.C., 2006. Sodium oxybate improves excessive daytime sleepiness in narcolepsy. *Sleep*. 29(7):939-946. PubMed PMID: 16895262.

Blanchflower, D.G., Oswald, A.J., 2011. Antidepressants and age. June. Available at: http://ftp.iza.org/dp5785.pdf
Accessed 14 February 2015.

Bluelight., 2014. GBL/GHB, dosage, duration, withdrawals. Available at: http://www.bluelight.org/vb/threads/196006-GBL-GHB-dosage-duration-withdrawals
Accessed 10 June 2014.

Bluet-Pajot, M.T., Schaub, C., Nassiet, J., 1978. Growth hormone response to hypoglycaemia under gamma-hydroxybutyrate narco-analgesia in the rat. *Neuroendocrinology.* 26(3):141-149. PubMed PMID: 683466.

BNF., 2014. Sodium oxybate. Section 4.1.2 Hypnotics. British National Formulary. 67. BMJ Group & Pharmaceutical Press, London.

Borgen, L., Lane, E., Lai, A., 2000. Xyrem® (sodium oxybate): a study of dose proportionality in healthy human subjects. *J. Clin. Pharmacol.* 40:1053.

Borgen, L., Okerholm, R., Morrison, D., Lai, A., 2003. The influence of gender and food on the pharmacokinetics of sodium oxybate oral solution in healthy subjects. *J. Clin. Pharmacol*. 43(1):59-65. PubMed PMID: 12520629.

Bosch, O.G., Quednow, B.B., Seifritz, E., Wetter, T.C., 2012. Reconsidering GHB: orphan drug or new model antidepressant? *J. Psychopharmacol*. 26(5):618-628. doi: 10.1177/0269881111421975.

Bosman, I.J., Lusthof, K.J. 2003. Forensic cases involving the use of GHB in The Netherlands. *Forensic Sci. Int*. 133(1-2):17-21.

Bourne, A., Reid, D., Hickson, F., Torres Rueda, S., Weatherburn, P., 2014. *The Chemsex Study: drug use in sexual settings among gay and bisexual men in Lambeth, Southwark & Lewisham*. Sigma Research, London School of Hygiene & Tropical Medicine, London. Available at: http://www.sigmaresearch.org.uk/projects/project59/
Accessed 7 September 2014.

Boyd, J.J., Kuisma, M.J., Randell, T.T., 2012. Temporal differences in γ-hydroxybutyrate overdoses involving injecting drug users versus recreational drug users in Helsinki: a retrospective study. *Scand. J. Trauma Resusc. Emerg. Med*. 20, 7. doi: 10.1186/1757-7241-20-7. PubMed PMID: 22296777;

Brailsford, A.D., Cowan, D.A., Kicman, A.T. 2010. Urinary γ-hydroxybutyrate concentrations in 1126 female subjects. *J. Ana.l Toxicol*. 34(9):555-561. PubMed PMID: 21073808.

Brenneisen, R., Elsohly, M.A., Murphy, T.P., Passarelli, J., Russmann, S., Salamone, S.J., Watson, D.E., 2004. Pharmacokinetics and excretion of gamma-hydroxybutyrate (GHB) in healthy subjects. *J. Anal. Toxicol*. 8(8):625-630. PubMed PMID: 15538955.

Brunt, T.M., van Amsterdam, J.G.C., Van den Brink, W., 2014. GHB, GBL and 1,4-BD addiction. *Curr. Pharm. Des*. 20(25):4076-4085. PMID: 24001290. doi: 10.2174/1381612811319990624.

Burch, H.J., Clarke, E.J., Hubbard, A.M., Scott-Ham, M., 2013. Concentrations of drugs determined in blood samples collected from suspected drugged drivers in England and Wales. *J. Forensic Leg. Med*. 20(4):278-289. doi: 10.1016/j.jflm.2012.10.005.

Busardò, F.P., Bertol. E., Vaiano, F., Baglio, G., Montana, A., Barbera, N., Zaami, S., Romano, G., 2014. Post mortem concentrations of endogenous gamma hydroxybutyric acid (GHB) and in vitro formation in stored blood and urine samples. *Forensic Sci. Int.* 243:144-148. doi: 10.1016/j.forsciint.2014.07.019. PMID: 25123534.

Cagnin, A., Pompanin, S., Manfioli, V., Briani, C., Zambon, A., Saladini, M., Dam, M., 2011. γ-Hydroxybutyric acid-induced psychosis and seizures. *Epilepsy Behav*. 21(2):203-205. doi: 10.1016/j.yebeh.2011.03.009. PubMed PMID: 21530412.

Caldicott, D.G., Chow, F.Y., Burns, B.J., Felgate, P.D., Byard, R.W., 2004. Fatalities associated with the use of γ-hydroxybutyrate and its analogues in Australasia. *Med. J. Aust*. 181(6):310-3. PubMed PMID: 15377240.

Caputo, F., Francini, S., Brambilla, R., Vigna-Taglianti, F., Stoppo, M., Del Re, A., Leggio, L., Addolorato, G., Zoli, G., Bernardi, M., 2011. Sodium oxybate in maintaining alcohol abstinence in alcoholic patients with and without psychiatric comorbidity. *Eur. Neuropsychopharmacol*. 21(6):450-456. doi: 10.1016/j.euroneuro.2010.12.005. PubMed PMID: 21276717.

Caputo, F., Francini, S., Stoppo, M., Lorenzini, F., Vignoli, T., Del Re, A., Comaschi, C., Leggio, L., Addolorato, G., Zoli, G., Bernardi, M., 2009. Incidence of craving for and abuse of gamma-hydroxybutyric acid (GHB) in different populations of treated alcoholics: an open comparative study. *J. Psychopharmacol*. 23(8):883-890. doi: 10.1177/0269881108094620. PubMed PMID: 18635689.

Carai, M.A., Colobo, G., Reali, R., Serra, S., Mocci, I., Castelli, M.P., Cignarella, G., Gessa, G.L. 2002. Central effects of 1.4-butanediol are mediated by GABA(B) receptors via its conversion into gamma-hydroxybutyric acid*. Eur. J. Pharmacol*. 441(3):157-163.

Carter, L.P., Chen, W., Wu, H., Mehta, A.K., Hernandez, R.J., Ticku, M.K., Coop, A., Koek, W., France, C.P., 2005. Comparison of the behavioral effects of gamma-hydroxybutyric acid (GHB) and its 4-methyl-substituted analog, gamma-hydroxyvaleric acid (GHV). *Drug Alcohol Depend.* 78(1):91-99. PubMed PMID: 15769562.

Catalano, M.C., Glass, J.M., Catalano, G., Burrows, S.L., Lynn, W.A., Weitzner, B.S., 2001. Gamma butyrolactone (GBL) withdrawal syndromes. *Psychosomatics*. 42(1):83-88. PubMed PMID: 11161128.

Cheston, P., 2014. Three men die within months of each other after taking party drug at London gay sauna. 24 June*. Evening Standard*. Available at: http://www.standard.co.uk/news/london/three-men-die-within-months-of-each-other-after-taking-party-drug-at-london-gay-sauna-9558766.html
Accessed 7 September 2014.

Chien, J., Ostermann, G., Turkel, S.B., 2013. Sodium oxybate-induced psychosis and suicide attempt in an 18-year-old girl. *.J Child Adolesc. Psychopharmacol*. 23(4):300-301. doi: 10.1089/cap.2012.0130. PubMed PMID: 23647134.

Chin, M.Y., Kreutzer, R.A., Dyer, J.E., 1992. Acute poisoning from gamma-hydroxybutyrate in California. *West. J. Med*. 156(4):380-384.

Chin, R.L., Sporer, K.A., Cullison, B., Dyer, J.E., Wu, T.D., 1998. Clinical course of gamma-hydroxybutyrate overdose. *Ann. Emerg. Med*. 31(6):716-722. PubMed PMID: 9624311.

Coleman, K., 2013. *Seizures of drugs in England and Wales, 2012/13*. Home Office Statistical Bulletin 04/2013. 31 October. Home Office Statistics Unit, London. Available at:
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/254123/1213_seizure_drugs_statistical_bulletin.pdf
Accessed 7 September 2014.

Collier, B., De Feudis, F.V., 1970. Conversion of gamma-hydroxybutyrate to gamma-aminobutyrate by mouse brain in vivo. *Experientia*. 26(10):1072-1073. PubMed PMID: 5483746.

Colombo, G., Agabio, R., Lobina, C., Reali, R., Fadda, F., Gessa, G.L., 1995a. Symmetrical generalization between the discriminative stimulus effects of gamma-hydroxybutyric acid and ethanol: Occurrence within narrow dose ranges. *Phystology & Behavior*, 57(1):105-111. PubMed PMID: 7878101.

Colombo, G., Agabio, R., Lobina, C., Reali, R., Fadda, F., Gessa, G.L., 1995b.Cross-tolerance to ethanol and gamma-hydroxybutyric acid. *Eur. J. Pharmacol*. 273(3):235-8. PMID: 7737330.

Cook, C.D., Aceto, M.D., Coop, A., Beardsley, P.M., 2002. Effects of the putative antagonist NCS382 on the behavioral pharmacological actions of gammahydroxybutyrate in mice. *Psychopharmacology (Berl)*. 160(1):99-106. PubMed PMID: 11862379.

Corkery, J., Claridge, H., Loi, B., Goodair, C., Schifano, F., 2014a. *Drug-related deaths in the UK: January-December 2012; Annual Report 2013*. Drug-related deaths reported by Coroners in England, Wales, Northern Ireland, Guernsey, Jersey and the Isle of Man; Police forces in Scotland; & the Northern Ireland Statistics and Research Agency –. London: International Centre for Drug Policy, St George's University of London. Available at:
http://www.sgul.ac.uk/images/docs/idcp%20pdfs/National%20programme%20on%20substance%20abuse%20deaths/National_Programme_on_Substance_Abuse_Deaths-Annual_Report_2013_on_Drug-related_Deaths_in_the_UK_January-December_2012_PDF.pdf or
http://www.sgul.ac.uk/research/population-health/our-projects/national-programme-on-substance-abuse-deaths
Accessed 7 September 2014.

Corkery, J.M., Loi, B., Claridge, H., Goodair, C., Corazza, O., Elliott, S., Schifano, F., 2014b. The evolution and characteristics of UK deaths involving GHB and its analogues. Abstract of oral presentation. 3rd International Conference on Novel Psychoactive Substances (NPS), Rome on 15-16 May 2014 in collaboration with the EMCDDA and La Sapienza University. Supplement on Novel Psychoactive Substances, *Research and Advances in Psychiatry*. 1(1):16.
http://www.rapjournal.eu/index.php?PAGE=articolo_dett&ID_ISSUE=748&id_article=6447
Accessed 7 September 2014.

Corkery, J.M., Schifano, F., Ghodse, A.H., 2012. Mephedrone-related fatalities in the United Kingdom: contextual, clinical and practical issues, in: Gallelli, G. (ed.) *Pharmacology*. InTech - Open Access Publisher, Rijeka, Croatia, pp. 355-380. ISBN 979-953-307-482-4 Published 14 March 2012. doi: 10.5772/32935 Available at: http://www.intechopen.com/books/pharmacology/mephedrone-related-fatalities-in-the-united-kingdom-contextual-clinical-and-practical-issues.

Accessed 7 September 2014.

Couper, F.J., Logan, B.K., 2000. Determination of gamma-hydroxybuyrate (GHB) in biological specimens by gas chromatography-mass spectrometry. *J. Anal. Toxicol*, 24(1):1-7.

Couper, F.J., Logan, B.K., 2001. GHB and driving impairment. *J. Forensic. Sci*. 46(4):919-923. PMID: 11451079.

Couper, F.J., Logan, B.K., 2004. Addicted to driving under the influence--a GHB/GBL case report. *J. Anal. Toxicol*. 28(6):512-515. PMID: 15516306.

Couper, F.J., Marinetti, L.J., 2002. γ-Hydroxybutyrate (GHB) - effects on human performance and behavior. *Forensic Sc.i Rev*. 14(1-2):102-121.

Couper, F.J., Thatcher, J.E., Logan, B.K., 2004. Suspected GHB overdoses in the emergency department. *J. Anal. Toxicol*. 28(6):481-484. PMID: 15516299.

Crookes, C.E., Faulds, M.C., Forrest, A.R., Galloway, J.H., 2004. A reference range for endogenous gamma-hydroxybutyrate in urine by gas chromatography-mass spectrometry. *J. Anal. Toxicol*. 28(8):644-649. PubMed PMID: 15538958.

Daily Mail, 2006. Alert over fatal party drug. 30 November. Available at: http://www.dailymail.co.uk/news/article-419593/Alert-fatal-party-drug.html
Accessed 7 September 2014.

Dargan, P.I., Button, J., Davies, S., Ramsey, J., George, S., Holt, D.W., Wood, D.M., 2009. The first reported UK fatality related to gamma-butyrolactone (GBL) ingestion. *J. R. Soc. Med*. 102(12):546-547. doi: 10.1258/jrsm.2009.090283. PubMed PMID: 19966131; PubMed Central PMCID: PMC2789020.

Dargan, P.I., Jayachandran, A., Button, J., Davies, S., Northall, F., Lidder, S., Holt, D.W., Wood, D.M., 2008. A Significant Xyrem® Overdose Managed Conservatively Despite High GHB Concentrations. Abstract 251. Program of the 2008 North American Congress of Clinical Toxicology Annual Meeting, September 11–16, 2008, Toronto, Canada. *Clin. Toxicol*. 46(7):588.

Davies, J.A., 1978. The effect of gamma-butyrolactone on locomotor activity in the rat. *Psychopharmacology (Berl)*. 60(1):67-72. PubMed PMID: 104348.

Davis, L., 1999. Fatalities attributed to GHB and related compounds. *South. Med. J.* 92(10):1037.

DEA., 2002. Drugs and chemicals of concern: Gamma Hydroxybutyric Acid. US Drugs Enforcement Agency.

