Deaths in the Lesbian, Gay, Bisexual and Transgender United Kingdom communities associated with GHB and precursors

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Abstract

Background
Misuse of gammahydroxybutrate (GHB) and its prodrugs gammabutyrolactone (GBL) and 1,4 butanediol (1,4-BD) has increased greatly since the early 1990s, particularly amongst lesbian, gay, bisexual and transgender (LGBT) individuals in recreational and sexual settings, e.g. 'chemsex'.
Objective and method
This paper presents an overview of GHB pharmacotoxicology and provides analyses of cases in the LGBT population associated with use of these substances extracted from the UK's National Programme on Substance Abuse Deaths database, to which notification is voluntary.
Results
From 1995 to September 2013, 21 GHB/GBL-associated fatalities were reported. None involved 1,4-BD. Typical victims were: Male (100%); White (67%), young (mean age 34 years); employed (90%); with a drug misuse history (81%). Most deaths were accidental (67%) or related to recreational drug use (19%), the remaining (potential) suicides. The majority of fatalities (83%) occurred in private residences, typically following recreational use; others occurred in specific 'gay'-oriented locales including clubs and saunas. Three London boroughs accounted for 62% of all notified deaths, reflecting the concentration of both resident and visiting 'gay' individuals. However, this may be an artefact of the voluntary nature of the data submission procedure in particular areas. GHB/GBL alone was implicated in 10% of fatalities. The following substances were implicated either alone or in combination in the remaining cases (percentages may add to more than 100%): cocaine (38%); alcohol (33%); amphetamines (29%); ecstasy (29%); diazepam (24%); ketamine (24%); mephedrone (24%). Post-mortem blood levels: mean 660 (range 22 - 2335; S.D. 726) mg/L.
Conclusions
Significant caution is needed when ingesting GHB/GBL, particularly with alcohol, benzodiazepines, stimulants, and ketamine. Risk of death is increased due to their CNS-depressant properties. Of these, 'chemsex' drugs such as cocaine, mephedrone and ketamine are of note. More awareness is needed in the 'gay' community about risks associated with the consumption of such substances.
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1. INTRODUCTION

Gammahydroxybutyrate (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 [1, 2]. 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 [3, 4].

The misuse of GHB and these prodrugs increased greatly in Western countries from the early 1990s, especially in the club and dance scenes [1, 5]. The period since has been marked by a rising number of deaths in the United States of America (USA), United Kingdom (UK), Western Europe, Australasia, and other developed countries [6-9].

The purpose of this paper is to place in the public domain detailed particulars of fatalities associated with GHB and its prodrugs within the Lesbian, Gay, Bisexual and Transgender (LGBT) community in the UK. It highlights the dangers associated with its consumption, especially with regard to recreational and sexual uses. It also contributes to the pool of knowledge being built up on this drug.

2. OVERVIEW OF GHB/GBL PHARMACOTOXICOLOGY

GHB chemistry and pharmacology, metabolism and pharmacokinetics, medical uses, addiction potential, routes of administration, effects, hospital presentations, and a detailed analysis of all GHB/GBL deaths notified in the UK up to September 2013 have been previously reported [9, 10].

2.1. Chemistry and pharmacology

GHB is a natural substance found in the human central nervous system (CNS) as a degradation product of the neurotransmitter gamma-aminobutyric acid (GABA) and other organs including the liver, kidney, heart, bones as well as in brown fat [11]. Like GABA, GHB possesses distinct excitatory properties which may be due to its effect on the mesolimbic dopaminergic system [2, 4]. It can be metabolised *in vivo* to GABA and trans-4-hydroxycrotonic acid (THCA); the first of these being pharmacologically active at $GABA_B$ receptors [12] and the second one binds to the GHB receptor with a four-fold higher affinity than GHB [13]. Absorption of large amounts of GHB desensitises GHB receptors [14] which, along with direct stimulation of $GABA_B$ receptors by the molecule, results in GABA, dopamine and opiate release. This process is likely to be responsible for exogenous GHB's recreational effects.

GBL, a naturally occurring lactone precursor, is readily and irreversibly metabolised to GHB by peripheral lactonases [15]. 1,4 Butanediol is a naturally occurring aliphatic alcohol (dihydroxy) precursor of GHB [16]. Both of these prodrugs or precursors can be synthesised *in vitro* and *in vivo* into GHB [12, 15-23], and are readily available as industrial solvents.

2.2. Metabolism and pharmacokinetics

Following its exogenous (oral) ingestion, GHB is rapidly absorbed from the gastro-intestinal tract; time to peak is 20-60 min [24]. Its elimination half-life is 27 min, proceeding in a dose-dependent saturable manner [24]. The percentage of GHB eliminated unchanged in urine is only 2-5% [25-27]. The dosage-response curve for GHB is steep. Time to peak concentration for 1,4-BD is about 25 min [28].

GBL is rapidly metabolised to GHB by non-enzymatic hydrolysis or by peripheral calcium dependent serum lactonases [29-31]; the half-life of this conversion is considered to be < 1 min [32]. Time to peak serum concentration of the molecule is 36-57 min, with the half-life of elimination being 30-52 min [33, 34]. GBL is regarded as more potent than GHB due to its more rapid absorption and greater bioavailability [35].