DEA., 2004. N-Methylpyrrolidinone in a *Gamma*-hydroxybutyrate solution in Copley, Ohio. *Microgram Bulletin*, 37(3): 46-47.

DEA., 2012. Gamma Hydroxybutyric Acid. 7 June. Drug Enforcement Administration. US Department of Justice. Available at: http://www.justice.gov/dea/druginfo/drug_data_sheets/GHB.pdf.
Accessed on 7 September 2014.

de Fiebre, C.M., de Fiebre, N.E., Coleman, S.L., Forster, M.J., 2004. Comparison of the actions of gamma-butyrolactone and 1,4-butanediol in Swiss-Webster mice. *Pharmacol. Biochem. Behav*. 77(4):705-710.

Dhani, A., 2014. *Seizures of drugs in England and Wales, 2013/14.* Home Office Statistical Bulletin 03/14. 30 October. Home Office Statistics Unit, London. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/1367761/hosb0314.pdf Accessed 12 February 2015.

Dick, D., Torrance, C., 2010. Mixmag Drugs Survey. *Mixmag*, 226, 44-53.

Dietze, P.M., Cvetkovski, S., Barratt, M.J., Clemens, S., 2008. Patterns and incidence of γ-hydroxybutyrate (GHB)-related ambulance attendances in Melbourne, Victoria. *Med. J. Aust*. 188(12):709-711. PubMed PMID: 18558893.

Divry, P., Baltassat, P., Rolland, M.O., Cotte, J., Hermier, M., Duran, M., Wadman, S.K., 1983. A new patient with 4-hydroxybutyric aciduria, a possible defect of 4-aminobutyrate metabolism. *Clin. Chim. Acta*. 129(3):303-309. PubMed PMID: 6133657.

DPA., 2013. Registered for the first time in Italy 2 cases of abuse and robbery with analytical identification of NMP, a substance allegedly given to the intoxicated subjects without their knowledge. *Activity Report N.E.W.S.* 22: 15-16. Dipartimento Politiche Antidroga: Roma. Available at: http://www.allertadroga.it/sapd/login/ Accessed 1 November 2013.

Drugs-Forum., 2014. G.B.L dosage and effects. Available at: http://www.drugs-forum.com/forum/showthread.php?t=37413. Accessed 7 September 2014.

Dudek, B.C., Fanelli, R.J., 1980. Effects of gamma-butyrolactone, amphetamine, and haloperidol in mice differing in sensitivity to alcohol. *Psychopharmacology (Berl)*. 68(1):89-97.

Duer, W.C., Byers, K.L., Martin, J.V., 2001. Application of a convenient extraction procedure to analyse gamma-hydroxybutyric acid in fatalities involving gamma-hydroxybutyric acid, gamma-butyrolactone and 1,4-butanediol. *J. Anal. Toxicol.* 25(7):576-582.

Dunn, M., Topp, L., Degenhardt, L., 2009. GHB in Sydney, Australia, 2000-2006: a case study of the EDRS as a strategic early warning system. *Int. J. Drug Policy*. 20(5):413-417. doi: 10.1016/j.drugpo.2009.01.002. PubMed PMID: 19237274.

Dupont, P., Thornton, J., 2001. Near-fatal gamma-butyrolactone intoxication - first report in the UK. *Hum. Exp. Toxicol*. 20(1):19-22.

Durgahee, S., Allen, G., Williams, H., 2014. The 'G' men: a profile of GBL/GHB users in an area of high drug-related mortality. *Ir. J. Psychol. Med*. 31:275-280. doi: 10.1017/ipm.2014.39.

Dyer, J. E., Isaacs, S. M., Keller, K. H., 1994. Gamma-hydroxybutyrate (GHB)-induced coma with serum and urine drugs levels, *Vet. Human Toxicol.* 36:339.

Dyer, J.E., Roth, B., Hyma, B.A., 2001. Gamma-hydroxybutyrate withdrawal syndrome. *Ann. Emerg. Med.* 37(2):147-153. PubMed PMID: 11174231.

Elian, A.A., 2002. Determination of endogenous gamma-hydroxybutyric acid (GHB) levels in antemortem urine and blood. *Forensic Sci. Int*. 128(3):120-122. PubMed PMID: 12175790.

Elliott, S.P., 2000. Analysis of GHB in biological fluid using gas chromatography, Meeting of Association Clinical Biochemists (ACB), Birmingham, UK.

Elliott, S.P., 2001. The Presence of Gamma-Hydroxybutyric Acid (GHB) in Postmortem Biological Fluids (letter). *J. Anal. Toxicol*. 25(2):152. doi:10.1093/jat/25.2.152.

Elliott, S.P., 2003. Gamma hydroxybutyric acid (GHB) concentrations in humans and factors affecting endogenous production. *Forensic Sci. Int*. 133(1-2):9-16.
Elliott, S.P., 2004a. Further evidence for the presence of GHB in postmortem biological fluid: implications for the interpretation of findings. *J. Anal. Toxicol*. 28(1):20-26. PubMed PMID: 14987420.

Elliott, S.P., 2004b. Nonfatal instances of intoxication with gamma-hydroxybutyrate in the United Kingdom. *Ther. Drug Monit*. 26(4):432-440. PubMed PMID: 15257074.

EMCDDA., 1998. *Quality and comparability of data on drug-related deaths (feasibility study)*. July. European Monitoring Centre for Drugs & Drug Addiction, Lisbon. Available at: http://www.emcdda.europa.eu/html.cfm/index58085EN.html
Accessed 7 September 2014.

EMCDDA., 1999. *Guidelines for the risk assessment of new synthetic drugs.* August. European Monitoring Centre for Drugs & Drug Addiction, Lisbon. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_33362_EN_RiskGuidelines.pdf
Accessed 7 September 2014.

EMCDDA., 2001 'Rising European concern over misuse of two synthetic drugs', News Release No. 2/2001. 15 March. European Monitoring Centre for Drugs and Drug Addiction, Lisbon. Available at: http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=2&ved=0CDMQFjAB&url=http%3A%2F%2Fwww.emcdda.europa.eu%2Fattachements.cfm%2Fatt_1059_EN_14en.pdf&ei=F4nmUY-7FvGg7AbUx4G4Cw&usg=AFQjCNFDx_1tb2gvhmfnEVMtMVAZPND0Xw&sig2=dYNvFqW3I4M9YDPNPDfe7g&bvm=bv.49405654,d.ZGU&cad=rja
Accessed 7 September 2014.

EMCDDA., 2002. *Report on the risk assessment of GHB in the framework of the joint action on new synthetic drugs.* June. European Monitoring Centre for Drugs and Drug Addiction, Lisbon. 26 September. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_33346_EN_Risk4.pdf
Accessed 7 September 2014.

EMCDDA., 2008. *GHB and its precursor GBL: an emerging trend case study.* March. European Monitoring Centre for Drugs and Drug Addiction, Lisbon. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_58668_EN_TP_GHB%20and%20GBL.pdf
Accessed 7 September 2014.

EMCDDA., 2014. EMCDDA-Europol 2013 Annual Report on the implementation of Council Decision 2005/387/JHA. July 2014. European Monitoring Centre for Drugs and Drug Addiction, Lisbon. Available at: http://www.emcdda.europa.eu/attachements.cfm/att_229598_EN_TDAN14001ENN.pdf
Accessed 7 September 2014.

EMEA., 2007. Xyrem. EPAR (European Public Assessment Report) Summary for the Public. 6 July. European Medicines Agency, London. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000593/WC500057100.pdf
Accessed 7 September 2014.

EMEA., 2014. Xyrem: EPAR - Product Information. 17 July. Available at: http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Product_Information/human/000593/WC500057103.pdf
Accessed 7 September 2014.

Erowid., 2004. Sodium 4-hydroxy valerate, a novel GHB analog. Available at: hhttp://www.erowid.org/archive/rhodium/chemistry/4-methyl-ghb.html
Accessed 4 March 2015.

Erowid., 2013a. GHB. Available at: http://www.erowid.org/chemicals/ghb/.
Accessed 7 September 2014.

Erowid., 2013b. GBL. Available at: http://www.erowid.org/chemicals/ghb/gbl_info1.shtml
Accessed 7 September 2014.

Erowid., 2013c. 1,4-butanediol. Available at: http://www.erowid.org/chemicals/14b/14b.shtml
Accessed 7 September 2014.

Evans, R., Sayal, K., 2012. Gammabutyrolactone: withdrawal syndrome resembling delirium tremens. *J. Subst. Use*. 17(4):384–387.

Fadda, F., Argiolas, A., Melis, M.R., De Montis, G., Gessa, G.L., 1983. Suppression of voluntary ethanol consumption in rats by gamma-butyrolactone. *Life Sci*. 32(13):1471-1477.
PMID: 6339856.

Feigenbaum, J.J., Howard, S.G., 1996. Gamma hydroxybutyrate is not a GABA agonist. *Prog. Neurobiol*. 50(1):1-7. PubMed PMID: 8931105.

Ferrara, S.D., Tedeschi, L., Frison, G., Rossi, A., 1995. Fatality due to gamma-hydroxybutyric acid (GHB) and heroin intoxication*. J. Forensic. Sci*. 40(3):501-504.

Ferrara, S., Tedeschi, L., Frison, G., Orlando, R., Mazzo, M., Zordan, R., Padrini, R., Palatini, P., 1996. Effect of moderate or severe liver dysfunction on the pharmacokinetics of gamma-hydroxybutyric acid. *Eur. J. Clin. Pharmacol*. 50(4):305-310. PubMed PMID: 8803524.

Ferrara, S.D., Zotti, S., Tedeschi, L., Frison, G., Castagna, F., Gallimberti, L., Gessa, G.L., Palatini, P., 1992. Pharmacokinetics of gammahydroxybutyric acid in alcohol dependent patients after single and repeated oral doses. *Br. J. Clin. Pharmacol.* 34(3):231-235. PubMed PMID: 1389947; PubMed Central PMCID: PMC1381393.

Fieler, E.L., Coleman, D.E., Baselt, R.C., 1998. γ-Hydroxybutyrate concentrations in pre- and postmortem blood and urine. *Clin. Chem*. 44(3):692. PubMed PMID: 9510892.

FIRE., 2006. FIRE statement on GHB death. 30 November. Available at:
http://discodamaged.typepad.com/ddnews/2006/12/fire_statement_.html.
Accessed 7 September 2014.

Franchitto, N., Pelissier, F., Lauque, D., Simon, N., Lançon, C., 2014. Self-intoxication with baclofen in alcohol-dependent patients with co-existing psychiatric illness: an emergency department case series. *Alcohol Alcohol*. 49(1):79-83. doi: 10.1093/alcalc/agt169. PubMed PMID: 24226812.

Frase, L., Schupp, J., Sorichter, S., Randelshofer, W., Riemann, D., Nissen, C., 2013. Sodium oxybate-induced central sleep apneas. *Sleep Med*. 14:922-924. doi: 10.1016/j.sleep.2013.03.023. PubMed PMID: 23834969.

Friedman, J., Westlake, R., Furman, M., 1996. “Grieious bodily harm”: gamma hydroxybutyrate abuse leading to a Wernicke- Korsakoff syndrome. *Neurology* . 46(2):469-471.

Gahr, M., Freudenmann, R.W., Eller, J., Schönfeldt-Lecuona, C., 2014. Abuse liability of centrally acting non-opioid analgesics and muscle relaxants--a brief update based on a comparison of pharmacovigilance data and evidence from the literature. *Int. J. Neuropsychopharmacol*. 17(6):957-959. doi: 10.1017/S1461145713001600. PubMed PMID: 24552880.

Galicia, M., Nogue, S., Miró, O., 2011. Liquid ecstasy intoxication: clinical features of 505 consecutive emergency department patients. *Emerg. Med. J*. 28(6):462-466. doi: 10.1136/emj.2008.068403. PubMed PMID: 21602168.

Gallimberti, L., Cibin, M., Pagnin, P., Sabbion, R., Pani, P.P., Pirastu, R., Ferrara, S.D., Gessa, G.L., 1993. Gamma-hydroxybutyric acid for treatment of opiate withdrawal syndrome. *Neuropsychopharmacology*. 9(1):77-81. PubMed PMID: 8397726.

Gallimberti, L., Gentile, N., Cibin, M., Fadda, F., Canton, G., Ferri, M., Ferrara, S.D., Gessa, G.L., 1989. Gammahydroxybutyric acid for treatment of alcohol withdrawal syndrome. *Lancet.* 2(8666):787-789.

Gallimberti, L., Schifano, F., Forza, G., Miconi, L., Ferrara, S.D., 1994. Clinical efficacy of gamma-hydroxybutyric acid in treatment of opiate withdrawal. *Eur. Arch. Psychiatry Clin. Neurosci*. 244(3):113-114.

Galloway, G.P., Frederick, S.L., Staggers, F.Jr., 1994. Physical dependence on sodium oxybate. *Lancet*. 343(8888):57.

Galloway, G.P., Frederick, S.L., Staggers, F.E. Jr., Gonzales, M., Stalcup, S.A., Smith, D.E., 1997. Gamma-hydroxybutyrate: an emerging drug of abuse that causes physical dependence. *Addiction*. 92(1): 89-96.

Galloway, G.P., Frederick-Osborne, S.L., Seymour, R., Contini, S.E., Smith, D.E.,2000. Abuse and therapeutic potential of gamma-hydroxybutyric acid. *Alcohol*. 20(3):263-269. PubMed PMID: 10869868.

Gerra, G., Caccavari, R., Fontanesi, B., Marcato, A., Fertonani Affini, G., Maestri, D., Avanzini, P., Lecchini, R., Delsignore, R., Mutti, A., 1994. Flumazenil effects on growth hormone response to gamma-hydroxybutyric acid. *Int. Clin. Psychopharmacol*. 9(3):211-215. PubMed PMID: 7814832.

Gheshlaghi, F., Eizadi-Mood, N., Emamikhah-Abarghooeii, S., Arzani-Shamsabadi, M., 2012. Evaluation of serum sodium changes in tricyclic antidepressants toxicity and its correlation with electrocardiography, serum pH, and toxicity severity. *Adv. Biomed. Res*. 1:68. doi: 10.4103/2277-9175.102972. PubMed PMID: 23326798; PubMed Central PMCID: PMC3544084.

Gianutsos, G., Moore, K.E., 1978. Tolerance to the effects of baclofen and gamma-butyrolactone on locomotor activity and dopaminergic neurons in the mouse. *J. Pharmacol. Exp. Ther*. 207(3):859-869. PubMed PMID: 731436.

Gerot Lannach Pharma GmbH., 2011. Alcover® (sodium gamma hydroxybutyric acid): Austrian summary of product characteristics. Available at: http://www.gl-pharma.at/gebrauchsinfo/1191413585.pdf Accessed 7 September 2014.

Goodwin, A.K., Gibson, K.M., Weerts, E.M., 2013. Physical dependence on gamma-hydroxybutrate (GHB) prodrug 1,4-butanediol (1,4-BD): Time course and severity of withdrawal in baboons. *Drug Alcohol Depend*. 132:427-433. doi: 10.1016/j.drugalcdep.2013.02.035.

Guidotti, A., Ballotti, P.L., (1970). Relationship between pharmacological effects and blood and brain levels of gamma-butyrolactone and gamma-hydroxybutyrate. *Biochem. Pharmacol.* 19(3):883-894.

Hagemann, C.T., Helland, A., Spigset, O., Espnes, K.A., Ormstad, K., Schei, B., 2013. Ethanol and drug findings in women consulting a Sexual Assault Center – associations with clinical characteristics and suspicions of drug-facilitated sexual assault. *J. Forensic Leg. Med*. 20(6):777-84. doi: 10.1016/j.jflm.2013.05.005.

Hansard., 2000. Gammahydroxybutyrate. HC Deb 24 May 2000, Vol 350, cc. 1084-90. Available at: http://www.publications.parliament.uk/pa/cm199900/cmhansrd/vo000524/debtext/00524-35.htm. Accessed 7 September 2014.

Harty, L., Kemp, P., 2002. Postmortem distribution of gamma-hydroxybutyrate: 2 cases from Oklahoma. (Abstract). Spring Meeting of the Southwestern association of Toxicologists, Wichita, Kansas.

Hechler, V., Ratomponirina, C., Maitre, M., 1997. Gamma-Hydroxybutyrate conversion into GABA induces displacement of $GABA_B$ binding that is blocked by valproate and ethosuximide. *J. Pharmacol. Exp. Ther*. 281(2):753-760. PubMed PMID: 9152382.

Helrich, M., McAslan, T.C., Skolnick, S., Bessman, S.P., 1964. Correlation of blood levels of 4-hydroxybutyrate with state of consciousness. *Anesthesiology*. 25:771-775.

Herbert, D., 2014. Number of Scots on antidepressants hits a record high. *Daily Express*. 1 October. Available at: http://www.express.co.uk/news/uk/517290/Number -of-Scots-on-anti-depressants-hits-a-record-high.
Accessed 14 February 2015.

Heytens, L., Neels, H., Van Regenmortel, N., van den Brink, W., Henckes, M., Schouwers, S., Dockx, G., Crunelle, C.L., 2014. Near-fatal persistent anion- and osmolal-gap acidosis due to massive gamma-butyrolactone/ethanol intoxication. *Ann. Clin. Biochem*. Sep 9. pii: 0004563214553278. [Epub ahead of print] PubMed PMID: 25205856.

Hibell, B., Anderseon, B., Bjornason, T., Ahlström, S., Balakireva, O., Kokkevi, A., Morgan, M., 2004. *The ESPAD Report 2003: Alcohol and other drug use among students in 35 European countries*. May. Stockholm, Sweden: The Swedish Council for Information on Alcohol and Other Drugs (CAN) & Council of Europe Co-operation Group to Combat Abuse and Illicit Trafficking in Drugs (Pompidou Group). Available at: http://www.espad.org/Uploads/ESPAD_reports/2003/The_2003_ESPAD_report.pdf.
Accessed 7 September 2014.

Hibell, B., Guttormsson, U., Ahlström, S., Balakireva, O., Bjornason, T., Kokkevi, A., Kraus, L., 2009. *The 2007 ESPAD Report: Substance use among students in 35 European countries*. 26 March. Stockholm, Sweden: The Swedish Council for Information on Alcohol and Other Drugs (CAN), The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) & Council of Europe, Co-operation Group to Combat Drug Abuse and Illicit Trafficking in Drugs (Pompidou Group). Available at: http://www.espad.org/Uploads/ESPAD_reports/2007/The_2007_ESPAD_Report-FULL_091006.pdf
Accessed 7 September 2014.

Hibell, B., Guttormsson, U., Ahlström, S., Balakireva, O., Bjornason, T., Kokkevi, A., Kraus, L., 2012. *The 2011 ESPAD Report: Substance use among students in 36 European countries*. 31 May. Stockholm, Sweden: The European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Council of Europe, Co-operation Group to Combat Drug Abuse and Illicit Trafficking in Drugs (Pompidou Group) & The Swedish Council for Information on Alcohol and Other Drugs (CAN). Available at: http://www.espad.org/Uploads/ESPAD_reports/2011/The_2011_ESPAD_Report_FULL_2012_10_29.pdf
Accessed 7 September 2014.

Hodges, B., Everett, J., 1998. Acute toxicity from home-brewed gamma hydroxybutyrate. *J. Am. Board Fam. Pract*. 11(2):154-157. PubMed PMID: 9542708.

Hoes, M.J., Vree, T.B., Guelen, P.J., 1980. Gamma-hydroxybutyric acid as hypnotic. Clinical and pharmacokinetic evaluation of gamma-hydroxybutyric acid as hypnotic in man. *Encephale*. 6(1):93-99. PubMed PMID: 7449723.

Home Office., 2012. *Drug misuse declared: findings from the 2011 to 2012 Crime Survey for England and Wales (CSEW)* (second edition). 27 September. Statistical Bulletin. Home Office, London. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/147938/drugs-misuse-dec-1112-pdf.pdf
Accessed 7 September 2014.

Home Office., 2014. *Drug misuse: findings from the 2013/14 Crime Survey for England and Wales (CSEW).* updated 15 August. Statistical Bulletin. Home Office, London. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/335989/drugs-misuse-201314.pdf
Accessed 14 February 2015.

Hopkins, A., 2012. Gay sauna deaths. How many more will die? 30 October. *Beige News*. Available at: http://www.beigeuk.com/2012/10/gay-sauna-deaths-how-many-more-will-die/.
Accessed 7 September 2014.

Horyniak, D., Degenhardt, L., Smit, D.V., Munir, V., Johnston, J., Fry, C., Dietze, P., 2014. Pattern and characteristics of ecstasy and related drug (ERD) presentations at two hospital emergency departments,Melbourne, Australia, 2008-2010. *Emerg. Med. J*. 31:317-322. doi: 10.1136/emermed-2012-202174. Epub 2013 Feb 12. PubMed PMID: 23404807.

Hunter, L.J., Dargan, P.I., Benzie, A., White, J.A., Wood, D.M., 2014. Recreational drug use in men who have sex with men (MSM) attending UK sexual health services is significantly higher than in non-MSM. *Postgrad. Med. J.* 90:133-138. doi: 10.1136/postgradmedj-2012-131428.

Itzhak, Y., Ali, S.F., 2002. Repeated administration of gamma-hydroxybutyric acid (GHB) to mice: assessment of the sedative and rewarding effects of GHB. *Ann. N. Y. Acad. Sci*. 965:451-460. PubMed PMID: 12105120.

Jones, C., 2001. Suspicious death related to gamma-hydroxybutyrate (GHB) toxicity. *J. Clin. Forensic Med.* 8(2):74-76. PubMed PMID: 15274975.

Jones, A.W., Holmgren, A., Kugelberg, F.C., 2007. Gamma-hydroxybutyrate concentrations in the blood of impaired drivers, users of illicit drugs, and medical examiner cases. *J. Anal. Toxicol*. 31(9):566-572. PubMed PMID: 18093415.

Kalasinsky, K.S., Dixon, M.M., Schmunk, G.A., Kish, S.J., 2001. Blood, brain, and hair GHB concentrations following fatal ingestion. *J. Forensic Sci*. 46(3):728-730. PMID: 11373018.

Kam, P.C., Yoong, F.F., 1998. Gamma-hydroxybutyric acid: an emerging recreational drug. *Anaesthesia*. 53(12):1195-1198. Review. PubMed PMID: 10193223.

Kamal, R.M., Qurishi, R., De Jong, C.A., 2015. Baclofen and γ-Hydroxybutyrate (GHB), a Dangerous Combination. *J. Addict. Med*. 9, 75-77. doi: 10.1097/ADM.0000000000000084. PubMed PMID: 25494007.

Kapil, V., Green, J.L., Le Lait, M.C., Wood, D.M., Dargan, P.I., 2014. Misuse of the γ-aminobutyric acid analogues baclofen, gabapentin and pregabalin in the UK. *Br. J. Clin. Pharmacol*. 78, 190-191. PubMed PMID: 25083536; PubMed Central PMCID: PMC4168395.

Karch, S.B., Stephens, B.G., Nazareno, G.V., 2001. GHB: club drug or confusing artifact?. *Am. J. Forensic. Med. Pathol*. 22(3):266-269.

Kaufman, E.E., Porrino, L.J., Nelson, T., 1990. Pyretic action of low doses of gamma-hydroxybutyrate in rats. *Biochem. Pharmacol*. 40(12):2637-2640. PubMed PMID: 2260987.

Keating, G.M., 2014. Sodium oxybate: a review of its use in alcohol withdrawal syndrome and in the maintenance of abstinence in alcohol dependence. *Clin. Drug Investig*. 34(1):63-80. doi: 10.1007/s40261-013-0158-x. PubMed PMID: 24307430.

Kelly, B.C., Parsons, J.T., Wells, B.E., 2006. Prevalence and predictors of club drug use among club-going young adults in New York City. *J. Urban Health*. 83(5):884-895. doi: 10.100-7/s11524-006-9057-2

Kilgore, E., Petullo, D., 2010. Sodium Oxybate Fibromyalgia Indication. Available at: http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/ArthritisAdvisoryCommittee/UCM223959.pdf
Accessed 7 September 2014.

Kim, S.Y., Anderson, I.B., Dyer, J.E., Barker, J.C., Blanc, P.D., 2007. High-risk behaviors and hospitalizations among gamma hydroxybutyrate (GHB) users. *Am. J. Drug Alcohol Abuse*. 33(3):429-438. PubMed PMID: 17613970; PubMed Central PMCID: PMC2257866.

Kintz, P., Villain, M., Cirimele, V., Ludes, B., 2004. GHB in postmortem toxicology. Discrimination between endogenous production from exposure using multiple specimens. *Forensic Sci. Int*. 143(2-3):177-181.

Kintz, P., Villain, M., Pélissier, A.L., Cirimele, V., Leonetti, G., 2005. Unusually high concentrations in a fatal GHB case. *J. Anal. Toxicol*. 29(6):582-585. PMID: 16168184.

Knudsen, K., Jonsson, U., Abrahamsson, J., 2010. Twenty-three deaths with gamma-hydroxybutyrate overdose in western Sweden between 2000 and 2007. *Acta Anaesthesiol. Scand*. 54(8):987-992. doi: 10.1111/j.1399-6576.2010.02278.x. PubMed PMID: 20701597.

Korb, A.S., Cooper, G., 2014. Endogenous concentrations of GHB in postmortem blood from deaths unrelated to GHB use. *J. Anal. Toxicol.* 38(8):582-588. doi: 10.1093/jat/bku088. PubMed PMID: 25217550.

Korf, D., Nabben, T., Leenders, F., Benschop, A., 2002. *GHB: Tussen Extase en Narcose*. Rozenberg Publishers, Amsterdam.

Kraner, J., Plassard, J., McCoy, D., Rorabeck, J., Witeck, M., Evans, M., 2005. Fatal overdose from ingestion of 1,4-butanediol, a GHB precursor. *Clin. Toxicol*. 38(5):534.

Krul, J., Blankers, M., Girbes, A.R., 2011. Substance-related health problems during rave parties in The Netherlands (1997-2008). *PLoS One*. 6(12):e29620. doi: 10.1371/journal.pone.0029620. PubMed PMID: 22216332; PubMed Central PMCID: PMC3247283.

Kugelberg, F.C., Holmgren, A., Eklund, A., Jones, A.W., 2010. Forensic toxicology findings in deaths involving gamma-hydroxybutyrate. *Int. J. Legal Med*. 124(1):1-6. doi: 10.1007/s00414-008-0299-2. PubMed PMID: 19048269.

Laboratorio Farmaceutico C.T.Srl., 2007. Alcover® (sodium oxybate: 4-hydroxybutyric acid sodium salt): Italian summary of product characteristics.

Laborit, H., 1964. Sodium 4-hydroxybutyrate. *Int. J. Neuropharmacol.* 3:433–451.

Laborit, H., Buchard, F., Laborit, G., Kind, A., Weber, B., 1960a. Emploi du 4-hydroxybutyrate de Na en anesthésie et en reanimation. [Use of sodium 4-hydroxybutyrate in anesthesia and resuscitation.] *Agressologie*, 1(5):549-560.

Laborit, H., Jouanny, J.M., Gérard, J., Fabiani, P., 1960b. Généralités concernant l'étude expérimentale de l'emploi clinique du gamma-hydroxybutyrate de Na. [Generalities concerning the the experimental study of the clinical use of sodium gamma-hydroxybutyrate.] *Agressologie*, 1(4):397-406.

Lamb, R.J., Munn, J., Duiker, N.J., Coop, A., Wu, H., Koek, W., France, C.P., 2003. Interactions of γ-hydroxy butyrate with ethanol and NCS 382. *Eur. J. Pharmacol*. 470(3):157-162. PubMed PMID: 12798953.