1,4-BD is subject to a two-stage *in vivo* conversion process in the liver via enzymatic biotransformation to gamma-hydroxy butyraldehyde by alcohol dehydrogenase (ADH) and then by aldehyde dehydrogenase to GHB [12, 20, 23, 35-37]. Its elimination half-life is 39 ± 11 min, suggesting its effects last longer than those of GHB [38]. There is a

common metabolic pathway for 1,4-BD and ethanol, leading to potential interactions between them [19, 36]. These substances also have a synergistic effect [39, 40], as there is between ethanol and GHB in respect of synergistic sedative effects [39, 41].

2.3. Addiction potential

GHB induces several psychopharmacological effects. Its acute effects include: euphoria, ataxia, confusion, hallucinations, anxiolysis, amnaesia, sedation/hypnosis, loss of consciousness, and anaesthesia [27, 42-45].

Tolerance develops to GHB and its prodrugs' effects in rodents [46-48] and humans. It is suggested that GHB is both physically and psychologically addictive [49], and has a high abuse potential. Cross-tolerance may exist between GHB and alcohol [7].

Dependence on GHB and its precursors is more are likely to develop amongst chronic users [50, 51]. Withdrawal syndrome is observed with GHB [52, 53], GBL/GHB [54], and GBL and 1,4-BD [8, 55-57]. It is characterised by insomnia, muscular cramps, tremors and anxiety. Symptoms appear within a few fours of the last dose taken, becoming severe by 24 h [58].

GHB was added to Schedule IV of the 1971 UN Convention on Psychotropic Substances on 29 March 2001. It became controlled in the UK under the Misuse of Drugs Act 1971 as a Class C drug on 1 July 2003; and also became a substance listed under Schedule 4 Part I of the Misuse of Drugs Regulations 2001. From 23 December 2009, GBL and 1,4-BD became Class C drugs, under Schedule 2, where they are intended for human consumption.

2.4. Non-medical uses of GHB and its prodrugs

GHB was first sold as a dietary supplement, and by the late 1980s was marketed in the USA as a steroid replacement for body-builders and weight lifters. Its use as an appetite suppressant has also been noted [1]. GHB's more recent primary mode of abuse worldwide has been for its subjective (empathogenic), hypnotic, euphoric, disinhibitive and potentially hallucinogenic effects [59]. Illicit users of GHB/GBL report their subjective effects as comparable to alcohol [46], MDMA/ 'ecstasy' [60], and flunitrazepam [49].

GHB and its prodrugs are often used recreationally with other substances [61, 62], including alcohol, cannabis, and stimulants (ecstasy/ Methylenedioxymethylamphetamine (MDMA), cocaine, amphetamine/"ice"), sildenafil [54, 63-67]. Many GHB users employ MDMA to extend GHB's effects [65, 68]. GHB and its derivatives are more likely to be used in private settings rather than in public night-life settings [64].

2.5. Use in the UK 'gay' community

The molecule first appeared on the UK dance and club scenes during the spring of 1994, initially in 'gay' circles before spreading to other populations [9]. A survey in July 2010 of clients in "gay friendly" dance clubs in south London found that GHB and GBL were used relatively more often than in other types of venue [69]. Lifetime use of these molecules was 34% and 27%, with last year use being 22% and 24% respectively. These patterns were echoed in a survey conducted in London during July-September 2011 of genito-urinary clinics attendees which found higher rates of lifetime and previous month use of both GHB and GBL by gay men than by heterosexual males. Lifetime use of GHB and GBL amongst gay men was 22.7% and 16.1% respectively. Previous month rates were 2.4% and 3.1% [70]. Lifetime use of GHB/GBL amongst gay males in south London between August 2013 and March 2014 was found to be 30.6%, with 10.5% using in the previous four weeks [71], contrasting with 1.6% elsewhere in England [71, 72].

Although GHB's use as an aphrodisiac has been advocated in both heterosexual and homosexual markets [73], it is used particularly in the latter community, including bi-sexuals [74], due to its ability to boost energy and increase libido [75], enhance sex [64], assist relaxation (muscles) and promote increased confidence [71], and to facilitate sex-work and 'chemsex' [54]. Other perceived benefits include: sexual disinhibition [63, 74-80]; heightened sense of touch (tactility) [63, 64, 76, 77, 79]; more intense orgasms (especially amongst males) [63, 64, 71, 75-77]; and enhancement of male erectile capacity [79]. It is postulated that the sexual arousal caused by GHB and its prodrugs is connected with their ability to decrease anxiety and increase disinhibition via GAB_{AB} receptor agonist actions [81]. It has also been suggested that such behavioural effects entail altered transmission of dopamine [82], oxytocin [83] and

neurosteroids [84]. Sharing GHB/GBL is common in the male 'gay' community between not only friends and partners, but also relative strangers in some settings, e.g. parties, clubs and saunas [71].

GHB, GBL and similar substances have also been linked to cases of so-called 'date-rape' (alleged sexual assault) reported by the media in the USA, Europe [85, 86] and the UK [87]. In four murders GHB was administered to the victims [88-90].

2.6. Availability, route of administration and dosage

GHB typically exists as either the free acid or as the sodium base (sodium oxybate), and typically very pure in its solid form. GHB is soluble in water. It is usually sold as an odourless, clear, liquid with a salty taste; but can be found in powder or tablet form, and occasionally as a bright blue liquid ('blue nitro'). Retailers are still easy to find on the Internet, together with recipes to prepare the compound [1, 7, 91]. Individuals also manufacture GHB themselves, being able to easily obtain legal supplies of the precursors/prodrugs [38].

Commonly, GHB and its prodrugs are used orally. Powder is usually dissolved in water or other drinks prior to use [1]. Occasionally, capsules containing sodium oxybate are used [85]. Despite GHB being available as a salt or powder form, there are only occasional reports of nasal insufflation [77]. There are some reports of intravenous (IV) use [1], of "shafting" (insertion into the rectum), and of "shelving" (insertion into the vagina) [92].

In one study, the median quantity of GHB used orally by recreational users was 3 ml in a typical session and 4 ml in a heavy session [93]. Depending upon tolerance levels, recreational doses vary according to the effects sought, ranging from 1-5g daily, 15-70 mg/kg for a 70 kg adult [93, 94]. Mean daily usage of 53 ml (median 40, range 5-200) is reported in a group of patients (n=27) presenting to drug services during 2008-13 in Brighton & Hove (UK) with primary GHB/GBL dependence, with 'top ups' at 1 hr (41%) or 2 hr (44%) intervals [54]. Oral dosages suggested by users are: 0.5g for relaxation and disinhibition, 1g for euphoric effects, and 2-3 g for deep sleep [95-97]. Issues can occur due to inter-person variability in effects [98], the choice of correct dosage or taking doses too close together [1]. In addition, variation in the GHB concentrations in solutions, as well as pre-prepared ones, can give rise to some of the dangers associated with illicit use [94, 99, 100]. GHB 40 ml (3-9 doses) could hold a dose of as little as 3 g or a potentially toxic one of 20 g [101]. These factors mean an increased risk because of GHB's narrow therapeutic window and steep dose-response association [102]. The GBL oral dose range is typically 1-3 ml, with user fora suggesting taking initial doses of 1.5-2 ml with a follow-up dose of 1 ml between 30 to 60 mins later [103]. Suggested dosages are: "a good relaxing/mood enhancing" 0.5-1 ml; "f**k you up" 1.5-2 ml; and "knock you out" 3 ml, based on a conversion rate of 1 ml pure GBL = 1.65 g GHB [103-105].

2.7. Effects

Initial feelings after ingestion are euphoria and calmness, and then intoxication [106]. A low to moderate oral dose of 10 mg/kg (0.75 g) can lead to short-term amnaesia and hypotonia, lowered inhibitions and increased libido. A high dose of 20-30 mg/kg (1.5-2.5 g) produces drowsiness and sleep, and can generate dizziness and confusion, muscle stiffness, nausea and vomiting. Very high doses of 50-70 mg/kg (4-5 g) can cause convulsions [107], amnaesia, hypotonia, and coma; it may also cause bradycardia and enhance cardiopulmonary depression. Doses in excess of 70 mg/kg (5 g) can cause cardio-respiratory collapse [57, 99]. A potentially lethal dose of GHB ranges from 15-50 g (250-750 mg/kg) [60], with the effects of GHB being exacerbated by use with alcohol and other drugs, especially sedatives [1]. Loss of consciousness for short periods during sex after using GHB/GBL appears to be common and is considered "relatively normal" [71].

2.8. Hospital presentations

The growing recreational use of GHB has led to increased numbers of admissions to emergency departments (EDs) and calls to poisons centres in the EU [9]. One central London ED, whose catchment area includes a "substantial" 'gay' club scene, recorded 158 GHB/GBL presentations in 2006 [108] and 270 in 2010 [109]; with most presentations having involved males aged 20-34 [70]. Only 34% reported having used GHB/GBL alone; other combinations included alcohol (34%), MDMA (32%) and ketamine (22%). A 2013-14 survey of European hospitals, including the UK, found GHB/GBL was the fourth highest substance responsible for acute ED drug toxicity presentation [110].

EDs receive patients with a variety of states, ranging from initial confusion, dizziness or euphoria, to vomiting and collapse, through to loss of consciousness or even coma, and hypothermia [1, 111-113].

2.9. Fatalities

One measure of the risks inherent in the misuse of GHB and its prodrugs is deaths associated with their use. Our 2015 paper [9] analysed data on 159 UK deaths. This present paper focuses on a sub-set of these cases; those related to members of the LGBT community. This is because they appear to be disproportionately represented in the wider study.

3. METHODS OF DATA COLLECTION AND ANALYSIS

3.1. 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. Between 2004 and 2011 information was also received from the Scottish Crime and Drug Enforcement Agency; data from the General Register Office for Northern Ireland has also been received since 2004. Since 1997 details of about 32,000 deaths have been received. 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.

3.2. 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.

For the main study [9] 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'. For this paper, 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. Such information was typically found in police reports, witness statements from partners, families, friends, etc. Details of the cases analysed here are given in the supplementary material published with our main study [9]. These cases were extracted based on this additional information, which was flagged in the main study.

For further details regarding the interpretation of toxicological levels and toxicological screening for GHB and its prodrugs see the main study [9]. All cases reported here have either confirmatory evidence of GHB, GBL, etc. ingestion and/or the tissue levels are consistent with exogenous intake/misuse.

3.3. Data analysis

Data entry and analysis were performed using IBM® SPSS™ Statistics for Windows version 19 employing descriptive statistics. Data on blood, urine GHB/GBL concentrations are presented as mean, minimum, maximum, and standard deviation based on all cases with valid data for the variables used.