Langford, J., Gross, W.L., 2011. Psychosis in the context of sodium oxybate therapy. *J. Clin. Sleep. Med*. 7(6):665-666. doi: 10.5664/jcsm.1478. PMCID: PMC3227714; PMID: 22171207

LeBeau, M., Andollo, W., Hearn, W.L., Baselt, R., Cone, E., Finkle, B., Fraser, D., Jenkins, A., Mayer, J., Negrusz, A., Poklis, A., Walls, H.C., Raymon, L., Robertson, M., Saady, J.,1999. Recommendations for toxicological investigations of drug-facilitated sexual assaults. *J. Forensic Sci*. 44(1):227-230. PubMed PMID: 9987892.

Lenz, D., Rothschild, M.A., Kröner, L., 2008. Intoxications due to ingestion of γ-butyrolactone: organ distribution of γ-hydroxybutyric acid and γ-butyrolactone. *Ther. Drug Monit.* 30(6):755-761. doi: 10.1097/FTD.0b013e3181898c2e. PubMed PMID: 18824955.

LeTourneau, J.L., Hagg, D.S., Smith, S.M., 2008. Baclofen and Gama-Hydroxybutyrate withdrawal. *Neurocritical Care*. 8:430-433.

Lettieri, J., Fung, H.L., 1978. Improved pharmacological activity via pro-drug modification: comparative pharmacokinetics of sodium gamma-hydroxybutyrate and gamma-butyrolactone. *Res. Commun. Chem. Pathol. Pharmacol*. 22(1):107-118. PubMed PMID: 725311.

Li, J., Stokes, S.A., Woeckener, A., 1998. A tale of novel intoxication: a review of the effects of gamma-hydroxybutyric acid with recommendations for management. *Ann. Emerg. Med*. 31(6):729-736. PubMed PMID: 9624313.

Liechti, M.E., Kunz, I., Greminger, P., Speich, R., Kupferschmidt, H., 2006. Clinical features of gamma-hydroxybutyrate and gamma-butyrolactone toxicity and concomitant drug and alcohol use. *Drug Alcohol Depend*. 81(3):323-326. PubMed PMID: 16143455.

Liechti, M.E., Kupferschmidt, H., 2004. Gamma-hydroxybutyrate (GHB) and gamma-butyrolactone (GBL): analysis of overdose cases reported to the Swiss Toxicological Information Centre. *Swiss Med. Wkly*. 134(35-36):534-537. PMID: 15517507.

Louagie, H.K., Verstraete, A.G., De Soete, C.J., Baetens, D.G., Calle, P.A., 1997. A sudden awakening from a near coma after combined intake of gamma-hydroxybutyric acid (GHB) and ethanol. *J.Toxicol. Clin. Toxicol*. 35(6):591-594. PubMed PMID: 9365424.

Luby, S., Jones, J., Zalewski, A., 1992. GHB use in South Carolina. *Am. J. Public Health.* 82(1):128. PMID: 1536324.

Lycaeum., 1998. GHB. Complete FAQ. Available at: http://www.lycaeum.org/~ghbfaq/complete.html Accessed 7 September 2014.

Maitre, M., 1997. The γ-hydroxybutyrate signalling system in brain: organization and functional implications. *Prog. Neurobiol*. 51(3):337-361.

Maitre, M., Humbert, J.P., Kemmel, V., Aunis, D., Andriamampandry, C., 2005. Mécanismes d'action d'un médicament détourné : le γ-hydroxybutyrate. [A mechanism for γ-hydroxybutyrate (GHB) as a drug and a substance of abuse.] *Med. Sci. (Paris)*. 21(3):284-289.

Mamelak, M., 1997. Neurodegeneration, sleep, and cerebral energy metabolism: a testable hypothesis. *J. Geriatr. Psychiatry Neurol*. 10(1):29-32.

Mamelak, M., Scharf, M., Woods, M., 1986. Treatment of narcolepsy with gamma-hydroxy butyrate: A review of clinical and sleep laboratory findings. *Sleep*. 9 (1 pt 2):285-289. PMID: 3704454.

Maremmani, I., Pacini, M., 2007. Use of Sodium Gamma-Hydroxybutyrate (GHB) in alcoholic heroin addicts and polydrug-abusers. *Heroin Addict Re.l Cl*. 9(1):55-76.

Mari, F., Politi, L., Trignano, C., Di Milia, M.G., Di Padua, M., Bertol, E., 2009. What constitutes a normal ante-mortem urine GHB concentration? *J. Forensic Leg. Med*. 16(3):148-151.

Marinetti, L.M., 2001. γ-Hydroxybutyric acid and its analogs, γ-butyrolactone and 1,4-butanediol., in: Salamore, S.J., (Ed.), *Benzodiazepines and GHB: detection and pharmacology*. Humana Press, Totowa, NJ. pp. 95-126

Marinetti, L.J., Isenschmid, D.S., Hepler, B.R., Kanluen, S., 2005. Analysis of GHB and 4-methyl-GHB in postmortem matrices after long-term storage. *J. Anal. Toxicol*. 29(1):41-47. PMID: 15808012.

Marston, L., Nazareth, I., Petersen, I., Walters, K., Osborn, D.P., 2014. Prescribing of antipsychotics in UK primary care: a cohort study. *BMJ Open*. 4, e006135. doi: 10.1136/bmjopen-2014-006135. PubMed PMID: 25524544; PubMed Central PMCID: PMC4281533.

Mason, P.E., Kerns, W.P. 2nd., 2002. Gamma hydroxybutyric acid (GHB) intoxication. *Acad. Emerg. Med*. 9(7):730-739. PubMed PMID: 12093716.

Mazarr-Proo, S., Kerrigan, S., 2005. Distribution of GHB in tissues and fluids following a fatal overdose. *J. Anal. Toxicol*. 29(5):398-400. PubMed PMID: 16105269.

McCabe, E.R., Layne, E.C., Sayler, D.F., Slusher, N., Bessman, S.P., 1971. Synergy of ethanol and a natural soporific--gamma hydroxybutyrate. *Science*. 171(3969):404-406. PMID: 4321477.

McCambridge, J., Winstock, A., Hunt, N., Mitcheson, L., 2007. 5-year trends in use of hallucinogens and other adjunct drugs amongst UK dance drug users. *Eur. Addict. Res*. 13(1):57-64. PMID: 17172780

McCusker, R.R., Paget-Wilkes, H., Chronister, C.W., Goldberger, B.A., 1999. Analysis of gamma-hydroxybutyrate (GHB) in urine by gas chromatography-mass spectrometry. *J. Anal. Toxicol*. 23(5):301-305. PubMed PMID: 10488915.

McDaniel, C.H., Miotto, K.A., 2001. Gamma hydroxybutyrate (GHB) and gamma butyrolactone (GBL) withdrawal: five casestudies. *J. Psychoactive Drugs*. 33(2):143-149. doi: 10.1080/02791072.2001.10400479. PMID: 11476261.

McDonough, M., Kennedy, N., Glasper, A., Bearn, J., 2004. Clinical features and management of gamma-hydroxybutyrate (GHB) withdrawal: a review. *Drug Alcohol Depend*. 75(1):3-9. PubMed PMID: 15225884.

McDowell, D., 2000. Gay men, Lesbians and Substances of Abuse and the “Club and Circuit Party Scene”: what clubbers should know. *JGLP*. 3(3-4):37-57. doi: 10.1300/j236v03n03_04

Measham, F., Moore, K., Welch, Z., 2012. Emerging drug trends in Lancashire: night club surveys: Phase Three Report. Department of Applied Social Science, Lancaster University & Lancashire Drug and Alcohol Action Team, Lancaster, UK.

Measham, F., Wood, D. M., Dargan, P. I., Moore, K., 2011. 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. *J. Subst. Use*. 16(40):263-272.

Mégarbane, B., Fompeydie, D., Garnier, R., Baud, F.J., 2002. Treatment of a 1,4-butanediol poisoning with fomepizole. *J. Toxicol. Clin. Toxicol*. 40(1):77-80. PubMed PMID: 11990207.

Meyer, R., Jenewein, J., Boettger, S., 2014a. Management of Gamma-Butyrolactone dependence with assisted self-administration of GBL. *Case Rep. Neurol. Med*. 2014:485178. doi: 10.1155/2014/485178. Epub 26 June. PubMed PMID: 25054071; PubMed Central PMCID: PMC4099022.

Meyer, R., Jenewein, J., Boettger, S., 2014b. Severe Gamma-Hydroxy-Butyric Acid (GHB) dependence with repeated withdrawal syndrome and induced delirium. *J. Alcoholism & Drug Dependence*, 2, 156-157. doi: 10.4172/2329-6488-1000156.

Mikelsson, K., 2005. *Gamma-butyrolactone (GBL) and 1,4-butanediol (1,4-BD) as industrial chemicals and drugs of abuse. Can they be regulated?* Swedish National Institute of Public Health (FHI), Stockholm. Available at: https://www.yumpu.com/en/document/view/20602103/gamma-butyrolactone-gbl-and-14-butanediol-14-bd-as-.
Accessed 14 September 2014.

Mindandmuscle., 2014. GBL dosage. Available at: http://www.mindandmuscle.net/forum/399-gbl-dosage Accessed 7 September 2014.

Miotto, K., Darakjian, J., Basch, J., Murray, S., Zogg, J., Rawson, R., 2001. Gamma-hydroxybutyric acid: patterns of use, effects and withdrawal. *Am. J. Addict*. 10(3):232-241. PubMed PMID: 11579621.

Miró O., Nogué, S., Espinosa, G., To-Figueras, J., Sánchez, M., 2002. Trends in Illicit Drug Emergencies: The Emerging Role of Gamma-Hydroxybutyrate. *J. Toxicol. Clin. Toxicol*. 40(2):129-135.

Mixmag., 2002. The Mixmag Survey 2001. *Mixmag,* 129, 84-109.

Mixmag., 2011. The 2011 Mixmag drugs survey, *Mixmag*, 238, 49-59.

Mixmag. 2012. Mixmag's Drug Survey: the results. 14 March. Available at: http://www.mixmag.net/drugssurvey. Accessed 7 September 2014.

Morbidity and Mortality Weekly Report., 1997. Gamma Hydroxy Butyrate Use - New York and Texas, 1995-1996. *MMWR*. 46(13):281-283.

Moriya, F., Hashimoto, Y., 2004. Endogenous gamma-hydroxybutyric acid levels in postmortem blood. *Leg. Med. (Tokyo)*. 6(1):47-51. PMID: 15177073.

Moriya, F., Hashimoto, Y., 2005. Site-dependent production of gamma-hydroxybutyric acid in the early postmortem period. *Forensic Sci. Int*. 148,(2-3):139-142. PubMed PMID: 15639608.

Morse, B.L., Morris, M.E., 2013. Toxicokinetics/Toxicodynamics of γ-hydroxybutyrate-ethanol intoxication: evaluation of potential treatment strategies. *J. Pharmacol. Exp. Ther*. 346(3):504-513. doi: 10.1124/jpet.113.206250. PubMed PMID: 23814094.

Mozayani, A., Small, P., De Cuir, L., Jachimczyk, J.A., 1998. A fatality involving GHB, Society of Forensic Toxicologists (SOFT) – The International Association of Forensic Toxicologists (TIAFT) Joint Meeting, USA.

Munir, V.L., Hutton, J.E., Harney, J.P., Buykx, P., Weiland, T.J., Dent, A.W., 2008. Gamma-hydroxybutyrate: A 30 month emergency department review. *Emerg. Med. Australas*. 20(6):521-530. doi: 10.1111/j.1742-6723.2008.01140.x. PMID: 19125832.

Murali, H., Kotagal, S., 2006. Off-Label Treatment of Severe Childhood Narcolepsy-Cataplexy With Sodium Oxybate. *Sleep*. 29(8):1025-1029. PubMed PMID: 16944670.

Nava, F., Carta, G., Bortolato, M., Gessa, G.L., 2001. Gamma-hydroxybutyric acid and baclofen decreases extracellular actylcholine levels in the hippocampus via GABA-B receptors. *Eur. J. Pharmacol*. 430(2):261-263. PMID: 11711039.

Navarro, J.F., Pedraza, C., Martín, M., Manzaneque, J.M., Dávila, G., Maldonado, E., 1998. Tiapride-induced catalepsy is potentiated by gamma-hydroxybutyric acid administration. *Prog. Neuropsychopharmacol Biol. Psychiatry*. 22(5):835-844. PubMed PMID: 9723123.

Neels, H., Heytens, L., Dockx, G., Schouwers, S., Crunelle, C.L., 2014. A case report of persistent near fatal anion gap acidosis due to a massive gamma-butyrolactone (GBL) /ethanol intoxication. *ToxAC*. 26(2):S47 [Analytical, Clinical and Forensic Toxicology International Meeting, 10-14 June 2014, Bordeaux]. doi: 10.1016/s2352-0078(14)70101-5.

Nelson, T., Kaufman, E., Kline, J., Sokoloff, L., 1981. The extraneural distribution of gamma-hydroxybutyrate. *J. Neurochem*. 37(5):1345-1348. PubMed PMID: 7299403.

Németh, Z., Kun, B., Demetrovics, Z., 2010. The involvement of gamma-hydroxybutyrate in reported sexual assaults: a systematic review. *J. Psychopharmacol.* 24(9):1281-1287. doi: 10.1177/0269881110363315. PMID: 20488831.

NPIS., 2013. National Poisons Information Service – Annual Report 2012/2013. September. Health Protection Agency, London. 30 August. Available at: http://www.npis.org/NPISAnnualReport2012-13.pdf Accessed on 14 February 2015.

Nutt, D., King, L.A., Saulsbury, W., Blakemore, C., 2007. Development of a rational scale to assess the harm of drugs of potential misuse. *Lancet*. 369(9566):1047-1053. PubMed PMID: 17382831.