4. RESULTS

4.1. Number of deaths

A total of 21 fatalities that met the above inclusion criteria were identified on the NPSAD database as having been reported by September 2013. The first reported death in the UK amongst the LGBT community related to GHB/GBL consumption occurred in 2001. GHB was consumed in just over half of cases (n=11), the remainder involved GBL ingestion; there were none attributed to the taking of 1,4-BD. The highest number of deaths occurred in the period

2006-8 (12 cases) with one or two cases occurring in subsequent years. (However, at least nine further deaths have occurred in the period 2011-5 and are detailed in the Discussion section.)

4.2. Socio-demographics of decedents

All decedents were male: 81.0% confirmed as homosexual, 9.5% as suspected homosexuals and 9.5% (two cases) reported as being both transgender and transvestite. Mean age was 34.4 (range 21.1 – 52.6) years (Table 1); 95% were aged less than 45 years. Where information was available, the decedents' main characteristics were: White ethnicity 82.4%; UK-born 61.1%; in employment 89.5%; two-thirds were living with someone else; 81.3% had previously used drugs or had been dependent on them; one-third had used GHB/GBL.

Information on prescribed psychoactive medications was available for only four cases. One case was on diazepam and fluoxetine. A second case received sodium valproate. A third case was on a course of testosterone. The final (Attention Deficit Hyperactivity Disorder) case was prescribed: haloperidol, modafinil, dexamphetamine, amphetamine, clonazepam and gabapentin.

Table 1: Socio-demographics of UK deaths in the LGBT community associated with GHB/GBL reported to NPSAD by September 2013.

Variable	Category	Number (%)
Total		21 (100.0)
Gender	Male	21 (100.0)
Sexual orientation	Confirmed homosexual	17 (81.0)
	Suspected homosexual	2 (9.5)
	Transgender & transvestite	2 (9.5)
Country of birth	England	10 (47.6)
	Scotland	1 (4.8)
	other European countries	2 (9.5)
	Africa	3 (14.3)
	Asia	1 (4.8)
	Australia	1 (4.8)
	Not known	3 (14.3)
Employment status	Unemployed	1 (4.8)
	Employed manual	4 (19.0)
	Employed non-manual	13 (61.9)
	Student	1 (4.8)
	Not known	2 (9.5)
Living arrangements	Alone	6 (28.6)
	With others	12 (57.1)
	Not known	3 (14.3)
Ethnicity	White	14 (66.7)
	Chinese	1 (4.8)
	Other	2 (9.5)
	Not known	4 (19.0)
History of any drug use	Yes	13 (61.9)
	No	3(14.3)
	Not known	5 (23.8)
of which, history of GHB/GBL use	Yes	7 (33.3)
	No	0 (0.0)
	Not known	14 (66.7)
Injecting status	Yes	1 (4.8)
	No	8 (38.1)
	Not known	12 (57.1)
Age-group (years)	15-24	1 (4.8)
	25-34	12 (57.1)
	35-44	7 (33.3)
	45-54	1 (4.8)
Age at death (years)	Male	Mean 34.37; Min 21.07, Max 52.57, SD 7.33

4.3. Circumstances of death

All of the deaths reported to NPSAD occurred in England (19) and Scotland (2). Of note is that three-quarters (76.2%) of all cases occurred in Greater London, including 61.9% in the three London Boroughs of Lambeth, Southwark and Westminster. The peak number of deaths occurred between 2006 and 2009, with another peak in 2012. Where known, the majority (66.7%) of cases died at home or in another private residence (friend's or relative's home), and 33.3% in hospital (Table 2). The manner of death in most cases was accidental (85.7%), with 14.3% being regarded as undetermined. This closely reflects the verdicts of coroners or other formal determinations, where accidental/misadventure verdicts were given in 66.7% of cases; along with non-dependent abuse of drugs (19.0%); and possible suicides for the remaining cases (14.3%). Deaths were proportionately (38.1%) more likely to occur on Saturday than on a week-day or Sunday.

4.4. Events leading to death

In at least four cases GHB was sourced from the Internet, as well as one case of GBL. In line with two-thirds of the deaths occurring at home, four-fifths (83.3%) of the events leading to such events also occurred at the home of the deceased or the home of another person. In many instances, such deaths followed recreational use of GHB/GBL in these settings. A range of other locations witnessed GHB consumption including LGBT-oriented pubs/clubs and other venues, including saunas (Table 2).

Table 2: Circumstances of UK deaths in the LGBT community associated with GHB/GBL reported to NPSAD by September 2013.

Variable	Category	Number (%)
Total		*21 (100.0)*
Circumstances of death/events leading to death	Recreational drug use/party - at home	5 (23.8)
	Recreational drug use/party - other private residence	1 (4.8)
	Recreational drug use/party - pub/club	4 (19.0)
	Recreational drug use/party gay-oriented health spa	2 (9.5)
	Body-building/ fitness	3 (14.3)
	Accidentally mistaken for water	1 (4.8)
	In sexual activity	3 (14.3)
	Open verdict	1 (4.8)
	Not known	4 (19.0)
Location of events leading to death	Home	13 (62.0)
	Other specified place	5 (23.8)
	Of which, friends/relative's home	1 (4.8)
	Third party's home	1 (4.8)
	Hotel	1 (4.8)
	Gay-oriented health spa	2 (9.5)
	Not known	3 (14.3)
Place of death	At home	11 (52.4)
	Private residential address	3 (14.3)
	Hotel	1 (4.8)
	Hospital	5 (23.8)
	Gay sauna	1 (4.8)
Verdict (conclusion)	Accident/Misadventure	14 (66.7)
	Open/Undetermined	3 (14.3)
	Non-dependent abuse of drugs	4 (19.0)
Manner of death	Accidental	18 (85.7)
	Undetermined	3 (14.3)
Form of GHB consumed	GHB	11 (52.4)
	GBL	10 (47.6)
Day of death	Sunday	2 (9.5)
	Monday	3 (14.3)
	Tuesday	3 (14.3)
	Wednesday	1 (4.8)
	Thursday	2 (9.5)
	Friday	2 (9.5)
	Saturday	8 (38.1)

GHB/GBL consumption was not always for recreational purposes. For example, three cases used it for body-building/fitness, and at least three cases to enhance sexual experiences. Whilst there were three cases of probable suicide where GHB/GBL was deliberately consumed so as to apparently cause death, some deaths were 'accidental' in the widest sense of the term, e.g. being mistaken for water.

4.5. Cause of death

When considering the underlying cause of death (Table 3), the majority of deaths were attributed to accidental poisoning (76.2%) and poisoning of undetermined intent (14.3%). There were other deaths where natural causes played a role as a consequence of taking GHB/GBL and other substances. The principal causes in this category were: cardio-respiratory (14.3%); cardiac (9.5%); and respiratory (4.8%). It may well be that the cardio-respiratory effects resulted from GHB/GBL ingestion.

Table 3: Proximal and Underlying cause of deaths in the LGBT community associated with GHB/GBL reported to NPSAD by September 2013.

ICD-10 code	Description	Proximal cause	Underlying cause
		Number (%)	Number (%)
Mental & behavioural disorders due to psychoactive substance use			
F19.2	Multiple drug use - dependence	1 (4.8)	1 (4.8)
Accidental poisoning by and exposure to			
X41	Anti-epileptic, sedative-hypnotic, anti-Parkinsonism and psychotropic drugs, not elsewhere classified	10 (47.6)	16 (76.2)
X44	Other and unspecified drugs, medicaments and biological substances	2 (9.5)	0 (0.0)
Poisoning by and exposure to - of undetermined intent			
Y11	Anti-epileptic, sedative-hypnotic, anti-Parkinsonism and psychotropic drugs, not elsewhere classified	2 (9.5)	3 (14.3)
Other causes			
I26.9	Pulmonary embolism without mention of cor pulmonale	1 (4.8)	1 (4.8)
I50.9	Heart failure, unspecified	2 (9.5)	0 (0.0)
R09.2	Respiratory arrest	3 (14.3)	0 (0.0)
All codes		*21 (100.0)*	*21 (100.0)*

4.6. Post-mortem toxicology

Although GHB was detected in all 21 cases, quantifiable blood concentrations of GHB were available in only 18 (85.7%) (Table 4). The mean blood level was 659.8 (range 22-2355; S.D. 726) mg/L (Table 4). Urine levels were available for six cases (28.6%). The mean urine level for cases was 1139.8 (range (144-3000; S.D. 945.8) mg/L.

The commonest groups of substances found, apart from GHB/GBL, were: alcohol; stimulants (cocaine, amphetamine/methylamphetamine, MDMA/MDA, mephedrone); benzodiazepines (principally diazepam); and ketamine (Table 4). There was a mean of 3.8 (range 1-9, SD 1.97) post-mortem substances, reflecting polysubstance use. The range of substance types listed above were also evident in the most common combinations reported: GHB/GBL and stimulant (28.6%); GHB/GBL and stimulant and ketamine (14.3%); GHB/GBL and stimulants and alcohol (9.5%); and GHB/GBL and alcohol (9.5%). GHB on its own was only found in one case.

Table 4: Post-mortem blood and urine levels in deaths in the LGBT community associated with GHB/GBL reported to NPSAD by September 2013