O'Connell, C.W., Schneir, A.B., Hwang, J.Q., Cantrell, F.L., 2014. Phenibut, the appearance of another potentially dangerous product in the United States. *Am. J. Med*. 127:e3-4 doi: 10.1016/j.amjmed.2014.03.029. PubMed PMID: 24713208.

ONDCP., 2002. *Gamma Hydroxybutyrate (GHB)*. Office of National Drug Control Policy. Available from: http://www.whitehousedrugpolicy.gov/publications/factsht/gamma/.
Accessed 28 December 2002.

ONS., 2009. *General Household Survey, 2007 Report*. 22 January. Office for National Statistics Newport, Gwent:, . Available at: www.ons.gov.uk/ons/rel/ghs/general-household-survey/2007-report/index.html
Accessed 14 February 2015.

ONS., 2013. *Key findings for the Integrated Household Survey: January 2012 to December 2012* (Experimental Statistics). 3 October. Office for National Statistics Newport, Gwent. Available at: www.ons.gov.uk/ons/dcp171778_329407.pdf.
Accessed 9 September 2014.

ONS., 2014. *Deaths related to drug poisoning in England and Wales, 2013*. Statistical Bulletin. 3 September. Office for National Statistics Newport, Gwent. Available with accompanying spreadsheets at: http://www.ons.gov.uk/ons/dcp171778_375498.pdf
http://www.ons.gov.uk/ons/rel/subnational-health3/deaths-related-to-drug-poisoning/england-and-wales---2013/rft---table-1.xls
Accessed on 3 September 2014.

Ortega-Albás, J.J., López-Bernabé, R., García, A.L., Gómez, J.R., 2010. Suicidal ideation secondary to sodium oxybate. *J. Neuropsychiatry Clin. Neurosci*. 22(3):352r.e26-352.e26. doi: 10.1176/appi.neuropsych.22.3.352-r.e26. PubMed PMID: 20686162.

Our Insight., 2011. Survey Results: Antidepressant use in the UK. ourinsight.opinion.co.uk. 2 December. Available at: ourinsight.opinion.co.uk/Survey-results/antidepressant-use-uk
Accessed 14 February 2015.

Palamar, J.J., Halkitis, P.N., 200). A qualitative analysis of GHB use among gay men: Reasons for use despite potential adverse outcomes. *Int. J. Drug Policy.* 17(1):23-28. PubMed PMID: 23543728; PubMed Central PMCID: PMC3611333.

Palatini, P., Tedeschi, L., Frison, G., Padrini, R., Zordan, R., Orlando, R., Gallimberti, L., Gessa, G.L., Ferrara, S.D., 1993. Dose-dependent absorption and elimination of gamma-hydroxybutyric acid in healthy volunteers. *Eur. J. Clin. Pharmacol*. 45(4):353-6. PubMed PMID: 8299669.

Pan, Y.M., Gill, G.N., Tilson, C.S., Wall, W.H., McCurdy, H.H., 2001. Improved procedure for the analysis of gamma-hydroxybutyrate and ethylene glycol in whole blood. *J. Anal. Toxicol*. 25(5): 328-32. PMID: 11499886.

Pazos, D., Giannasi, P., Rossy, Q., Esseiva, P., 2013. Combining Internet monitoring processes, packaging and isotopic analyses to determine the market structure: example of Gamma Butyrolactone. *Forensic Sci. Int*. 230(1-3:29-36. doi: 10.1016/j.forsciint.2013.02.033. PMID: 23523397.

Penberthy, J.K., Ait-Daoud, N., Vaughan, M., Fanning, T., 2010. Review of treatment for cocaine dependence. *Curr. Drug Abuse Rev*. 3(1): 49-62. PMID: 20088819.

Poldrugo, F., Barker, S., Basa, M., Mallardi, F., Snead, O.C., 1985. Ethanol potentiates the toxic effects of 1,4-butanediol. *Alcohol Clin. Exp. Res*. 9(6):493-497. PMID: 3911807.

Poldrugo, F., Snead, O.C. 3rd., 1984. 1,4 Butanediol, gamma-hydroxybutyric acid and ethanol: relationships and interactions. *Neuropharmacology*. 23(1):109-113. PubMed PMID: 6717752.

Poldrugo, F., Snead, O.C. 3rd., 1986. 1,4-butanediol and ethanol compete for degradation in rat brain and liver *in vitro*. *Alcohol.* 3(6):367-370. PMID: 3814347

Pounder, D.J., Jones, G.R., 1990. Post-mortem drug redistribution--a toxicological nightmare. *Forensic Sci. Int*. 45(3):253-263. PubMed PMID: 2361648.

Quang, L.S., Desai, M.C., Kraner, J.C., Shannon, M.W., Woolf, A.D., Maher, T.J., 2002). Enzyme and receptor antagonists for preventing toxicity from the gamma-hydoxybutyric acid precursor 1,4-butanediol in CD1 mice. *Ann. N.Y. Acad. Sci.* 965:461-472. PMID: 12105121.

Quang, L.S., Shannon, M.W., Woolf, A.D., Desai, M.C., Majer, T.J., 2002b. Pretreatment of CD-1 mice with 4-methylpyrazole blocks toxicity from the gamma-hydroxybutyrate precursor, 1,4 butanediol. *Life Sci*. 71(7):771-778. PMID: 12074936.

Rahbeeni, Z., Ozand, P.T., Rashed, M., Gascon, G.G., al Nasser, M., al Odaib, A., Amoudi, M., Nester, M., al Garawi, S., Brismar, J., 1994. 4-Hydroxybutyric aciduria. *Brain Dev.*16 Suppl:64-71. PubMed PMID: 7726383.

ReDNet., 2012. Fact sheet: GHB and GBL. The ReDNet Research Group, University of Hertfordshire.

Reisch, M., 2008. Solvent users look to replace NMP: N-Methylpyrrolidone ebabled friendlier products, but now has toxicity problems. *Chem. Eng. News*, 86(29):32. doi: 10.1021/cen-v086n029.p032

Roberts, D.M., Smith, M.W., Gopalakrishnan, M., Whittaker, G., Day, R.O., 2011. Extreme γ-butyrolactone overdose with severe metabolic acidosis requiring hemodialysis. *Ann. Emerg. Med*. 58(1):83-85. doi: 10.1016/j.annemergmed.2011.01.017. PubMed PMID: 21435738.

Romanelli, F., Smith, K.M., Pomeroy, C., 2003. Use of club drugs by HIV-seropositive and HIV-seronegative gay and bisexual men. *Top HIV Med*. 11(1):25-32. PubMed PMID: 12717048.

Rønning, S.A., 2013. Akutte forgiftninger ved sykehus i Oslo 1980-2008: Insidens, forgiftningsagens og mortalitet. [Acute poisonings in Oslo hospitals 1980-2008: incidence, poisoning agents and mortality.] Norwegian. PhD thesis, School of Medicine, University of Oslo, 5 March 2013. Available at: https://www.duo.uio.no/bitstream/handle/10852/35672/Prosjektoppgave%5B1%5D-KE2.pdf?sequence=1. Accessed 7 September 2014.

Rossetti, A.O., Heinzer, R.C., Tafti, M., Buclin, T., 2010. Rapid occurrence of depression following addition of sodium oxybate to modafinil. *Sleep Med*. 11(5):500-501. doi: 10.1016/j.sleep.2009.11.006. PubMed PMID: 20133191.

Roth, R.H., Giarman, N.J., 1966. Gamma-butyrolactone and gamma-hydroxybutyric acid: distribution and metabolism. *Biochem. Pharmacol.* 15:1333-1348.

Roth, R.H., Delgado, J.M.R., Giarman, N.J., 1966. γ-butyrolactone and γ-hydroxybutyric acid – II. The pharmacologically active form. *Int. J. Neuropharmacol*, 5(6): 421-428. PMID: 4293055

Roth, R.H., Giarman, N.J., 1968. Evidence that central nervous system depression by 1,4-butanediol in mediated through a metabolite, gamma-hydroxybutyrate. *Biochem. Pharmacol*. 17(5):735-9. PubMed PMID: 5649891.

Roth, R.H., Giarman, N.J., 1965. Preliminary report on the metabolism of gamma-butyrolactone and gamma-hydroxybutyric acid. *Biochem. Pharmacol.* 14:177-178. PMID: 14332463

Roth, R.H., Levy, R., Giarman, N.J., 1967. Dependence of rat serum lactonase upon calcium. *Biochem. Pharmacol.* 16(3):596-8. PMID: 4962217.

Sakurada, K., Kobayashi, M., Iwase, H., Mukoyama, H., Takatori, T., Yoshida, K., 2002. Production of gamma-hydroxybutyric acid in postmortem liver increases with time after death. *Toxicol. Lett.* 129(3):207-217. PMID: 11888704.

Samokhvalov, A.V., Paton-Gay, C.L., Balchand, K., Rehm, J., 2013. Phenibut dependence. *BMJ Case Rep*. Feb, pii: bcr2012008381. doi: 10.1136/bcr-2012-008381. PubMed PMID: 23391959.

Sanguineti, V.R., Angelo, A., Frank, M.R., 1997. GHB: a home brew. *Am. J. Drug. Alcohol Abuse*. 23(4):637-642. PubMed PMID: 9366979.

Schifano, F., Orsolini, L., Duccio Papanti, G., Corkery, J.M., 2015. Novel psychoactive substances of interest for psychiatry. *World Psychiatry*. 14, 15-26. doi: 10.1002/wps.20174. PubMed PMID: 25655145.

Schmitt, C., Gégu, C., Spadari, M., de Haro, L., 2013. Utilisation du phenibut en France à propos de deux cas provençaux [Use of phenibut in France: report of two cases]. *Therapie*. 68(2):123-124. doi: 10.2515/therapie/2013014. French. PubMed PMID: 23773355.

Schneidereit, T., Burkart, K., Donovan, J.W., 2000. Butanediol toxicity delayed by preingestion of ethanol. *Int. J. Med. Toxicol*. 3(1):1-3.

Sewell, C.A., Roberts, R., Abel, W.D., Martin, J., 2015. Gamma-hydroxybutyrate (GHB) withdrawal in Jamaica – a case report. *WIMJ Open*. 2, pp. 8. doi: 10.7727/wimjopen.2104.263.

Sevak, R.J., France, C.P., Koek, W., 2004. Neuroleptic-like effects of gamma-hydroxybutyrate: interactions with haloperidol and dizocilpine. *Eur. J. Pharmacol*. 483(2-3):289-293. PMCID: PMC3774313; PMID: 14729119

Shannon, M., Quang, L.S., 2000. Gamma-hydroxybutyrate, gamma-butyrolactone, and 1,4-butanediol: a case report and review of the literature. *Pediatr. Emerg. Care*. 16(6):435-440. PubMed PMID: 11138892.

Shima, N., Miki, A., Kamata, T., Katagi, M., Tsuchihashi, H., 2005. Endogenous level and *in vitro* Production of GHB in blood from healthy humans, and the interpretation of GHB levels detected in antemortem blood samples. *J. Health Sci.* 51(2):147-154.

Shröck, A., Hari, Y., König, S., Auwärter, V., Schürch, S., Weinmann, W., 2014. Pharmacokinetics of GHB and detection window in serum and urine after single uptake of a low dose of GBL – an experiment with two volunteers. *Drug Test. Anal*. 6(4):363-366. doi: 10.1002/dta.1498. PMID: 23733593.

Sindicich, N., Burns, L., 2013. *Australian trends in Ecstasy and Related Drug Markets 2012: Findings from the Ecstasy and Related Drugs Reporting System (EDRS)*. Australian Drug Trend Series No. 100. National Drug and Alcohol Research Centre, University of New South Wales, Sydney.

Simonsen, K.W., Edvardsen, H.M., Thelander, G., Ojanperä, I., Thordardottir, S., Andersen, L.V., Kriikku, P., Vindenes, V., Christoffersen, D., Delaveris, G.J., Frost, J., 2015. Fatal poisoning in drug addicts in the Nordic countries in 2012. *Forensic Sci. Int*. 248C:172-180. doi: 10.1016/j.forsciint.2015.01.003. PubMed PMID: 25645132.

Sivilotti, M.L., Burns, M.J., Aaron, C.K., Greenberg, M.J., 2001. Pentobarbital for severe gamma-butyrolactone withdrawal. *Ann. Emerg. Med.* 38(6): 660-665. PMID: 11719746.

Skala, K., Caputo, F., Mirijello, A., Vassallo, G., Antonelli, M., Ferrulli, A., Walter, H., Lesch, O., Addolorato, G., 2014. Sodium oxybate in the treatment of alcohol dependence: from the alcohol withdrawal syndrome to the alcohol relapse prevention. *Expert Opin. Pharmacother*. 15(2):245-257. doi: 10.1517/14656566.2014.863278. PubMed PMID: 24283802.

Smith, K.M., Larive, L.L., Romanelli, F., 2002. Club drugs: methylenedioxymethamphetamine, flunitrazepam, ketamine hydrochloride, and gamma-hydroxybutyrate. *Am. J. Health Syst. Pharm*. 59(11):1067-1076. PubMed PMID: 12063892.

Snead, O.C..3rd., 1982. An investigation of the relationship between the dopaminergic and electroencephalographic effects of gamma-butyrolactone. *Neuropharmacology.* 21(6):539-543. PMID: 7110537.

Snead, O.C. 3rd., 1990. The ontogeny of GABAergic enhancement of the gamma-hydroxybutyrate model of generalized absence seizures. *Epilepsia*. 31(4):363-368. PubMed PMID: 2369873.

Snead, O.C. 3rd., Furner, R., Liu, C.C., 1989. In vivo conversion of gamma-aminobutyric acid and 1,4-butanediol to gamma-hydroxybutyric acid in rat brain. Studies using stable isotopes. *Biochem. Pharmacol*. 38(24):4375-4380. PMID: 2604740.

Snead, O.C. 3rd., Gibson, K.M., 2005. Gamma-hydroxybutyric acid. *N. Engl. J. Med*. 352, 2721-2732. Review. Erratum in: *N. Engl. J. Med*. 2006 354(5):537. PubMed PMID: 15987921.