Case number	Drug(s) present at pm, with levels
1	GHB
2	GHB bl 270mg/L ur 824mg/L; cocaine bl 1.6mg/L; benzodiazepines, other bl diazepam 0.12mg/L desmethyldiazepam 0.14mg/L temazepam 0.01mg/L; alcohol bl 47mg/100ml; methylamphetamine 0.02mg/L
3	GHB 22mg/L; alcohol 15 mg/100ml; u:10mg; amphetamine 0.3 ug/L; heroin 0.16mg/L; diazepam <0.02mg/L; phenobarbitone. Other drugs at pm: gabapentin, ibuprofen
4	MDMA bl 7.69 ug/ml; MDA bl 0.09ug/ml; GHB bl 800 mg/L; methylamphetamine bl 0.28ug/ml; amphetamine bl 0.11ug/ml; temazepam bl high therapeutic level
5	Alcohol <10 mg/100ml; ecstasy AM bl 0.46ug/ml PM 0.02ug/ml ur + AM bl MDA +; GHB PM bl 42mg/L
6	MDMA bl 0.60ug/ml; MDA: 0.07ug/ml; Ketamine bl 0.59 ug/ml; cocaine +; GHB bl 200 mg/L
7	GHB bl 530ug/ml; alcohol bl 79mg/100ml, ur 148mg/100ml; cocaine bl & ur + consistent with recreational use; Cocaethylene +
8	MDMA bl 0.31ug/ml ur +; MDA bl 0.2ug/ml ur +; methylamphetamine ur +; cocaine ur +; GHB bl 508mg/L
9	GHB; cocaine; ecstasy
10	GHB bl 311ug/ml ur 3000ug/ml
11	GHB bl 77mg/L; Ketamine 0.05mg/L; cocaine 0.14mg/L
12	Alcohol 263 mg/100ml: Flox urine: 309 ug/ml; GHB bl: 245 ug/ml
13	Amphetamine bl 0.08mg/L; cocaine bl benzoylecgonine 1.24mg/L; GHB bl 1348mg/L; MDMA bl 0.46mg/L
14	GHB bl 648ug/ml; Ketamine bl 1.61ug/ml; methylamphetamine bl 0.19ug/ml; ur +; amphetamine bl 0.02ug/ml; ur +; alcohol bl & ur <10mg/100ml
15	Alcohol bl 156mg/dl ur 220mg/100ml VH 200mg/100ml; chlordiazepoxide bl 0.23mg/L; diazepam nordiazepam 0.38mg/L VH 0.14mg/L; GHB bl 520mg/L ur 1300mg/L
16	Alcohol bl 230mg/dl; GHB bl 1400mg/L
17	GBL bl 260ug/ml ur1300ug/ml VH 130ug/ml; Mephedrone bl 0.21ug/ml ur +; TFMPP - 3-Trifluoromethylphenylpiperazine monohydrochloride bl 0.02ug/ml ur +; methylamphetamine bl 0.04ug/ml ur +; Ketamine bl <0.01ug/ml ur +; diazepam bl <0.05ug/ml & metabs. pholcodine, zopiclone, carboxy-THC also in PM.
18	Mephedrone bl 0.12mg/L; GHB bl 474mg/L ur 1442mg/L; cocaine metabolites ur +. Hair analysis suggested had a history of use of mephedrone, MDMA and exposure to cocaine in 3 months prior to death.
19	Alcohol bl >240mg/100ml; GHB; Mephedrone
20	Mephedrone bl 0.13 mg/L; ur+; Normephedrone ur+; GHB + GBL bl 2335 mg/L; +GBL ur 1471 mg/L
21	Alcohol bl 181mg/L; gammahydroxybutyrate (GHB) bl 2313mg/L; Ketamine bl 0.15mg/L; Mephedrone bl 0.12mg/L; diazepam bl diazepam 0.71mg/L, bl desmethyldiazepam 0.46mg/L, bl oxazepam 0.040mg/L, bl temazepam 0.11mg/L; fluoxetine bl 0.060mg/L
Abbreviations	AM = Ante Mortem; Carboxy-THC = 11-nor-9-carboxy-delta-9-THC; GBL = Gamma butyrolactone; GHB = Gammahydroxybutyrate; MDA = Methylenedioxyamphetamine; MDMA = Methylenedioxymethylamphetamine; PM = Post Mortem; VH = Vitreous humour

Table 5: Additional UK deaths involving GHB/GBL in the LGBT community reported in the media, 2012-6.

Source	Date	Location	Case details
[114]	25 February 2012	London Borough of Lambeth, England	A 41 year-old Greek supervisor was found dead in a locked private room by the manager of a gay-oriented sauna after being alerted by a friend of the deceased who said he was unwell. First aid and CPR were administered. Police later found a bottle of GHB and a bag of white powder. The Coroner recorded a narrative verdict saying: "his death was drug related from a combination of mephedrone and GHB. There is no evidence the drugs were forcibly given to him and there is no evidence he tried to take his life."
	27 October 2012		A 41 year-old communications officer was found dead at 08:00 on a Saturday morning at the same gay sauna. PM toxicology indicated blood levels of GHB 803mg/l ("enough for a fatality"), cocaine 0.13mg/L ("relatively high"), and alcohol ("mild levels").The pathologist found that the deceased died as a result of GHB causing significant brain injury.
	29 October 2012		A 46 year-old HIV+ security officer was found collapsed at the same time as the previous case at the same locus. He was taken to hospital but died two days later. PM toxicology revealed that GHB and MPA had been consumed. The pathologist concluded that GHB had caused significant brain injury and eventually pneumonia.
[87, 115]	21 January 2013	Bristol, England	Alcoholic homosexual aged 47 had consumed 2,5-Dimethoxy-4-chloroamphetamine (DOC) bought on the Internet by a third party convicted of assaulting him. Witnesses said the deceased had been acting strangely and danced on the sofa, later lying on the floor shaking in an uncomfortable position. At 05:30 when he had stopped breathing an ambulance was called but the crew were unable to save him. The pathologist was unable to ascertain the cause of death but GHB/GBL, DOC and alcohol (at nearly three times the UK limit for driving) were found in the deceased's body.
[88-90]		East London, England	A chef aged 40 is appearing in court at the time of writing (October 2016*) charged with 4 counts of murder and of administering a poison with intent to endanger life or inflict grievous bodily harm. He is alleged to have met his victims on gay websites, invited back to his house where he gave them GHB "within the range at which deaths from GHB intoxication have been reported", before having sex with them whilst they were unconscious. After suffering overdoses in the early hours of the morning, the victims were dumped in or near a churchyard in east London.
	19 June 2014		White fashion and design student aged 23.
	20 August 2014		Artist from Slovakia aged 22. Inquest found he had GHB and methadone in his system.
	20 September 2014		White aged 21. Inquest found he had GHB and methadone in his system.
	20 September 2015		White forklift driver aged 25.
[116]	10 November 2014	Manchester, England	White, officer administrator, aged 22, with a history of drug use GHB and ketamine) at week-ends, as well as injecting mephedrone. Was on prescribed anti-depressants and hypnotic/sedatives to help come off the drugs. He died after taking GHB, mephedrone, ecstasy and ketamine during an all-night party in a private apartment. Moments before he died the decedent was seen crawling around a bed "making weird noises" before entering and leaving the bathroom saying he was feeling sick. He then collapsed in front of his partner. A post-mortem showed he died from multiple drug toxicity. The Coroner recorded a conclusion of 'drug-related death'.
[117-119]	20 January 2015	City of London, England	Colombian-born 18 year-old café-worker, a regular drug user from age of 15. Had consumed GBL and mephedrone along with alcohol during an evening spent with his boyfriend and another male. When the boyfriend awoke the other individual had left, but the deceased was lying beside him in bed with blood and vomit round his mouth. Paramedics attended the scene and pronounced life extinct. The PM concluded that the deceased had died of a lethal combination of drugs including GBL and mephedrone. The police found glass containers with 482 ml of GBL and 60 plastic bags containing 82 g of mephedrone, which had been purchased by the deceased's boyfriend. He subsequently pleaded guilty to two counts of possession with intent to supply GBL and mephedrone for the all-night 'chem-sex' party.

*Subsequently found guilty of all 4 offences

5. DISCUSSION

5.1. Number of cases

Since the first known death in the UK associated with the ingestion of GHB and its prodrugs in 1995, [120] there have been a minimum of 159 cases in which these substances were implicated up to September 2013 [9]. This paper examines in detail the 21 deaths of these related to the LGBT community. It is believed that this is the first paper to look at such cases within this sub-population of GHB/GBL users.

Whilst the first death in this community occurred in 2001, there appears to have been two peaks, e.g. in 2006-8 and 2012 onwards [121, 122]. The patterns described here do not reflect the effects of control of GHB in 2003 and GBL in 2009, suggesting that use of GHB/GBL within the UK LGBT community may be unaffected by the substances' legal status.

5.2. Socio-demographics

At least two of the NPSAD cases were known to be both transgender and transvestite, a further case was a well-known 'drag-artist', confirming previous reports [123]. The proportion of homosexual men in the general population of the UK is about 2.0% [124]. However, in some areas, such as Brighton & Hove, the LGBT community may account for as much as 15% of the local population; four-fifths of the GHB/GBL dependence sample in the area identified themselves as being from the LGBT community [54].

All deaths notified to NPSAD by the end of September 2013, and the additional cases reported here, occurred in England and Scotland, although most cases appear to have occurred in specific south London areas, where there is a concentration of well-known gay clubs and gay-friendly saunas and gyms, bars and cafes. This led to a range of initiatives, including provision of materials on safer use of GHB/GBL [125, 126]; a 'zero tolerance' approach to the possession and use of drugs; presence in specific clubs of paramedics on duty [127].

The mean age at death in this study was slightly higher and more concentrated (34.4, range 21.1 – 52.6 years) compared to those in all NPSAD GHB/GBL cases (32.1, range 18.9 – 60.1 years) during the same period. However, thus difference is not statistically significant (Mann-Whitney two-tailed U-test, Z-Score = -1.38358, p value = 0.16758, $p < 0.05$). This result is lower than the mean age of 46 years found for HIV+ MSM clients in the ASTRA study [123]. As with most reported GHB-related deaths in our main study [9], as well as in the USA and elsewhere, the cases detailed here mostly involved Caucasian/White individuals (82.4%, where known, of NPSAD cases). Where known, most victims (61.1%) were born in the UK compared to 77% of the main NPSAD study (Ratio of proportions two-tailed test, Z-Score = -1.4578, p = 0.1443, not significant at $p < 0.05$) but there were also a number of individuals born elsewhere in Europe (11.1%) or on other continents, including 16.7% in Africa. This diversity is also reflected in the additional cases reported in Table 5. Drug-use status was known for 16 cases, with 13 (81.3%) of these being known drug users. This proportion is higher than that (70.7%) of the main study, but not statistically significant (Ratio of proportions, two-tailed test, Z-Score = 0.9429, p-value = 0.34722, $p < 0.05$). Only one decedent was known to be an injector compared to about 18% of those in the main study, also statistically non-significant (Ratio of proportions, two-tailed test, Z-Score = -1.1381, p-value = 0.25428, $p < 0.05$). This low rate of injecting is in line with that for gay males in England. [128]

The temporal pattern of most GHB/GBL deaths occurring amongst this community on Saturday (38.1%) is much higher than for Saturday and Sunday combined (36%) in the main study [9], and compared to an expected proportion of 14.1%. This probably reflects higher consumption rates on Friday to Sunday, echoing findings for ED admissions in studies of GHB/GBL [101, 129-131].