Snead, O.C. 3rd., Liu, C.C., Bearden, L.J., 1982. Studies on the relation of gamma-hydroxybutyric acid (GHB) to gamma-aminobutyric acid (GABA). Evidence that GABA is not the sole source for GHB in rat brain. *Biochem Pharmacol.* 31(23):3917-3923. PubMed PMID: 7159469.

Sporer, K.A., Chin, R.L., Dyer, J.E., Lamb, R., 2003. Gamma-hydroxybutyrate serum levels and clinical syndrome after severe overdose. *Ann. Emerg. Med*. 42(1):3-8. PubMed PMID: 12827115.

Stephens, B.G., Baselt, R.C., 1994. Driving under the influence of GHB? *J. Anal. Toxicol.* 18(6):357-358. PMID: 7823545.

Stephens, B.G., Coleman, D.E., Baselt, R.C., 1999. In vitro stability of endogenous gamma-hydroxybutyrate in postmortem blood. *J. Forensic Sci*. 44(1):231. PMID: 9987893.

Strickland, R.M., Felgate, P., Caldicott, D.G., 2005. Survival of massive gamma-hydroxybutyrate/1,4-butanediol overdose. *Emerg. Med. Australas*. 17(3):281-283. PubMed PMID: 15953232.

Sturman, P., 2000. *Drug assisted sexual assault:* A study for the Home Office under the Police Research Award Scheme. Home Office, London.

Sumnall, H.R., Woolfall, K., Edwards, S., Cole, J.C., Beynon, C.M., 2008. Use, function, and subjective experiences of gamma-hydroxybutyrate (GHB). *Drug Alcohol Depend*. 92(1-3):286-290. PubMed PMID: 17766059.

Takahara, J., Yunoki, S., Yakushiji, W., Yamauchi, J., Yamane, Y., 1977. Stimulating effects of gamma-hydroxybutyric acid on growth hormone and prolactin release in humans. *J. Clin. Endocrinol. Metab.* 44(5):1014-1017. PMID: 858775.

Teter, C.J., Guthrie, S.K., 2001. A comprehensive review of MDMA and GHB: two common club drugs. *Pharmacotherapy*. 21(12):1486-1513. PubMed PMID: 11765302.

Thai, D., Dyer, J.E., Benowitz, N.L., Haller, C.A., 2006. Gamma-hydroxybutyrate and ethanol effects and interactions in humans. *J. Clin. Psychopharmacol*. 26(5):524-529. PubMed PMID: 16974199; PubMed Central PMCID: PMC2766839.

Thai, D., Dyer, J.E., Jacob, P., Haller, C.A., 2007. Clinical pharmacology of 1,4-butanediol and gamma-hydroxybutyrae after oral 1,4-butanediol administration to healthy volunteers.*Clin. Pharm. Ther.* 81(2): 178-184. PMID: 17192771.

Theron, L., Jansen, K., Skinner, A., 2003. 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*. 116(1184):U650. PubMed PMID: 14583808.

Thomas, G., Bonner, S., Gascoigne, A., 1997. Coma induced by abuse of gamma-hydroxybutyrate (GBH or liquid ecstasy): a case report. *BMJ*. 314(7073):35-36. PubMed PMID: 9001478; PubMed Central PMCID: PMC2125568.

U.S. Xyrem® Multicenter Study Group., 2003. A 12-month, Open-Label, Multicenter Extension Trial of Orally Administered Sodium Oxybate for the Treatment of Narcolepsy. *Sleep*. 26(1):31-35.

Uys, J.D., Niesink, R.J., 2005. Pharmacological aspects of the combined use of 3,4-methylenedioxymethamphetamine (MDMA, ecstasy) and gamma-hydroxybutyric acid (GHB): a review of the literature. *Drug Alcohol Rev*. 24(4):359-368. PubMed PMID: 16234132.

van Amsterdam, J.G.C., van Laar, M., Brunt, J.M., van den Brink, W., 2012. Risk assessment of gamma-hydroxybutyric acid (GHB) in the Netherlands. *Regul. Toxicol. Pharmacol.* 63(1):55-63. doi: 10.1016/j.yrtph.2012.03.005. PubMed PMID: 22440552.

van Amsterdam, J., Brunt, T., Pennings, E., van den Brink, W. (2014). Risk assessment of GBL as a substitute for the illicit drug GHB in the Netherlands. A comparison of the risks of GBL versus GHB. *Regul. Toxicol. Pharmacol*. 70(2):507-513. doi: 10.1016/j.yrtph.2014.08.014. [Epub ahead of print] PubMed PMID: 25204614.

van Noorden, M.S., Kamal, R.M., Dijkstra, B.A.G., Mauritz, R., de Jong, C.A.J., 2014. A case series of pharmaceutical gamma-hydroxybutyrate (GHB) in three patients with severe benzodiazepine resistant GHB-withdrawal in the hospital. *Psychosomatics*. Epub 14 March. doi: 10.1016/j.psym.2014.03.002.

van Rij, CM., Wilhelm, A.J., van Loenen, A.C., 2004. Herkenning en behandeling van hydroxyboterzuur intoxicaties. [Recognition and treatment of gamma hydroxybutyric acid poisoning]. *Ned. Tijdschr. Geneeskd*. 148(17):844-846. Dutch. PubMed PMID: 15141653.

Van Sassenbroeck, D.K., De Neve, N., De Paepe, P., Belpaire, F.M., Verstraete, A.G., Calle, P.A., Buylaert, W.A., 2007. Abrupt awakening phenomenon associated with gamma-hydroxybutyrate use: a case series. *Clin. Toxicol. (Phila)*. 45(5):533-538. PubMed PMID: 17503262.

Van Sassenbroeck, D.K., De Paepe, P., Belpaire, F.M., Buylaert, W.A., 2003a. Characterization of the pharmacokinetic and pharmacodynamic interaction between gamma-hydroxybutyrate and ethanol in the rat. *Toxicol. Sci*. 73(2):270-278. PMID: 12700396.

Van Sassenbroeck, D.K., Calle, P.A., Rousseau, F.M., Verstraete, A.G., Belpaire, F.M., Monsieurs, K.G., Haentjens, R., Allonsius, J., Van Brantegem, J., Haenen, W., Buylaert, W.A., 2003b. Medical problems related to recreational drug use at nocturnal dance parties. *Eur. J. Emerg. Med*. 10(4):302-308. PubMed PMID: 14676509.

van Vugt, R., Hofhuizen, C.M., 2012. Two cases of near-fatal gamma-butyrolactone (GBL) ingestion and intoxication. *Acta Anaesthesiol. Belg*. 63(3):139-141. PubMed PMID: 23397667.

Vayer, P., Mandel, P., Maitre, M., 1985. Conversion of gamma-hydroxybutyrate to gamma-aminobutyrate in vitro. *J. Neurochem*. 45(3):810-814. PubMed PMID: 2863327.

Vayer, P., Mandel, P., Maitre, M., 1987. Gamma-hydroxybutyrate, a possible neurotransmitter. *Life Sci*. 41(13):1547-1557. PubMed PMID: 2887998.

Vickers, M.D., 1969. Gammahydroxybutyric Acid. *Int. Anesthesiol. Clin*, 7(1):75-89. PMID: 5392628

Vogels, N., Croes, E., 2011. Monitor Drugs Incidenten: factsheet 2010. Trimbos-instituut, Utretcht. Available at:

http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=6&cad=rja&uact=8&ved=0CEgQFjAF&url=http%3A%2F%2Fre-set.nu%2Fdownload.php%3Fid%3D42&ei=m_fDU9eeDaXH7AbvxYEw&usg=AFQjCNEOnhtmrO7_EqPYyOfpsbGEQvaVMw
Accessed on 7 September 2014.

Vree, T.B., Baars, A.M., van der Kleijn, E., 1975. Capaciteits-gelimiteerde eliminatie van 4-hydroxybutyrate, ethanol envinylbital. [Capacity -limited elimination of 4 - hydroxybutyrate , ethanol envinylbital.] *Pharmac. Weekbl*., 110(5):1257-1262.

Wang, L., 2007. Industrial chemical sullies popular children's toy. 1,4-BD rapidly converts to y-hydroxybutyric acid in the body. *Chem. Eng. News*, 9 Nov.

Wang, Y.G., Swick, T.J., Carter, L.P., Thorpy, M.J., Benowitz, N.L., 2009. Safety overview of postmarketing and clinical experience of sodium oxybate (Xyrem): abuse, misuse, dependence, and diversion. *J.Clin. Sleep Med*. 5(4):365-371. Erratum in: *J. Clin. Sleep. Med*. 2011 Aug, 7:415-416. PubMed PMID: 19968016; PubMed Central PMCID: PMC2725257.

Wang, Y.G., Swick, T.J., Carter, L.P., Thorpy, M.J., Benowitz, N.L., 2011. Sodium oxybate: updates and correction to previously published safety data. *J. Clin. Sleep Med*. 7(4):415-6. doi: 10.5664/JCSM.1214. PubMed PMID: 21897784; PubMed Central PMCID: PMC3161779.

Ward, D., Morgenthaler, J., Fowkes, S., 1998. *GHB- the natural mood enhancer*. Smart Publications, California, USA.

Weißhaar, G.F., Hoemberg, M., Bender, K., Bangen, U., Herkenrath, P., Eifinger, F., Rothschild, M., Roth, B., Oberthuer, A., 2012. Baclofen intoxication: a "fun drug" causing deep coma and nonconvulsive status epilepticus--a case report and review of the literature. *Eur. J. Pediatr*. 171(10):1541-1547. PubMed PMID: 22729246.

Wellendorph, P., Høg, S., Greenwood, J.R., de Lichtenberg, A., Nielsen, B., Frølund, B., Brehm, L., Clausen, R.P., Bräuner-Osborne, H., 2005. Novel cyclic gamma-hydroxybutyrate (GHB) analogs with high affinity and stereoselectivity of binding to GHB sites in rat brain. *J. Pharmacol. Exp. Ther*. 315(1):346-351. PubMed PMID: 16014570.

WHO., 2001. Expert Committee on Drug Dependence: thirty-second report (WHO technical report series 903). Geneva, Switzerland: WHO Expert Committee on Drug Dependence. Available at: http://www.google.co.uk/url?sa=t&rct=j&q=&esrc=s&source=web&cd=1&ved=0CCgQFjAA&url=http%3A%2F%2Fwhqlibdoc.who.int%2Ftrs%2FWHO_TRS_903.pdf&ei=loiNU6SrEY67Pa-DgdAK&usg=AFQjCNFkNYd9OykaNYY633TRwE8ZQsvXHA
Accessed 7 September 2014.

Williams, S.R., 1998. gamma-Hydroxybutyric acid poisoning. *West. J. Med*. 168(3):187-188. PubMed PMID: 9549423; PubMed Central PMCID: PMC1304865.

Winstock, A. , 2001. The Mixmag Survey 2000. *Mixmag,* , 117,54-62.

Winstock, A., 2012. Mixmag Global Drug Survey, *Mixmag*, 251, 68-74.

Winstock, A., 2013. Mixmag Global Drug Survey, *Mixmag*, 264, 76-81.

Winstock, A., 2014. Global Drug Survey, *Mixmag*, 276, 86-89.

Wojtowicz, J.M., Yarema, M.C., Wax, P.M., 2008. Withdrawal from gamma-hydroxybutyrate, 1,4-butanediol and gamma-butyrolactone: a case report and systematic review. *CJEM.* 10(1):69-74. PMID: 18226321.

Wood, D.M., Brailsford, A.D., Dargan, P.I., 2011. Acute toxicity and withdrawal syndromes related to γ-hydroxybutyrate (GHB) and its analogues γ-butyrolactone (GBL) and 1,4-butanediol (1,4BD). *Drug Test. Anal*. 3(7-8):417-425. doi: 10.1002/dta.292. PubMed PMID: 21548140.

Wood, D.M., Nicolaou, M., Dargan, P.I., 2009. Epidemiology of recreational drug toxicity in a nightclub environment. *Subst. Use Misuse*. 44(11):1495-1502. doi: 10.1080/10826080802543580. PubMed PMID: 19938928.

Wood, D.M., Warren-Gash, C., Ashraf, T., Greene, S.L., Shather, Z., Trivedy, C., Clarke, S., Ramsey, J., Holt, D.W., Dargan, P.I., 2008. Medical and legal confusion surrounding gamma-hydroxybutyrate (GHB) and its precursors gamma-butyrolactone (GBL) and 1,4-butanediol (1,4BD). *QJM*. 101(1):23-29. doi: 10.1093/qjmed/hcm117. PubMed PMID: 18203723.

Yeatman, D.T., Reid, K., 2003. A study of urinary endogenous gamma-hydroxybutyrate (GHB) levels. *J. Anal. Toxicol*. 27(1):40-42. PubMed PMID: 12587682.

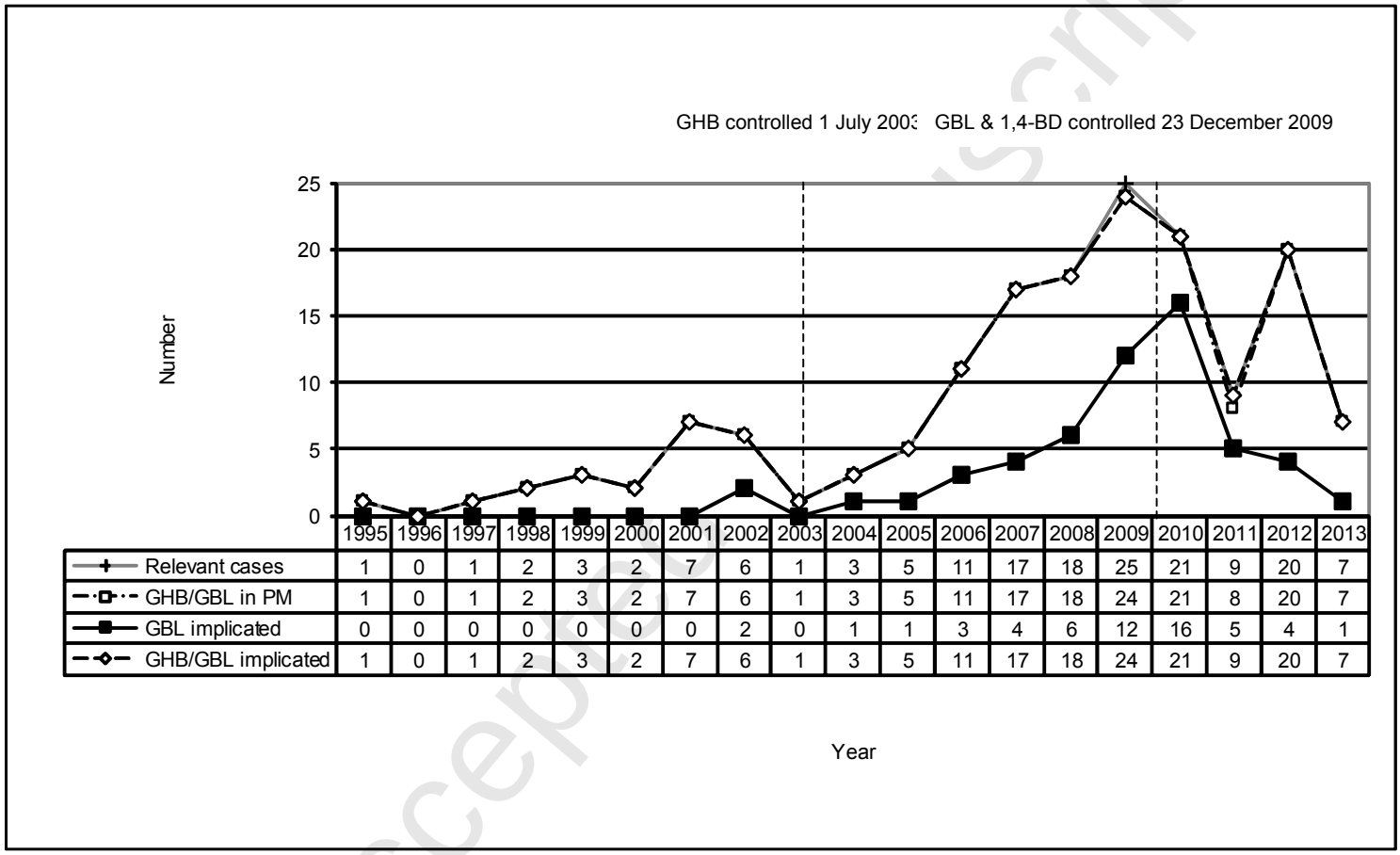
Zapata, J.P., 2013. Drugs, clubs and death: what can South London's gay community do? 10 May. *Gaystarnews.* Available at: http://www.gaystarnews.com/article/drugs-clubs-and-death-what-can-south-london%E2%80%99s-gay-community-do100513.
Accessed 7 September 2014.

Zvosec, D.L., Smith, S.W., Hall, B.J., 2009. Three deaths associated with use of Xyrem. *Sleep Med*. 10(4):490-493. doi: 10.1016/j.sleep.2009.01.005. PubMed PMID: 19269893.

Zvosec, D.L., Smith, S.W., McCutcheon, J.R., Spillane, J., Hall, B.J., Peacock, E.A., 2001. Adverse events, including death, associated with the use of 1,4-butanediol. *N. Engl. J. Med*. 344(2):87-94. PubMed PMID: 11150358.

Zvosec, D.L., Smith, S.W., Porrata, T., Strobl, A.Q., Dyer, J.E,. 2011. Case series of 226 γ-hydroxybutyrate-associated deaths: lethal toxicity and trauma. *Am. J. Emerg. Med*. 29(3):319-332. doi: 10.1016/j.ajem.2009.11.008. PubMed PMID: 20825811.

Figure 1: Evolution of UK deaths associated with the use of GHB, GBL and 1,4-BD reported to NPSAD by September 2013



	1995	1996	1997	1998	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011	2012	2013
Relevant cases	1	0	1	2	3	2	7	6	1	3	5	11	17	18	25	21	9	20	7
GHB/GBL in PM	1	0	1	2	3	2	7	6	1	3	5	11	17	18	24	21	8	20	7
GBL implicated	0	0	0	0	0	0	0	2	0	1	1	3	4	6	12	16	5	4	1
GHB/GBL implicated	1	0	1	2	3	2	7	6	1	3	5	11	17	18	24	21	9	20	7

Table 1: Socio-demographics of UK deaths associated with GHB, GBL and 1,4-BD reported to NPSAD by September 2013

Variable	Category	Number (%)
Total		159 (100.0)
Gender	Male	130 (82.4)
	Female	29 (17.6)
Sexual orientation	Confirmed homosexual	17 (10.6)
	Possible homosexual	2 (1.3)
	Transgender/Transvestite	2 (1.3)
Country of birth	England	78 (49.1)
	Wales	8 (5.0)
	Scotland	8 (5.0)
	Europe	13 (8.2)
	Americas	5 (3.1)
	Africa	4 (2.5)
	Asia	4 (2.5)
	Australia	1 (0.6)
	Not known	37 (23.3)
Employment status	Unemployed	22 (13.8)
	Employed	87 (54.7)
	Student	9 (5.7)
	House person/carer	3 (1.9)
	Retired/sickness/invalidity	2 (1.3)
	Not known	36 (22.6)
Living arrangements	Alone	43 (27.0)
	With others	82 (51.6)
	No fixed abode	1 (0.6)
	Other	1 (0.6)
	Not known	32 (20.1)
Ethnicity	White	113 (71.1)
	Black African	1 (0.6)
	Black Caribbean	1 (0.6)
	Indian	1 (0.6)
	Chinese	1 (0.6)
	Other	6 (3.8)
	Not known	36 (22.6)
History of drug use	Yes	74 (46.5)
	No	32(20.1)
	Not known	53 (33.3)
Injecting status	Yes	10 (6.3)
	No	46 (28.9)
	Not known	103 (64.8)
Age-group (years)	15-24	36 (22.6)
	25-34	70 (44.0)
	35-44	38 (23.9)
	45-54	14 (8.8)
	55-64	1 (0.6)
Age at death (years)	Male	Mean 32.63; Min 18.88, Max 60.10, SD 8.58
	Female	Mean 29.91; Min 19.00, Max 47.31, SD 8.24
	All	Mean 32.13; Min 18.88, Max 60.10, SD 8.56

Table 2: GHB/GBL cases with specified prescribed psychoactive medications reported to NPSAD by September 2013

Substance category	Medication	Number
ADHD drug	Amphetamine	1
	Dexamphetamine	1
	Modafinil	1
Antidepressant	Venlafaxine	3
	Dothiepin (tricyclic)	2
	Citalopram (SSRI)	5
	Mirtazapine	4
	Duloxetine	2
	Amitryptyline (tricyclic)	1
	Fluoxetine (SSRI)	2
Antiepileptic	Gabapentin	3
	Sodium valproate	1
	Clonazepam	1
Antihistamine	Cyclizine	1
	Cetirizine	1
Antimanic	Lithium	1
Antipsychotic	Olanzapine	2
	Chlorpromazine	1
	Quetiapine	3
	Risperidone	1
	Sulpiride	1
	Haloperidol	1
Anxiolytic	Chlordiazepoxide	1
Benzodiazepine	Diazepam	8
Non-Benzodiazepine hypnotic	Zopiclone	4
	Zolpidem	1
	Zaleplon	1
Opioid	Co-proxamol	1
	Co-codamol	2
	Tramadol	2
	Buprenorphine	1
Sex hormones	Testosterone	1
Total cases		29

Notes: Rows may sum to more than the total as same individuals may have been prescribed more than one medication.
SSRI: Selective Serotonin Re-uptake Inhibitor

Table 3: Geographic areas of place of UK deaths associated with GHB, GBL and 1,4-BD reported to NPSAD by September 2013

Area	Number	%
Northern Ireland	0	0.0
Isle of Man	0	0.0
Jersey	0	0.0
Guernsey	0	0.0
Wales	9	5.7
of which, Rhondda Cynon Taf	3	1.9
Cardiff	2	1.3
Scotland	27	17.0
of which, Lothian & Borders	17	10.7
Strathclyde	6	3.8
England	123	77.4
Greater London	40	25.2
Bromley	1	0.6
Camden	2	1.3
Croydon	1	0.6
Enfield	1	0.6
Greenwich	2	1.3
Hammersmith & Fulham	1	0.6
Islington	2	1.3
Lambeth	15	9.4
Newham	2	1.3
Southwark	2	1.3
Tower Hamlets	2	1.3
Waltham Forest	1	0.6
Westminster	7	4.4
Other selected areas		
Brighton & Hove	4	2,5
Kirklees	3	1.9
Manchester	3	2.5
Shropshire	4	2.5
N	*159*	*100.0*

Table 4: Circumstances of UK deaths associated with GHB, GBL and 1,4-BD reported to NPSAD by September 2013

Variable	Category	Number (%)
Total		*159 (100.0)*
Place of death	At home	80 (50.3)
	Private residential address	31 (19.5)
	Hotel/Hostel	4 (2.5)
	Hospital	21 (13.2)
	Street/road	1 (0.6)
	Open space, woodland, camp-site	3 (1.9)
	River/stream/lake	1 (0.6)
	Motor vehicle	2 (1.3)
	Gay sauna	1 (0.6)
	Not known	15 (9.4)
Verdict (conclusion)	Accident/Misadventure	95 (59.7)
	Suicide	11 (6.9)
	Open/Undetermined	18 (11.3)
	Non-dependent abuse of drugs	22 (13.8)
	Abuse of drugs	8 (5.0)
	Dependence on drugs	5 (3.1)
Manner of death	Accidental	126 (79.2)
	Suicidal	11 (6.9)
	Undetermined	21 (13.2)
	Unclassified	1 (0.6)
Circumstances of death/events leading to death	Recreational drug use/party - at home	44 (27.7)
	Recreational drug use/party – other private residence	17 (10.7)
	Recreational drug use/party – pub/club	16 (10.1)
	Recreational drug use/party - at festival	1 (0.6)
	Recreational drug use/party – in car	2 (1.3)
	Recreational drug use/party – public place	1 (0.6)
	Recreational drug use/party – gay health spa	1 (0.6)
	Body-building fitness	3 (1.9)
	Aid sleep	3 (1.9)
	Body-building & aid sleep	1 (0.6)
	Prevent craving for alcohol & aid relaxation	1 (0.6)
	Dependent use – trying to wean self off	1 (0.6)
	Accidentally mistaken for water	5 (3.1)
	Drank from drink not intended for deceased	2 (1.3)
	Drank undiluted accidentally	1 (0.6)
	In sexual activity	6 (3.8)
	Suicide	7 (4.4)
	Open verdict	2 (1.3)
	Cut own neck under influence of GHB	1 (0.6)
	Not known	44 (27.7)
Location of events leading to death	Home	81 (50.9)
	Other specified place	50 (31.4)
	Of which, friends/relative's home	21 (13.2)
	Third party's home	6 (3.8)
	Hotel	4 (2.5)
	Car	4 (2.5)
	Open space/canal/street	4 (2.5)
	Gay health spa	2 (1.3)
	Other	9 (5.7)
	Not known	28 (17.6)
Day of death	Sunday	35 (22.0)
	Monday	22 (13.8)
	Tuesday	22 (13.8)
	Wednesday	18 (11.3)
	Thursday	15 (9.4)
	Friday	18 (11.3)
	Saturday	29 (18.2)
Number of PM drugs	N =158	Mean 3.47, Median 3; Mode 3; Min 0, Max 13, SD 2.14

Table 5: Proximal and Underlying cause of deaths associated with GHB, GBL and 1,4-BD reported to NPSAD by September 2013

ICD-10 code	Description	Proximal cause	Underlying cause
		Number (%)	Number (%)
Mental & behavioural disorders due to psychoactive substance use			
F15.0	Use of stimulants – acute intoxication	0 (0.0)	1 (0.6)
F19.1	Multiple drug use – harmful use	0 (0.0)	1 (0.6)
F19.2	Multiple drug use - dependence	1 (0.6)	1 (0.6)
Accidental poisoning			
X40	Non-opioid analgesics, anti-pyretics and anti-rheumatics	0 (0.0)	1 (0.6)
X41	Anti-epileptic, sedative-hypnotic, anti-Parkinsonism and psychotropic drugs, not elsewhere classified	92 (57.9)	106 (66.7)
X42	Narcotics and psychodysleptics (hallucinogens), not elsewhere classified	2 (1.3)	12 (7.5)
X44	Other and unspecified drugs, medicaments and biological substances	1 (0.6)	2 (1.3)
Intentional self-poisoning			
X61	Anti-epileptic, sedative-hypnotic, anti-Parkinsonism and psychotropic drugs, not elsewhere classified	8 (5.0)	8 (5.0)
X62	Narcotics and psychodysleptics (hallucinogens), not elsewhere classified	1 (0.6)	2 (1.3)
Poisoning of undetermined intent			
Y11	Anti-epileptic, sedative-hypnotic, anti-parkinsonism and psychotropic drugs, not elsewhere classified	14 (8.8)	19 (11.9)
Y12	Narcotics and psychodysleptics (hallucinogens), not elsewhere classified	0 (0.0)	1 (0.6)
Other causes			
G93.1	Brain damage, anoxic or hypoxic	1 (0.6)	0 (0.0)
G97.8	Cerebral hypoxia, unspecified	2 (1.3)	0 (0.0)
I25.1	Atherosclerotic heart disease	1 (0.6)	0 (0.0)
I26.9	Pulmonary embolism	1 (0.6)	0 (0.0)
I50.1	Left ventricular failure	1 (0.6)	0 (0.0)
I50.9	Cardiac failure, unspecified	2 (1.3)	0 (0.0)
J18.0	Bronchopneumonia	1 (0.6)	0 (0.0)
J18.9	Pneumonia, unspecified	1 (0.6)	0 (0.0)
J43	Emphysema	1 (0.6)	0 (0.0)
J69.0	Aspiration pneumonia	1 (0.6)	0 (0.0)
J81.0	Pulmonary oedema or congestion	1 (0.6)	0 (0.0)
J96.0	Acute respiratory failure	1 (0.6)	0 (0.0)
J96.9	Respiratory failure/depression	3 (1.9)	0 (0.0)
J98.8	Other specified respiratory disorder	1 (0.6)	0 (0.0)
K22.2	Ulcer of oesophagus	1 (0.6)	0 (0.0)
K76.0	Fatty change of liver, not elsewhere specified	0 (0.0)	1 (0.6)
R09.0	Asphyxia general	2 (1.3)	0 (0.0)
R09.2	Cardiorespiratory failure/arrest	4 (2.5)	0 (0.0)
S02.9	Fracture of skull & facial bones, part unspecified	1 (0.6)	0 (0.0)
S15	Injury of blood vessels at neck level	1 (0.6)	0 (0.0)
T07	Multiple injuries, unspecified	1 (0.6)	0 (0.0)
T17.9	Aspiration of gastric contents	4 (2.5)	0 (0.0)
W66	Drowning/submersion whilst in bath	2 (1.3)	0 (0.0)
W69	Drowning whilst in natural water	1 (0.6)	1 (0.6)
W78	Aspiration of gastric contents	2 (1.3)	0 (0.0)
X70	Intentional hanging	1 (0.6	1 (0.6)
R99	Unascertained	1 (0.6)	1 (0.6)
All codes		*159 (100.0)*	*159 (100.0)*