5.3. Post-mortem toxicology and other findings

Consistent with previous findings [9], post-mortem GHB blood concentrations found in this study sample range from 22 to 2335 mg/L. GHB/GBL alone was identified at post-mortem in only two (9.5%) of these 21 cases compared to 36.5% in the full study; this difference is statistically significant (Ratio of proportions, two-tailed test, Z-Score = -2.4627, P-value = 0.0139, $p < 0.05$). ONS figures for death registrations in England and Wales for 1993-2013 show that overall the proportion of GHB/GBL cases involving the drug without other drugs was 54.7%, and with alcohol 36.7% [121]. The majority of cases here involved the ingestion of at least two (mostly three) other substances,

typically combinations of any of the following: alcohol; stimulants; diazepam; and ketamine, confirming previous findings [70, 132-135]

Co-ingestion with other sedatives such as alcohol or ketamine increases the likelihood of intoxication [38], with the effects on respiratory depression of GHB/GBL [136] being enhanced by the presence of sedatives. Both alcohol and GHB are metabolised by alcohol dehydrogenase and potentiate the effects of each other [60, 137, 138], a finding confirmed in preclinical studies [139]. In the present study GHB was used with alcohol in 9.5% of cases; with other drugs in 61.9%; and with other drugs and alcohol in 19.0%. The consumption of GHB/GBL alone or with other CNS depressants led here to cardiac, respiratory and cardio-respiratory failure; these findings are consistent with those of previous reports [8, 9, 106, 140, 141].

Pre-existing medical conditions may have contributed to death or been exacerbated by the use of GHB/GBL in some cases; for example, bradycardia has long been recognised as a complication in the therapeutic use of GHB and also in those using it recreationally [106], whilst arrhythmias, or even cardiac arrest, have been described when the drug is ingested with cocaine [106] or mephedrone [142]. Furthermore, GHB has a potentially important synergistic interaction with PCP and ketamine, as they act as NMDA receptor antagonists [143].

5.4. Limitations

A number of limitations have to be considered here. Since analysis for the presence of GHB is not usually performed routinely in clinical or post-mortem investigations in the UK, the number of cases reported is likely to be an underestimation. Furthermore, given that GHB is metabolised relatively quickly in the body, it may not be present in toxicology screens, even if they are performed. Finally, GHB is also an endogenous compound. The total number of cases reported here by NPSAD is likely to be an under-estimate due to: (a) incomplete geographical coverage; (b) further cases awaiting the conclusion of formal investigations; (c) the voluntary nature of the NPSAD reporting system; (d) information on the sexual orientation and/or the settings/circumstances of death may be unknown to the Coroner and/or not noted in the information submitted to the Programme, etc. Whilst coverage by NPSAD of Coroners' jurisdictions is not complete, it has remained at a consistently high level over the past decade or more. Other sources of information were used, including media reports, so as to counter this limitation [9]. There is a lack of robust research information about some aspects of GHB/GBL use, e.g. dosage levels, and it has been necessary to use anecdotal reports by consumers. In addition, it has been necessary to include information from media sources in order to obtain a more complete picture regarding the context(s) of some aspects. 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 index deaths during this period.

6. CONCLUSIONS

Although the number of cases reported here is relatively small, this is still the most comprehensive and detailed report of fatalities associated with non-medical use of GHB and its derivatives in the LGBT community produced to date, both in respect of the UK and globally, although other evidence is emerging [144].

Medical practitioners and other health professionals need to be aware of the likelihood of coming across patients consuming GHB and related substances. Awareness of such issues needs to be highlighted to drug treatment services, sexual health services, and genito-urinary clinics catering for the LGBT community [145]. Finally, the dangers of mixing GHB/GBL with alcohol and/or other CNS-depressant substances needs to be better described in prevention campaigns, as well as cautioning users regarding the concomitant use of stimulants.

ABBREVIATIONS

1,4-BD	1,4 butanediol
DEA	Drugs Enforcement Administration
EMCDDA	European Monitoring Centre for Drugs & Drug Addiction
EMEA	European Medicines Agency
GBL	Gammabutyrolactone
GHB	Gammahydroxybutyrate
MDA	Methylenedioxyamphetamine
MDMA	Methylenedioxymethylamphetamine
NPSAD	National Programme on Substance Abuse Deaths

ONDCP	Office of National Drug Control Policy
ONS	Office for National Statistics
PM	Post-mortem

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; JC is a member of the ACMD's Technical Committee; J.C. and the NPSAD are members of the ACMD's Drug-Related Deaths Working Group. The views expressed here reflect only the authors' views and not necessarily those of the Home Office or the ACMD.

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DECLARATION

This work has not been previously published and has not been submitted for publication elsewhere. 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.

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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. 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.

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Graphical abstract

Key characteristics of GHB/GBL deaths in the UK LGBT community

Characteristic	(*N=21*)
Male	100.0%
White	66.7%
Employed	89.5%
History of drug use	81.3%
Age	mean 34.4; range 21.1-52.6; SD 7.33 years
Aged 25-44 years	90.5%
Accidental manner of death	85.7%
Underlying cause of death – accidental poisoning	76.2%
Death following recreational GHB/GBL use	70.6%
Death occurring at private residential address	66.7%
Average number of drugs consumed	3.8
Death locus in 3 London boroughs	61.9%
Most common substances found in combination with GHB/GBL	cocaine (38.1%); alcohol (33.3%); amphetamine/"ice" (28.6%); ecstasy (28.6%); diazepam (23.8%); ketamine (23.8%); mephedrone (23.8%)
Post-mortem blood levels of GHB/GBL	mean 659.8; range 22.0-2335.0; SD 726.0 mg/L