Table 6: Blood levels of GHB/GBL by post-mortem substance combinations reported to NPSAD by September 2013

Substance combination	Mentions of GHB/GBL	Information available on levels	GHB/GBL blood levels (mg/L)			
	No (%)	No (%)	Mean	Minimum	Maximum	Std Dev
GHB implicated but not in PM	1 (0.6)	0 (0.0)	-	-	-	-
GHB implicated alone & sole drug in PM	27 (17.0)	13 (48.1)	1057.62	159	6500	1690.06
GHB implicated alone & other drugs in PM	16 (10.1)	12 (75.0)	531.42	45	2355	623.05
GHB implicated alone & other drugs and alcohol in PM	15 (9.4)	12 (80.0)	516.50	116	1400	413.96
GHB and alcohol only implicated & sole substances in PM	8 (5.0)	8 (100.0)	906.63	131	2794	1078.10
GHB and alcohol only implicated & other drugs in PM	14 (8.8)	11 (78.60)	326.35	0	1222	334.44
GHB and other drugs implicated & no alcohol in PM	38 (23.9)	32 (84.2)	354.92	> 10	1400	418.86
GHB and other drugs implicated & alcohol in PM	7 (4.4)	5 (71.4)	298.00	106	597	180.50
GHB and other drugs and alcohol implicated	23 (14.5)	17 (73.9)	451.64	30	2313	554.52
GHB not implicated but in PM after consumption	10 (6.3)	10 (100.0)	59.40	8	233	66.76
Total	159 (100.0)	121 (76.1)	481.70	8	6500	758.26

Table 7: Combinations of post-mortem drugs in deaths associated with GHB, GBL and 1,4-BD reported to NPSAD by September 2013

Commonest substance combination	No (%)
GHB/GBL + alcohol	22 (13.8)
GHB/GBL + stimulant	20 (12.6)
GHB/GBL + stimulant + alcohol	19 (11.9)
GHB/GBL + stimulant + benzodiazepine	7 (4.4)
GHB/GBL + stimulant + benzodiazepine + alcohol	7 (4.4)
GHB/GBL + benzodiazepine + alcohol	7 (4.4)
GHB/GBL + stimulant + ketamine	6 (3.8)
GHB/GBL + stimulant + benzodiazepine + opiate/opioid	5 (3.1)
GHB/GBL + benzodiazepine + opiate/opioid + alcohol	4 (2.5)
GHB/GBL + opiate/opioid	4 (2.5)
GHB/GBL + opiate/opioid + alcohol	4 (2.5)
Percentages of common substances: alcohol (45.9); diazepam (26.4); cocaine (23.9); MDMA/MDA (14.5); amphetamine (13.2); cannabinoids (10.1); ketamine (8.8); morphine/codeine (8.8); mephedrone (7.5)	N = 159
Note: The percentages given for single substances made sum to more than the total as some cases had more than one substance found at post-mortem	

Table 8: Cases involving GHB/GBL alone reported to NPSAD by September 2013

Key characteristic	Number (n = 59)
Male	52 (88.1%)
Age at death (years)	Mean = 32.21; Min = 19.00; Max = 52.57; SD = 8.78
Ethnicity	White = 41 (69.5%), Black Caribbean = 1 (1.7%), Chinese = 1 (1.7%); other = 3 (5.1%), Not known = 13 (22.0%)
History of drug use	Yes = 24 (40.7%); no = 12 (20.3%); Not known = 23 (40.0%)
Place of incident leading to death	Home = 28 (47.5%); Other specified place = 14 (23.7%); Street/road = 1 (1.7%); Sauna 1 (1.7%); Not known = 15 (25.4%)
Place of death	At home = 29 (49.2%); hospital = 8 (13.6%); Private residence = 7 (11.9%); open space = 3 (5.1%); Street/road = 1 (1.7%); Car = 1 (1.7%); Sauna = 1 (1.7%); Not known = 9 (15.3%)
Year of death	1991 – 1; 2001- 2; 2004 = 2; 2005 =2; 2006 = 3; 2007 = 6; 2008 = 6; 2009 = 9; 2010 = 9; 2011 = 5; 2012 = 10; 2013 = 4

Table 9: Dosage and levels of GHB/GBL in human tissues

Study, enrolment	Dosage (oral route unless specified)	GHB level (mg/L) in plasma (unless specified)	Other substances and levels
Dosages			
Marinetti, 2001	Therapeutic BI 24-88 mg/L		
Palatini *et al*., 1993	Drowsiness – 25 mg/kg (oral) – 80 mg/L peak plasma		
Baselt, 2008	Amnesia - 10 mg/kg; sleep/deep sedation – 20-30 mg/kg; recreational – 35 mg/kg; anaesthesia - >50mg/L		
Helrich *et al*., 1964	Sleep – 50 mg/kg (IV) peak blood 170 mg/L		
Hoes *et al*., 1980	Sleep – 75mg/kg (oral) peak plasma at 2 h 90 mg/L, plasma at 6 h 9 mg/L; 100 mg/kg (oral) ur peak at 4 h 1100 mg/L		
Baselt, 2008	Sleep/deep sedation - 20-30 mg/kg		
Baselt, 2008	Recreational – 35 mg/kg		
Baselt, 2008	Anaesthesia - >50mg/L		
Endogenous PM GHB			
Busardò *et al*., 2014	Deaths with no GHB ingestion		
Femoral blood (N = 30)		Range 0.54-24.12	
Urine (N = 30)		Range 0.58-22.13	
Kintz *et al*., 2004	Deaths with no GHB ingestion		
Cardiac blood (N = 71)		Range 0.4-409; mean 36.7; median 17.5	
Femoral blood (N = 5)		Range 16.8-44.1, mean 30.4; median 34.3	
Elliott, 2004a	Deaths with no GHB ingestion		
Femoral blood (N = 35)		Range 2-29; mean 12.6; median 12	
Moriya & Hashimoto, 2005	Deaths with no GHB ingestion		
Left cardiac chamber blood (N = 21)		Range ND-15.8, mean 4.0; median 3.1	
Right cardiac chamber blood (N = 19)		Range ND-14.4; mean 4.9; median 4.3	
Aortic blood (N = 20)		Range ND-23.7; mean 4.0; median 2.5	
Femoral venous blood (N = 23)		Range ND-11.6; mean 4.6; median 4.7	
Elliott, 2001	Deaths with no GHB ingestion	Range 0-197	
Fieler *et al*., 1998	Deaths with no GHB ingestion	3.2-168	
Marinetti *et al*., 2005	Deaths with no GHB ingestion	11-97	
Moriya & Hashimoto, 2004	Deaths with no GHB ingestion	0-43.0	
Stephens *et al*., 1999	Deaths with no GHB ingestion	5-77	
Anaethesia study			
Helrich *et al*., 1964			
Surgical patients (N = 14)	100mg/kg of GHB, intravenous, no pre-meds or other drugs administered	Peak blood level range 234-520; mean 307	
Pharmacokinetic studies			
Borgen *et al*., 2000			
Vounteers (N = 12), divided doses of Xyrem® administered 4 h apart	Regimen 1 (4.5 g total) GHB		
	Dose 1 – 2.25 g GHB	Mean peak 26.6	
	Dose 2 – 2.25 g GHB	Mean peak 60.1	
	Regimen 2 (9 g total) GHB		
	Dose 1 – 4.5 g GHB	Mean peak 77.6	
	Dose 2 – 4.5 g GHB	Mean peak 141.9	
Brenneisen *et al*., 2004			
Volunteers (N = 8)	25 mg/kg GHB	Peak range 4.7-76.3; mean peak 39.7 (SEM 10.6)	
Thai *et al*., 2007			
Volunteers (N = 8)	25 mg/kg GHB	Peak range 22.2-85.7; mean peak 45.6 (SD 19.7)	
Thai *et al*., 2006			

Volunteers (N = 16)	50 mg/kg GHB	Mean peak 72.6 (SD 16.2)	
Abanades *et al*., 2006			
Volunteers (N = 8)	40 mg/kg (N=4) GHB	Mean peak 79.1 (SD 26.4)	
	50 mg/kg (N=5) GHB	Mean peak 83.1 (SD 28.8)	
	60 mg/kg (N=4) GHB	Mean peak 113.5 (SD 20.1)	
	72 mg/kg (N=2) GHB	Mean peak 130.1 (SD 10.7)	
Non-fatal GHB toxicity cases		(Sample drawn in Emergency Department)	
Dyer *et al*., 1994	Unknown dose	101	Negative for co-intoxicants
Couper & Logan, 2000	Unknown dose	130	Negative for co-intoxicants
Zvosec *et al*., 2001	Unknown dose (BD)	317 (GHB dependent)	Negative for co-intoxicants
Megarbane *et al*., 2002	Unknown dose (BD)	222 (regular GHB user)	Negative for co-intoxicants
Couper *et al*., 2004	Unknown dose (BD)	Bl mean 137, median 103, min 29, max 490 mg/L	Negative for co-intoxicants
Strickland *et al*., 2005	Unknown dose (BD)	1200	Negative for co-intoxicants
Lenz *et al*., 2008	Unknown dose (GBL)	161	Negative for co-intoxicants
Dargan *et al*., 2008	600mg/kg of Xyrem	569 (serum) 7 h post ingestion; 377 8.5 h post ingestion	Negative for co-intoxicants
Driving samples			
Driving under the influence			
Stephens and Baselt, 1994; Couper and Logan, 2001, 2004		Bl mean 97, median 95, range 26-255 mg/L	
Pan *et al.*, 2001		Bl 16-350 mg/L	
Bosman and Lusthof, 2003		Bl 51-195 mg/L, ur 100-2000 mg/L	
Jones *et al*., 2007		Bl mean 90, median 84, max 340mg/L	
Al-Samarrie *et al*., 2010		Bl median 1262, range 592-2191mu mol/L	
Burch *et al*., 2013 (N = 5)		Bl 80-190, mean 126, median 120 mg/L	
Drug users			
Jones *et al*., 2007		Bl median 118, max 840 mg/L	
Intoxications			
Elliott, 2004b (N = 27); M = 25, age = 12-44, where known	Unknown dose	Bl mean 245, range 86-551; ur 1732, range 5-5581	Ethanol (7); drugs (15)
GHB-associated fatalities			
Duer *et al*., 2001	Unknown dose	303	Negative for co-intoxicants
Harty & Kemp, 2002	Unknown dose	1270	Negative for co-intoxicants
Caldicott *et al*., 2004	Unknown dose	PM 77; AM 210, 220	Negative for co-intoxicants
ACMD, 2007			
N = 6* in NPSAD sample	Unknown dose	PM 42, 120, 159, 403, 1575; AM 430	Negative for co-intoxicants
Lenz *et al*., 2008	Unknown dose	165	Negative for co-intoxicants
Medical examiner cases			
Jones *et al*., 2007 (N = 33)		Bl mean 307, median 190, max 2200 mg/L	
Known GHB uptake		Peripheral blood	
Kalasinsky *et al*., 2001		330	
Kintz *et al*., 2005		Femoral bl 2937 ; cardiac bl 3385 (ur 33; bile 727; vit. 1800 and 2856)	Femoral blood MDMA 144 ng/mL
Mazarr-Proo & Kerrigan, 2005		461	
Baselt, 2008		27-1030	
Lenz *et al*., 2008		165, 957	
Knudsen *et al*., 2010		170-2200	No or minor influence of other drugs
Kraner *et al*., 2010		280	
Zvosec *et al*., 2011			
Periphereal & heart		Range 18-4400; median	

		290	
Zvosec *et al*., 2009			
N = 3	Xyrem®	141	Alcohol 0.02%; phentermine 0.26; zolpidem 0.16; paroxetine 0.3
	Xyrem®	110	Alprazolam 0.016; nordiazepam 0.081; quetiapine 0.045
	Xyrem®	3500	Methylamphetamine 1.1; amphetamine 0.19; chlorpheniramine <0.05
Akins *et al*., 2009	Xyrem®	165.6, 140 (ur 90.7; gastric 142.0)	Tramadol 0.46; carisprodol 1.9; meprobamate 3.9
Ferrara *et al.*, 1995	Alcover®	11.5 (ur 258.3; vit 84.3)	Morphine 0.77 (vit. 0.3); 6-MAM 28.5